1985


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Louisiana State University and Agricultural & Mechanical College

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NICOTINIC ACID CROWN ETHERS: SYNTHESSES, CHARACTERIZATION, COMPLEXATION, AND NADH MODEL REACTION

The Louisiana State University and Agricultural and Mechanical Col. PH.D. 1985

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NICOTINIC ACID CROWN ETHERS: SYNTHESSES, CHARACTERIZATION, COMPLEXATION, AND NADH MODEL REACTION

A Dissertation

Submitted to the Graduate Faculty of the Louisiana State University and Agricultural and Mechanical College in partial fulfillment of the requirements for the degree of Doctor of Philosophy

in

The Department of Chemistry

by

Charles Ray Marston
B.A., Spring Arbor College, 1978
May, 1985
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ABSTRACT

This research effort dealt primarily with the synthesis of nicotinic acid derivatives, either incorporated into crown ether frameworks via 2,6-methylene bridges, or as appendage groups on nitrogen or carbon pivot lariat ethers. These crown ethers were also investigated as possible NADH mimics. During the course of this study three different types of nicotinic acid crown ethers were prepared:

1) 2,6-Methylene bridged nicotinic acid crown ethers
2) 6-Methylene bridged nicotinic acid lariat ethers
3) N-bridged nicotinic acid pyridinium salt lariat ethers

Various 1:1 and 2:2 isomeric macrocyclic 2,6-methylene bridged-(5,5-dimethyloxazolyl)pyridines were generated by treatment of 2,6-bis[bromomethyl-3-(5,5-dimethyloxazolyl)pyridine], prepared from ethyl 2,6-dimethylnicotinate, with cesium dibenzo-tetraethylene glycolate or a variety of sodium polyethylene glycolates. Ethyl 2,6-bis(bromomethyl)nicotinate, also prepared from ethyl 2,6-dimethylnicotinate, was converted to the corresponding 1:1-dibenzo-18-crown-6 macrocyclic analog. NMR and mass spectral data were used to ascertain the macrocyclic structures. Reduction of the 2,6-methylene bridged 3-oxazolylpyridine dibenzo 18-crown-6 macrocycle with ethylmagnesium bromide afforded, after oxidation, the
corresponding 4-substituted pyridino macrocycle in high yield. However, under identical conditions, the analogous non-oxazoline macrocycle was recovered in toto.

6-Methylene bridged nicotinic acid lariat ethers were prepared incorporating a chiral oxazoline which assisted in both stereospecific reductive metellation of the pyridine moiety and imparted asymmetry to the reactive site for NADH model reductions of suitable electrophiles. A chiral 6-methyl-3-oxazolylpyridine was converted to 6-methylene bridged 18-crown-6 and 15-crown-5 lariat ethers via conversion to the corresponding chiral 6-hydroxymethyl-3-oxazolylpyridine, followed by reaction with various electrophilic monoaza lariat ethers. One such lariat was converted to an enantiomerically enriched N-magnesio-1,4-dihydropyridine by stereoselective addition of methylmagnesium bromide. This N-metallo NADH mimic, along with its non-lariat analogue, was subsequently employed in the biomimetic reduction of $\alpha,\alpha,\alpha$-trifluoroacetophenone to give the first reported stereospecific reductions by N-metallo-1,4-dihydropyridines.

The third type of NADH model, the N-bridged pyridinium salt lariat, was synthesized by treatment of chiral (S)-proline nicotinamide derivatives with tosylated hydroxymethyl-15-crown-5. Attempted reductions of such "classical" models are described here.
"Life" by its very broadest definition, according to Norman Horowitz at the California Institute of Technology, is a system with the properties of replication, catalysis, and mutability. It has been suggested by Graham Cairns-Smith that clay (a commercial Zeolite catalyst), itself possessing each of these three properties, is a "life form". Hence, there is a probability, however finite, that out of a beginning as seemingly simple as a lump of clay, nature has mastered by repeated trial and error, the ingenuity and awe inspiring complexities of living organisms such as ourselves. To live, our bodies require billions of molecules to perform in synchronous harmony with unimaginable intricacy and efficiency; a degree of efficiency, which would be totally impossible without enzymes, the highly refined "life catalysts" of nature's design. Enzymes allow reactions to proceed with remarkable ease and stereospecificity under ambient conditions. The organic chemist has much to learn from the study and careful scrutiny of the reactions and structure of enzymatic systems as they perform in vivo. However, due to the inherent complexity of investigating reactions in living systems it is somewhat more convenient to "model" or mimic nature's enzymes by

1
employing simplified synthetic imitations. With simple models which resemble their bioenzymatic counterpart in both structure and reactivity, reactions characteristic of specific enzymes can be mimicked under highly controlled in vitro conditions dictated entirely by the experimenter, allowing him to employ every technology at his disposal in an attempt to unlock the secrets of the "life catalysts". Preparation of enzyme models, capable of mimicking enzyme functions with a high degree of precision requires the incorporation of prosthetic groups of varying complexity into the model's molecular architecture. Nevertheless, it would be inappropriate to oversimplify an enzyme model; for example, simple alkaline hydrolysis of p-nitrophenyl acetate does not seem meaningful as a model of hydrolytic enzymes.

Actual enzymes often consist of two separate structural units connected by either covalent bonds or secondary valence forces and referred to as the coenzyme and the apoenzyme. Collectively, they are known as a holoenzyme. Coenzymes are the reaction catalysts, in that they possess a reactive site, and are considered the business-end of the enzyme. The apoenzyme characteristically creates the appropriate micro-environment about the coenzyme to impart "fine tuned" stereoselectivity in the catalytic processes of it's partner coenzyme. Nevertheless, most coenzymes are
capable of functioning as catalysts in the absence of their natural apoenzyme counterpart, however, often weakly and unselectively. Hence, many enzyme models have been created by the replacement of the usually complex natural apoenzyme structure with a more elementary organic prosthetic group.

By varying these apoenzyme substitutes and sometimes altering the coenzyme's peripheral structure the organic chemist can obtain highly valuable information, which could be potentially useful in future preparation of catalysts and reagents for the simplified industrial preparation of a myriad of chemical products that, with present technology, are either too expensive or impossible to produce (i.e. pharmaceuticals, agrochemicals, etc.). It is, therefore, a prodigious challenge for the organic chemist to fashion enzyme mimics which are simplistic in structure, easy to
synthesize and yet retain the remarkable reactivity and stereospecificity of their bioenzymatic analogs. Numerous enzymes have been modeled by chemists over recent years and a wealth of information has been gained by these efforts.

One of the most extensively investigated enzymes is the pyridine nucleotide "nicotinamide adenine dinucleotide" 1 (NAD\(^+\)) and its reduced form 2 (NADH), which fall within the scope of this work. NADH was recognized\(^5a\) as a hydrogen transfer coenzyme in the 1930's; but it has been known only since the 1950's\(^5b\) that the catalytically active coenzyme functionality of NADH is the 1,4-dihydronicotinamide moiety. This moiety possesses a stereoselectively transferable hydrogen located in the dihydropyridine-4-position. NAD\(^+\) and NADH serve as coenzymes in a great number of enzymatic oxidation-reduction "in vivo" reactions.\(^6\)

\[
\begin{align*}
\text{NAD}^+ & \quad +H+2e^- \quad \text{NADH} \\
\text{NADH} & \quad \text{NAD}^+ 
\end{align*}
\]

\[
\begin{align*}
\text{NADH} & \quad \text{NAD}^+ 
\end{align*}
\]
The unique ability of the 1,4-dihydronicotinamide moiety of NADH to reduce unsaturated functionalities (such as carbonyls, conjugated olefins, and imines to mention but a few), via hydride transfer in biological systems, has been the subject of particular interest to organic and bioorganic chemists over recent years. This has resulted in the design and synthesis of numerous NADH mimics and their subsequent utilization in a variety of synthetic and mechanistic investigations. Presently, however, the exact mechanism of hydrogen transfer by NADH is not completely understood. Several excellent reviews have been published on the synthesis, structure, stereochemistry, and hydrogen-transfer reactions of these pyridine nucleotides.

Many NADH models have been designed specifically to investigate the NADH hydrogen transfer without regard for stereoselectivity. These mimics usually consist of symmetrical Hantzsch esters (3) or simple N-alkylnicotinamide pyridinium salts (4), which are characteristically converted to their 1,4-dihydro derivatives (5) by reduction with aqueous Na₂S₂O₄ under mildly alkaline conditions, a reaction which will be discussed in detail later.
Investigation of these non-stereoselective NADH mimics range from spectroscopic detection of radical-cation intermediates in transhydrogenation and kinetic isotope effects studies, to transition metal catalyzed reduction of either α,β-unsaturated carbonyl compounds or aryl iodides. However, only those mimics, which are stereoselective in their hydrogen transfer reactions (particularly to ketone substrates), will be herein considered.

Only since the mid 1970's have stereoselective NADH mimics been reported. Since then, several variations of NADH models have appeared in the literature, with some examples exhibiting stereospecificity comparable to enzymatic processes. Nevertheless, the enzymatic reaction is still superior to the models in versatility and reaction rate.

The first stereoselective NADH mimics to be investigated possessed chiral substituted amides rather than the simple amide function of the parent enzyme.
This produced an asymmetric environment about the transferable hydrogen atom in an analogous manner to the complex apoenzyme, which imparts a chiral environment around the reactive site in vivo. With an H-chiral center on the amide, serving the function of the natural apoenzyme, the model could be simplified by replacement of the original complex apoenzyme moiety with that of an alkyl group (6).

Only a few NADH mimics with chirality in their apoenzymatic N-substituent have yet been reported and they are typically less effective as stereoselective reducing agents than other chiral amides.

Early studies showed that the presence of a metal ion, particularly magnesium, was necessary for enantiomeric induction to occur in the reduction of activated carbonyl substrates by chiral NADH models. It was often found that the presence of the metal ion was necessary for reduction to occur. These findings are in
agreement with the fact that metal ions are known to be involved in the *in vivo* reductions of electrophilic centers by NADH.\textsuperscript{13,16} Evidence suggests\textsuperscript{17} that in NADH model reductions of carbonyl substrates, the metal ion is involved in some type of charge transfer complex between NADH and the substrate in the transition state which appears to be a prerequisite for hydrogen transfer to occur. Likewise, (as previously mentioned) the interaction of model NADH and its oxidized form, NAD\textsuperscript{+}, is known to be important for highly stereoselective ketone reductions. These two factors have resulted in two hypotheses of stereoselective transition states. Each of the two design strategies has proven quite effective. The first\textsuperscript{18} assumes that (in ketone reduction) the carbonyl substrate is involved in the charge transfer complex with the metal ion and NADH model in a sandwich-like array (for example 7).

The second hypothesis\textsuperscript{18b} assumes that the active charge transfer complex is between the oxidized (NAD\textsuperscript{+}) and
reduced form (NADH) of the model (8) which has a $C_2$ axis of symmetry.

The literature now holds several variations on the first theme (7) and relatively few variations of the second (8) (Table I).

In order for stereospecific reductions to occur with enzyme-like selectivity it is required that in the above mentioned transition state(s) (7, 8), only one of the reactive hydrogens (pro R or pro S) must be available for interaction with the electrophilic center. Each of the proposed transition states (7 or 8) is capable of inducing such "facial asymmetry" by conformationally locking the rotation of the amide function via metal coordination of either the nicotinamide carbonyl oxygen (often referred to in early works$^{18a,19}$ as "increased double bond character of the carbonyl nitrogen bond"), or some other ligand on the carboxamide functionality. In 7, this conformational "locking" of the amide is instrumental in blocking the "back" face of the ring when
at least one bulky group is bound to the N-substituted asymmetric center. On the other hand, the "back" face of 8 is blocked by the encapsulated Mg$^{2+}$ and its anions.

The enantioselective models that have been investigated are summarized in Table 1. Their stereoselectivities in biomimetic reductions of benzoyl formates are given.

![Chemical structure](image)

Table 1. Optical yield for the asymmetric reduction of benzoylformic acid esters.

<table>
<thead>
<tr>
<th>Model System</th>
<th>Optical Yield</th>
<th>Configuration</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>9</td>
<td>(R)</td>
<td>13-16</td>
<td>R</td>
</tr>
<tr>
<td></td>
<td>(S)</td>
<td>14-15</td>
<td>S</td>
</tr>
<tr>
<td>10</td>
<td>R=Me</td>
<td>47</td>
<td>S</td>
</tr>
<tr>
<td></td>
<td>R=CH$_3$CHMe$_2$</td>
<td>26</td>
<td>S</td>
</tr>
<tr>
<td></td>
<td>R=CH$_2$Ph</td>
<td>5</td>
<td>S</td>
</tr>
<tr>
<td>11</td>
<td>R = (-)-menthyl</td>
<td>17-21</td>
<td>R</td>
</tr>
<tr>
<td>12</td>
<td>(S,S)</td>
<td>26.3</td>
<td>S</td>
</tr>
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Table 1 (continued)

<table>
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<tr>
<th>Model System</th>
<th>Optical Yield</th>
<th>Configuration</th>
<th>Ref.</th>
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<td>13</td>
<td><img src="image1.png" alt="Chemical Structure" /></td>
<td>51.5</td>
<td>S</td>
</tr>
<tr>
<td>14</td>
<td><img src="image2.png" alt="Chemical Structure" /></td>
<td>(R)</td>
<td>27</td>
</tr>
<tr>
<td>15</td>
<td><img src="image3.png" alt="Chemical Structure" /></td>
<td>R = CH(CH$_3$)$_2$</td>
<td>86</td>
</tr>
<tr>
<td>16</td>
<td><img src="image4.png" alt="Chemical Structure" /></td>
<td>(R,R)</td>
<td>97.6</td>
</tr>
<tr>
<td>17</td>
<td><img src="image5.png" alt="Chemical Structure" /></td>
<td>(S,S)</td>
<td>94.7</td>
</tr>
<tr>
<td>18</td>
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<td>X = NH</td>
<td>26</td>
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Table 1 (continued)

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<th>Model System</th>
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<th>Configuration</th>
<th>Ref.</th>
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<tr>
<td>19</td>
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<td>28</td>
<td>R</td>
</tr>
<tr>
<td>20</td>
<td><img src="image2" alt="Chemical Structure" /></td>
<td>(a) $R = CH_2Ph$ 31-79</td>
<td>R</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(b) $R = CHCONHCH_2Ph$ 18.5</td>
<td>R</td>
</tr>
<tr>
<td>21</td>
<td><img src="image3" alt="Chemical Structure" /></td>
<td>37-53</td>
<td>R</td>
</tr>
<tr>
<td>22</td>
<td><img src="image4" alt="Chemical Structure" /></td>
<td>$X = o$-xylene</td>
<td>a 36.4</td>
</tr>
<tr>
<td></td>
<td></td>
<td>$p$-xylene</td>
<td>b 34.0</td>
</tr>
<tr>
<td></td>
<td></td>
<td>$m$-xylene</td>
<td>c 93.5-98.1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>$-(CH_2)_4$</td>
<td>d 39.9</td>
</tr>
<tr>
<td></td>
<td></td>
<td>$-(CH_2)_5$</td>
<td>e 43.0</td>
</tr>
<tr>
<td></td>
<td></td>
<td>$-(CH_2)_6$</td>
<td>f 95.6</td>
</tr>
<tr>
<td></td>
<td></td>
<td>$-(CH_2)_7$</td>
<td>g 58.7</td>
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<td></td>
<td>$-(CH_2)_8$</td>
<td>h 81.2</td>
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<td></td>
<td></td>
<td>mesitylene</td>
<td>i 17.6</td>
</tr>
<tr>
<td></td>
<td></td>
<td>tris</td>
<td></td>
</tr>
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<td>23</td>
<td><img src="image5" alt="Chemical Structure" /></td>
<td>(R)</td>
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Table 1 (continued)

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<tr>
<td>Cr</td>
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<tr>
<td>* h2 RK</td>
<td>0</td>
<td>R</td>
<td>31</td>
</tr>
<tr>
<td></td>
<td>BSA</td>
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<tr>
<td></td>
<td>EWA</td>
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<tr>
<th>Protein</th>
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<tr>
<td>PhCH₂</td>
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<th>25</th>
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<th>S</th>
<th>14b</th>
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<tr>
<td>R' = CH₃</td>
<td>10.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>R' = PhCH₂</td>
<td>9.1</td>
<td>R</td>
<td>14b</td>
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<table>
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<tr>
<th>24</th>
<th>R =</th>
<th>S</th>
<th>14b</th>
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</thead>
<tbody>
<tr>
<td>R' =</td>
<td>(S) 43.2</td>
<td>R</td>
<td></td>
</tr>
<tr>
<td>R' = PhCH₂</td>
<td></td>
<td></td>
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<table>
<thead>
<tr>
<th>26</th>
<th>R =</th>
<th>R</th>
<th>14b</th>
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<tbody>
<tr>
<td>R' = PhCH₂</td>
<td>8.8</td>
<td>S</td>
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<th>R</th>
<th>14b</th>
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<tbody>
<tr>
<td>R' = PhCH₂</td>
<td>5.7</td>
<td>R</td>
<td></td>
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Table 1 (continued)

<table>
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<tr>
<td><img src="image1" alt="Structure 27" /></td>
<td>45.6</td>
<td>R</td>
<td>14b</td>
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<td><img src="image2" alt="Structure 28" /></td>
<td>43.5</td>
<td>S</td>
<td>14b</td>
</tr>
<tr>
<td><img src="image3" alt="Structure 29" /></td>
<td>46.6[TFA]</td>
<td>BSA</td>
<td>14a</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cholate</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>G-cyclodextrin</td>
<td>0 - 1.4</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>0 - 10.0%</td>
</tr>
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</table>

In order to conduct the above reactions, the reducing 1,4-dihydropyridines were generated from their corresponding pyridinium salts. Reduction of pyridinium salts by NaBH$_4$\textsuperscript{32} and LiAlH$_4$\textsuperscript{4,33} gives 1,2- or 1,6-dihydropyridines, as the preferred products over the 1,4 isomers. However, reductions of various pyridinium
salts via Na$_2$S$_2$O$_4$ have long been known to give 1,4-dihydro derivatives exclusively. In every case presented in Table I, the reduced NADH models were generated by Na$_2$S$_2$O$_4$ reduction. This "net hydride" reduction is reported to proceed by attack of sulfoxylate followed by the irreversible expulsion of SO$_2$ (Fig. 1).

The stereospecific reductions noted in Table I were generally conducted most effectively [i.e., highest percent enantiomeric excess (% ee)] when equimolar quantities of the model, substrate, and Mg(ClO$_4$)$_2$ in dry CH$_3$CN or CH$_3$CN/CHCl$_3$ (2:1; 0.5 - 1.0 mM) were employed. The mixtures of model and substrate are typically allowed to react under inert atmosphere in the dark for 6 hrs to several days at 25-55°C. Reductions typically gave the substrate derived alcohols in yields of 50 - 100%. In each case %ee's (optical yields) were determined polarimetrically (ORD) from the purified mandelate products.

One of the most stereospecific NADH models, (16,
Table 1) yet reported was devised by Ohno et al. \(^{24}\) (% ee > 95%) and assumes the transition state depicted by 7. This unique model has an asymmetric center at the dihydropyridine 4-position which is particularly interesting since the hydrogen used for reduction is linked directly to the asymmetric carbon. This effectively "blocks" one entire "face" and limits the number of transferable hydrogens to one. By using this "doubly-chiral" model, \(^{24}\) Ohno et al. proposes a three-step mechanism to be operant: (1) initial electron transfer, (2) proton transfer, and (3) transfer of the second electron. Following the initial electron transfer process, the carbonyl substrate can orient itself into an electronically and sterically favorable configuration. Thus, the carbonyl-oxygen points toward the ring-nitrogen of the model and the most electronegative substituent of the ketone faces against the carboxamide. Interestingly, Ohno et al. found \(^{24}\) that high ee's (> 95%) in either the R or S mandelates could be acquired by employing models having opposite stereochemistry at the hydrogen transferring asymmetric center. Whereas inversion of the stereochemistry at the more remote chiral center had little effect on the selectivity of the model.

In contrast to Ohno's work, a series of models based on transition state 8, were prepared by the Oda \(^ {29}\) group. These models were designed to test the previously
mentioned "face-to-face" type blocking by bridging the dihydropyridine units via the pyridine nitrogens. Oda employed both xylene bridges and polymethylene bridges of 4 to 9 carbons in an apparently successful attempt to implement an archetypical intramolecular equivalent to 8 with remarkable results. The p-xylene derivative 22c gave reduction of the benzoylformate with enantiomeric excesses as great as 98%; whereas, the methylene bridged models produced ee's ranging from 40 to 96% with the 6-carbon-bridged model being optimum. These results strongly support the participation of transition state 8 in the hydrogen transfer mechanism by showing a relationship between fittedness and stereoselectivity. These observations do not disprove 7, they only support a discrete transition state to be workable.

Only the Hantzsch ester derivatives, having a C2 axis (Fig 2.) in the dihydropyridine itself, do not require a "blocking" conformation in the transition state as is required in 7 and 8, since the two faces appear identical to an approaching substrate. Nevertheless, a "locked" conformation is, or may be, advantageous. Unlike all other (NADH) models, the metal ion is not always necessary to accomplish "locking".
The Kellogg group has recently reported several intriguing NADH Hantzsch-type mimics incorporating a 3,5-pyridino bridged crown ether-like macrocycle designed to restrict, conformationally the orientation about the pyridine-carbonyl bonds and provide a locus for metal ion complexation. Kellogg has utilized the chiral amino acid L-alanine in macrocyclic 15 to impose the extremely high stereoselectivity (86% S) experienced in the reduction of benzoylfomate. In models like 15, the 4-position, which delivers the hydrogen, is covered by an asymmetric shroud which conformation dictates the positioning of the substrate in the transition state. However, evidence to support the hypothesis, that an encapsulated metal ion is involved in the transition state for hydrogen transfer, as forwarded by Kellogg (Fig. 3), is not conclusive. In fact, this enantiomeric induction is easily predicted as based on the Ohno transition state model 7 (Fig. 3).
Yet another interesting series of NADH models was prepared in light of the work concerning the salient effects of $C_2$-symmetry on asymmetric syntheses such as: alkylation of enamines, asymmetric reduction of prochiral carbonyl substrates by the use of LiAlH$_4$ modified with chiral l,l'-binaphthyl, borane-amine complexes modified with optically pure l,l'-binaphthyl, the previously mentioned bis(NADH) model (22), and Michael additions catalyzed by chirally-functionalized crown complexes. Oda et al. have prepared an intriguing class of chiral binaphthyl models. These models possess for the first time an axial dissymmetry caused by the l,l'-binaphthyls as a chiral moiety, instead of the typical centro-asymmetry. These axially chiral models (25-28) were employed in the
asymmetric reduction of benzoylformate. The results were compared with those of the corresponding binaphthyl model lacking a $C_2$ axis yet bearing the same axial chirality (Table 1). In addition, the influence of polar functionality, bonding modes of dihydropyridine to chiral binaphthyls, the distance between the reaction center and the binaphthyl moiety on the stereoselectivity were discussed. Oda found$^{14b}$ an increase in stereoselectivity when the NADH models have a $C_2$ axis. In each case, selectivity diminished as the distance between the dihydropyridine and the binaphthyl increased while the stereoselectivity showed a distinct dependence on the mole ratio of Mg$^{2+}$/NADH model with a maximum at 1:2. Such results are not unexpected considering the possible involvement of charge transfer complex 8 where the mole ratio is also 1:2 for maximum efficiency.

Stereoselective reductions have also been accomplished via NADH models immobilized in cross-linked polystyrene beads,$^{30}$ although, with greatly diminished stereospecificity ($\%$ ee = 0.9 - 1.1). On the other hand, by incorporating a spacer between the dihydropyridine and the insoluble support, the optical yield is improved (7.3$\%$). It was thus concluded$^{30}$ that the polymer support brings about an unfavorable influence on the stereospecific hydride transfer.

Other environmental effects on the reactivity of
NADH models have also been observed. Impressive optical yields have been realized by employing non-chiral reducing agents in chiral media, as demonstrated by the reduction of ketones with NaBH$_4$ in the presence of hydroxymonosaccharide derivatives of cholate micelle.$^{42}$ Similarly non-chiral NADH models have stereoselectively reduced trifluoroacetophenone in solutions of cholate micelle ($\%ee = 0 - 1.4\%$), $\beta$-cyclodextrin ($\%ee = 0 - 10.0\%$), and bovine serum albumin$^{34}$ ($\%ee - 46.6\%$). Because of these results, simple NADH models have been bound to various protein backbones (Table 1),$^{31}$ unfortunately, with the same diminished selectivity as was observed upon binding of NADH moieties to prosthetic polymers.

Research is continuing to elucidate the role of metal ions in these stereospecific processes. It is not unlikely that the true transition state or charge transfer complex falls somewhere between 7 and 8; since successful models have been produced with both transition states in mind. Since stereoselectivity tends to improve as the ratio of NADH to NAD$^+$ approaches 1:1,$^{18}$ one might speculate on the possibility of other charge transfer intermediates being involved in these reductions. As the dihydro species is oxidized and the concentration of pyridinium species increases, a charge transfer complex like that in Figure 4 may become prevalent. Several
kinetic and isotope scrambling studies have been performed to determine the extent of involvement of the pyridinium interaction in NADH model reactions. However, as of yet, little is known about the true identity of such charge transfer complexes.

Figure 4

It has been well established that, like typical N-alkyl NADH models, N-metallo-dihydropyridines are also capable of transferring a hydride to a suitable N-metallo-1,4-dihydro electrophilic center. Thus, pyridines, generated by reduction of pyridine with LiAlH₄, ZnH₂, MgH₂, or selected organometallic reagents have been used to reduce carbonyl substrates in an NADH-like fashion. Evidence has been given which suggests that the reduction of carbonyls by N-metallo-1,4-dihydropyridines, similar to classical NADH models, proceeds through a charge transfer complex, particularly in the case of aryl ketones (Fig. 5).
Such charge transfer complex can be envisioned in an array not unlike complex 7 (Fig. 6).

The N-bonded metal ion mediates the approach and juxtaposition of the carbonyl substrate prior to hydride transfer via an 8-centered transition state very much like the 6-centered mechanism accepted for the hydride reduction of ketones by Grignard reagents with \( \beta \)-hydrogens \(^{46} \) (Fig. 7),

or the often proposed 4-center mechanism for addition of
other alkyl or aryl Grignards\textsuperscript{47} to carbonyls (Fig. 8). 

The charge transfer complex depicted in Figure 6 can also be envisioned as a vinylogous analog of the cyclic hydride transfer transition state forwarded for the Meerwein-Ponndorf-Verley (MPV) reduction\textsuperscript{48} (Fig. 9).

Since the above mentioned organometallic reactions are effectively irreversible additions and occur \textit{via} cyclic transition states, two or more stereoisomers may form depending upon which face of the ketone undergoes addition. MPV reductions by asymmetric alkoxides are expected to be stereoselective, giving rise to one enantiomer in preference to the other. Cram and his
co-workers have provided a rationale for such stereoselective behavior,\textsuperscript{49} which states that the group being introduced to the substrate adds to the least hindered face of the carbonyl when in its most preferred conformation. The preferred conformation, according to Cram's Rule,\textsuperscript{49} is assumed to be a transition state in which the large group on the $\alpha$-carbon is away from the carbonyl oxygen (Fig 10).

Such organometallic reactions are considered exothermic processes;\textsuperscript{50} therefore, the transition state will tend to be reactant-like and the reaction will tend to be "steric approach controlled".\textsuperscript{50} The reductions of ketones by typical NADH models can often be fortuitously predicted by Cram's rule (or steric approach control\textsuperscript{50}), where the ketone's bulky substituent is oriented away from the models bulky carboxamide groups. However, if this same substituent happens to be its most electronegative group\textsuperscript{24} "product development control" may tend to take-over because of electronic constraints (Fig. 11). Such behavior is more successfully explained by the Karabatsos modification of Cram's rule,\textsuperscript{51} which predicts
a preferred syn conformation between carbonyl oxygen and the $\alpha$-substituted "large" group when the large group possesses a coordinating site (i.e. pyridine nitrogen).

Figure 11

If a charge transfer complex is indeed operative, in the reduction of carbonyls by $N$-metallo-1,4-dihydropyridines, chiral $N$-metallo derivatives may give stereospecific reductions reminiscent of those observed with the classical $N$-alkyl analogs. Previous to this work, asymmetric reduction by $N$-metallo-1,4-dihydropyridines had not been reported.

Since the early 1970's, the Newkome$^{52}$ group has been involved in the syntheses and reactivity of macrocyclic systems which incorporate heterocyclic subunits. In particular, crown ethers which incorporate pyridine moieties as integral ligand sites in the coronand structure (30, 31).
Pyridino crown ethers such as these 2,6-bridged examples could be envisioned to undergo reductive metallation via organometallic reagents and metallohydrides. Moreover, the presence of the crown ether moiety may present the possibility of 1,4-metallohydride addition by normally non-nucleophilic alkali metal hydrides (Scheme I).

Scheme I

In order for such an alkali hydride induced reductive metallation to occur, the pyridine should possess an activating group in the 3 position (like NAD) and the size and configuration of the crown ether must be such that, the cation fits snuggly, thus, forcing an
abnormally strong interaction between the cation and the pyridine N-electrons. Withdrawal of electron density via interaction with the encapsulated cation (N-metallation) should activate the pyridine 4-position (being less hindered than the substituted 2- or 6-positions) toward nucleophilic (hydride) attack. If such a 1,4-reductive metallation were successful, these pyridino crown ethers would provide a novel entry into the preparation of chelatively stabalized N-metallo-1,4-dihydropyridine NADH models (Scheme II).

Scheme II

Newkome's earliest attempt at a viable 2,6-pyridino crown ether NADH mimic utilized a series of "models" in which the polyether moiety was bridged to N,N-dimethylnicotinamide via oxygen linkages. For this series 2,6-dichloronicotinic acid (32) was a convenient starting point (Scheme III).
However, attempted 1,4-reductions of 35 with mild reducing agents such as: sodium dithionate or sodium borohydride, gave only unchanged starting macrocycle. Under more strenuous conditions [sodium bis(2-methoxyethoxy)aluminum hydride ("Vitride")], 35 was reduced exclusively to the corresponding amine 36.

Even though 35 has multiple sites for metal ion coordination, utilization of the lanthanide $^1$H NMR shift reagent Eu(fod)$_3$ indicated that the carbonyl oxygen was the preferred site of metal complexation (Fig 12) and not
the crown ether.

In contrast the unsubstituted macrocycle 30, showed a distinct interaction of the shift reagent with the outer arch of the crown ether bridge. This was demonstrated by the shifts in the \( \epsilon \) and \( \delta \) methylene protons of the crown bridge in 35 at low metal ion concentrations. The preferred complexation of the carbonyl oxygen with the shift reagent affords a rationale for the greater susceptibility of the amide group to nucleophilic attack.

In an attempt to minimize competition by sites other than the crown ether ring, the Newkome 52e group synthesized the macrocyclic nicotinonitrile 39 via a pathway similar to that utilized for the preparation of 35 (Scheme IV).
The possible sites of metal ion complexation were likewise evaluated via lanthanide shift reagent $^1\text{H}$ NMR investigation. Chart 1 shows the shifts induced by 10% Eu(fod)$_3$ for 35, 30, and 39. The striking similarity between 30 and 39 indicates that the predominant site(s) of europium ion coordination is the central bridging ethereal oxygens as demonstrated via the dramatic downfield shifts experienced by the singlet for the $\epsilon$-methylene hydrogens. As previously mentioned, the amide oxygen of 35, is the favored site of coordination with Eu(fod)$_3$. 

Chart 1
Alternatively, macrocycle 39 possessed the prerequisites for 1,4-reduction by mild reducing agents. The 4-position was activated by the presence of the 3-cyano group, the 2(6)-position(s) were sterically blocked by the bridging substituents, and the metal ion, indeed, complexed predominantly on (or in) the crown ether ring.

Nevertheless, treatment of 39 with mild reducing agents, such as: sodium dithionate and sodium borohydride, gave only unchanged starting macrocycle. With stronger reducing agents, such as: lithium aluminum hydride or Vitride, 39 underwent reduction to give pentaethylene glycol and the only discernible pyridine-based moiety upon hydrolytic workup (Scheme V) was the nitrile reduction product: amine 40.

Scheme V

\[
\begin{align*}
39 & \rightarrow \text{CH}_2\text{NH}_2 \\
& + \text{CN} \\
& \text{H}_2\text{O}^+ \\
& \text{CN} + \text{HO(CH}_2\text{CH}_2\text{O})_3\text{H}
\end{align*}
\]
Even though the nitrile moiety reduced slowly under these conditions, the pyridine nucleus was quickly reduced. It was proposed that 39 underwent 1,4 (or 1,2) reduction of the pyridine nucleus and then rearranged to 41. Hydrolysis of the labile imidate ester 41 occurred easily even under the mild conditions of aqueous workup.

Subsequently, X-ray analysis and MO calculations gave insight into the molecular geometry of the juxtapositioned groups. These data indicate that in closely related 2,6-disubstituted pyridines which possess at least one \( \text{N}=\text{COCH}_2 \) group (imidate moiety), there is a near-zero (\( \pm 10^\circ \)) dihedral angle for the \( \alpha \) - and/or \( \alpha' \) methylene group(s) (Fig 13):

![Figure 13](image)

thus, direct \( \text{N} \)-metal ion complexation will be greatly hindered in such macrocycles. This provides a rationale for the inability to obtain the desired crown ether stabalized \( \text{N} \)-metallo-1,4-dihydropyridine NADH model.

There has been only one other report of the possible
formation of a crown ether stabilized "self solvated" 
N-metallo-1,4-dihydropyridine. Kellogg et al.\textsuperscript{36} reported 
the formation of the symmetrical Hantzsch ester 
macrocycle 43 via condensation of the polyether bridged 
\textit{bis-} $\beta$-keto ester 42 with $(\text{NH}_2)_2\text{CO}_3$ and $\text{H}_2\text{CO}$. 
Treatment of 43 with sodium hydride gave a dark $\text{CH}_2\text{Cl}_2$ 
soluble material which partially deuterated on hydrolysis 
with $\text{D}_2\text{O}$, but was unreactive as a nucleophile when 
treated with methyl iodide. Kellogg stated that the 
N-metallo derivative apparently decomposed too quickly in 
methylene chloride to be alkylated, however, this is only 
speculative since the decomposition products were not 
identified.

The N-metallo intermediate of Kellogg's Hantzsch ester 
43 was not utilized in any NADH-type model reactions nor 
was any further investigation of such a system pursued. 
As previously mentioned, Kellogg\textsuperscript{23} has had great success 
in the preparation of stereoselective 3,5-polyethereal 
bridged "classical" (N-alkyl) NADH models in which the
crown ether may simply act as an efficient conformational locking device rather than a coordinating ligand.

Other "classical" NADH models have incorporated crown ethers with some success. Shinki et al.56 reported the nonstereoselective reduction of a crown ether flavin by NADH models (Fig. 14).

Figure 14

The crown ether flavin was less reactive toward reduction than its "parent" flavin owing to the electron-donating nature of the crown group; however, rate enhancements of reduction were observed on addition of alkali metal salts. Therefore, the metal ion, complexed in the crown ether ring, strengthened the oxidizability of the crown ether flavin. Rate enhancements were also observed for reduction of the flavin by incorporation of metal salts or ammonium ion into the structure of the NADH model reductant, presumably due to an increase in "local concentration" of reducing agent via binding by the crown ether.

Another report of the use of crown ethers in
conjunction with NADH models was made very recently by Baba et al.56 Stereoselectivity of the reduction of benzoylformate by the chiral prolinamide 20a was enhanced (20%) by the addition of the 2,2,2-cryptand 44 and slightly improved by dibenzo-18-crown-6 (45).

Other ligands, such as; 2,2,1-cryptand and quinaldine, decreased the stereoselectivity of the model reductions.

The following pages are an account of the continuation of our efforts toward a more representative and viable crown ether stabilized (self solvating) \( \text{N-metallo-1,4-dihydropyridino NADH mimic} \), as well as a brief account of preliminary efforts to produce a series of "classical" NADH models incorporating crown ethers as an integral part of their structure.
Chapter 1

NICOTINIC ACID CROWN ETHERS. SYNTHESSES, COMPLEXATION, AND REDUCTION.

Originally Printed in Great Britain
March 1, 1985

Dr. T. Stephen
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Dear Dr. Stephen:

I recently had the privilege of co-authoring a research paper in Tetrahedron (Vol. 39, No. 12, pp. 2001 to 2008, 1983) with my professor, Dr. George R. Newkome at Louisiana State University, Baton Rouge, Louisiana, USA. I would like to use that manuscript "as is" in my doctoral dissertation. According to LSU graduate school regulations as well as copyright laws, in order to do so, I need a written "copyright waiver" from the copyright owner. I am writing to you in request of such a written waiver. The manuscript will be reprinted only in my dissertation titled: NADH MODEL SYSTEMS INCORPORATING CROWN ETHERS, SYNTHESSES, COMPLEXATION, AND REDUCTION, and will not be published for sale.

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NICOTINIC ACID CROWN ETHERS. SYNTHESIS, COMPLEXATION, AND REDUCTION.

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(received August 15, 1982).

ABSTRACT. 2,6-Bis(bromomethyl)nicotinic oxazoline (15), prepared from ethyl 2,6-dimethylnicotinate, was converted into the 1:1-macro cyclic oxazolines 19 and 22 as well as the isomeric macro cyclic dimers 20. Ethyl 2,6-bis(bromomethyl)nicotinate (23), prepared from 6b, was converted to the corresponding 1:1-dibenzo-18-crown-6 macro cyclic analog 24. NMR and mass spectral data were used to ascertain the macro cyclic structures. Reaction of 22 with ethyl magnesium bromide afforded, after oxidation, the 4-substituted pyridino macrocycle 26 in high yield. However, under identical conditions, the non-oxazoline macrocycle 27 was recovered in toto.

Mimesis of the stereospecific reduction nicotinamide adenine dinucleotide (NAD) dehydrogenase has been a major concern of numerous research groups over the
past several decades. Metal ion participation in the stereospecific enzyme mediated hydride transfer to a carbonyl substrate in vivo is well established. It has also been demonstrated that N-metallo-N-dihydropyridines can similarly transfer hydride ion to a suitable electrophilic center; thus, N-metallo-1,4-dihydro-pyridines, generated by reduction of pyridine with LiAlH₄, ZnH₂, MgH₂, or selected organometallic reagents, have been used to reduce carbonyl compounds.

The incorporation of the 1,4-dihydronicotinic acid subunit within a macrocyclic framework has taken several different pathways. Kellogg et al. used two different models to accomplish this purpose; in each case the symmetrical Hantzsch-type intermediate was invoked.

In order to insure a more representative NAD model, Newkome et al. synthesized a series of 2,6-nicotino crown ethers (3) from 2,6-dichloronicotinic acid via
nucleophilic substitution. Even though the crown ether portion of 3 should stabilize an included metal ion (e.g. an alkali metal), the imidate moiety inherent in this series and the low ligandophilicity of the N-donor were, in part, detrimental to the generation of N-metallo-dihydronicotinic acid derivatives. Further, to establish the site of metal ion coordination in 3, $^1H$ NMR shift reagents were utilized$^{52d}$; in the cases evaluated, the ester, acid, and amide moieties were the preferred coordination site over the ethereal bridge. Only in the parent 3a ($R=CO_2H$) and nitrile 3d ($R=CN$), was metal ion coordination with the bridge realized; in these cases pyridine reduction was demonstrated by isolation of the open-chain polyethylene glycol and substituted imide. In order to circumvent the deleterious imidate moieties, a new series of nicotinic acid macrocycles was prepared and our preliminary studies in this series are described.
RESULTS AND DISCUSSION.

1. Syntheses of the Nicotino Macrocycles. Two general procedures were envisioned to generate macrocycles, such as 4: firstly a "one-step" self-condensation of 5 or secondly a more traditional approach based on dimethylnicotinic acid 6a, via free radical α-halogenation and subsequent nucleophilic substitution.
Since ethyl 2,6-dimethylnicotinate (6b) was a convenient starting material for the latter procedure as well as could be used to model the cyclization route, the desired enamine 7, prepared from ethyl acetooacetate with anhydrous ammonia\textsuperscript{6d}, was added to POCl\textsubscript{3} at 90°C from which the chloro derivative 8\textsuperscript{62} was isolated in 73% yield. Dechlorination of 8 under phase-transfer conditions [triethylamine, aqueous formic acid (88%), and palladium (10%) on carbon]\textsuperscript{63} at 80°C for several days gave 6b in 95% yield besides a \(4,4'\)-dimer 9 in 3.5% yield. The use of palladium (10%) on carbon in ethanol under 3 atm. of hydrogen circumvented dimer formation; 6b was prepared in 100% yield. The \(^1\)H NMR spectrum of 6b showed doublets at \(\delta\) 8.09 and 7.05 for the 4- and 5-ring hydrogens, respectively. The down-field singlet at \(\delta\) 2.81 for the 2-methyl group (vs 2.56 for the 6-methyl substituent) is indicative of the adjacent ethoxycarbonyl moiety. Dimer 9 was generated by a coupling of the stable 4-pyridinyl radical\textsuperscript{64} during the hydrodechlorination reaction.
In view of the successful conversion of 7 to 6b, ether 10a, prepared from ethyl 4-bromoacetoacetate by the method of Kellogg, et al. was transformed in near quantitative yield to the bis-enamine 11a upon treatment with anhydrous NH$_3$ under dehydrative conditions. Several attempts were made to cyclize 11a with POCl$_3$ under diverse conditions however polymeric residues were created from which the pyridine product (e.g. 4) was not detected. The simpler ethereal ester 10b was prepared, transformed to 11b, but cyclization conditions with POCl$_3$ also failed to generate the desired pyridine nucleus (12b).
To circumvent transesterification of the ethoxycarbonyl moiety under nucleophilic conditions\textsuperscript{52f}, ester 6b was treated with 2-amino-2-methylpropan-1-ol and P\textsubscript{2}O\textsubscript{5} in anhydrous xylene to give the oxazoline derivative 13 in 50% yield. Without P\textsubscript{2}O\textsubscript{5}, the intermediate amide 14 was isolated (93%), subsequent treatment with P\textsubscript{2}O\textsubscript{5}, caused cyclization to 13 in 70% yield; the use of pyridine, as solvent, enhanced (>80%) oxazoline formation.

![Chemical structures](image)

Oxazoline 13 was brominated with N-bromo-succinimide (NBS) in CH\textsubscript{2}Cl\textsubscript{2} under irradiation with a 125 watt incandescent light and AIBN, as the initiator, to give four major products, of which the bis-bromomethyl derivative 15 was isolated (24%) and characterized (\textsuperscript{1}H NMR) by the two singlets at δ 4.48 and 5.08 for the 6- and 2-methylene groups, respectively. Interestingly, 16 was the major (40%) monobrominated product as shown by the down-field singlet at δ 5.12 for the 2-CH\textsubscript{2}Br moiety as well as singlet at δ 2.57 for the 6-methyl
group. Bromination of 16 gives predominately 17 as suggested by the growth of the singlet at $\delta$ 6.63 for the methyne hydrogen. Monobromination at the remote 6-position of 13 afforded 18 in low yield, as shown by the singlet $\delta$ 2.87 for the 2-methyl group.

\[
\begin{align*}
13 \quad \xrightarrow{NBS} \quad 15 + 16 + 17 + 18
\end{align*}
\]

Synthesis of the polyethereal bridge was accomplished by treatment of 15 with sodium polyethylene-glycolate in dimethoxyethane under high-dilution conditions. With pentaethylene glycol, the 1:1-macrocycle 19a was isolated (45%) and characterized ($^1$H NMR) by the two singlets at $\delta$ 4.81 and 5.05 for the $\alpha'$- and $\alpha$-CH$_2$O moieties, respectively, as well as the intact oxazoline ring. Isomeric 2:2-macrocycles 20a were also isolated (48%) but not separated. The hexaethylene glycol macrocycles 19b (46%) and 20b (43%) were spectrally characterized; the $^1$H NMR data were nearly identical to that of 19a and 20a, respectively.
Treatment of diol 21 with 15 in the presence of cesium carbonate, as both base and template ion, gave the dibenzo macrocycle 22 in 46% yield. The use of cesium carbonate had been demonstrated to enhance the cyclization process. The up-field shift ($\Delta \delta \approx 0.5$) for both $\alpha,\alpha'$-methylene hydrogens in 22 is indicative of increased rigidity caused by the fused benzo moieties.

Under the milder reaction conditions and the use of
cesium carbonate competitive transesterification should be minimized. To test this hypothesis, ethyl 2,6-dimethyl-nicotinate was brominated with NBS under similar conditions, as described above. The desired bis-bromomethyl ester 23 was prepared (25%) and isolated as colorless crystals, which decomposed upon standing. The combination of diol 21 with 23 proceeded smoothly to give (78%) macrocycle 24. The presence ($^1$H NMR) of singlets at δ 5.68 and 5.38 for the $\alpha,\alpha'$-pyridyl methylenes as well as the quartet at δ 4.39 for the ethyl ester confirm the macrocyclization process to the near exclusion of transesterification.

2. Reactions of the Nicotino Macrocycles. These oxazoline macro-cycles can be envisioned to undergo reduction of the pyridine subunit by: (i) initial metal ion inclusion, followed by 1,4-nucleophilic addition; (ii) metal ion coordination, then directed nucleophilic attack; or (iii) a combination of directed metallation-addition, then metal ion rearrangement. Aromatization
of the dihydro intermediate(s) (after hydrolysis) is quite facile in the air or under mild oxidative conditions. In the presence of an electrophilic center, hydride transfer via metal ion coordination also leads to aromatization.

In the simple pyridine oxazolines, it has recently been shown that coordination of the organometallic reagent with the oxazoline directs the nucleophile to the 4-position of the pyridine nucleus. Subsequent aromatization gave the 4-substituted products. Asymmetric reduction has also been demonstrated with
chiral oxazolines. In our hands, dibenzooxazoline underwent addition of ethylmagnesium bromide at 0°C to give, after hydrolysis, the dihydro intermediate, which was readily oxidized to under standard work up conditions or by chloranil oxidation. The spectrum of exhibited a singlet at δ 1.40 for the gem-dimethyl group and a quartet at δ 2.77 for the methylene of the newly incorporated ethyl group. The indicated directivity (route ii) of the oxazoline group is inferred since the unsubstituted dibenzo crown analog (27) of 22 does not undergo 4-substitution under similar reaction conditions. Under more drastic conditions, 19a, 19b, and 22 with excess n-BuLi, gave ring-fragmented products, whereas with one equiv. of n-BuLi, starting materials were obtained.
Under low temperature reductive conditions:

$Na_2S_2O_6$, $LiAlH_4$ or $NaBH_4$, macrocycles 19a and 19b were recovered in toto. However, 22 with $LiAlH_4$ in THF at 25°C afforded cleavage of the macrocycle and recovery of an equal ratio of pentaethylene glycol and 13. Such a fragmentation probably results from hydride attack at the pyridine $\alpha$-methylene and loss of phenoxide ion. Macrocycle 19a smoothly complexes $KBH_4$, as implied by
the upfield shift (Δδ 0.9) of the 4-pyridine-H and the
downfield shift of the α-methylene groups. This
complex appears to be quite stable under normal
conditions but treatment with silver acetate
quantitatively regenerates ligand 19a. Such
complexation is comparable to known cavity chemistry of
cryptands and crown ethers.

The preliminary chemistry presented herein of these
macromolecules with different loci for metal ion
coordination suggests that the site(s) or mode(s) of
complexation will result through a selective reaction
pathway. The non-coplanarity of the oxazoline moiety
with the pyridine nucleus caused by the juxtaposition of
the bridge connection may diminish an ionic mechanistic
course in favor of a radical anion process. Further
studies are in progress to afford more insight into the
effect and locus preference in transition metal ion
complexation.

EXPERIMENTAL SECTION

General Comments. All melting points were taken in
capillary tubes with a Thomas-Hoover Uni-Melt apparatus
and are uncorrected. ¹H and ¹³C NMR spectra were
determined on an IBM-Bruker NR-80 NMR spectrometer using
CDCl₃, as solvent, except where noted, with Me₄Si, as
the internal standard. IR spectra were recorded on a
Perkin Elmer 621 grating-infrared spectrophotometer.
Mass spectral (MS) data (70eV) [reported herein (assignment, relative intensity)] were determined by Mr. D. Patterson on a Hewlett-Packard HP 5985 GC/mass spectrometer. Reported Rf values were ascertained by a standardized thin-layer chromatographic (TLC) procedure: Baker-flexR silica gel IB2-F plates eluting with the stipulated solvent system. For preparative thick-layer chromatography (ThLC), 2-mm silica gel PF-254-366 plates were used. Elemental analyses were performed by Mr. R. Seab in these laboratories.

Ethyl 2,6-dimethyl-4-chloronicotinate (8) was prepared (69%) via the procedure of Bachmann and Barker62, by the reaction of ethyl β-aminocrotonate63 and POC\textsubscript{3}: bp 92-94°C (0.5mm) [lit.62 bp 97-105°C (2mm)]; \textsuperscript{1}H NMR \( \delta \) 1.40 (t, CH\textsubscript{2}CH\textsubscript{3}, J=7.3Hz, 3H), 2.52 2.53 (2s, py Me, 6H), 4.44 (q, CH\textsubscript{2}CH\textsubscript{3}, J=7.3Hz, 2H), 7.28 (s, 5-pyH, 1H); IR (neat) 1730 (C=O), 855 (C-Cl) cm\(^{-1}\); MS m/e 215 [M\textsuperscript{+}(37Cl), 11], 213 [M\textsuperscript{+}(35Cl), 39], 168 (M\textsuperscript{+}-OEt, 100); Anal. Calcd. for C\textsubscript{10}H\textsubscript{12}ClNO\textsubscript{2}: C, 56.26; H, 5.68; N, 13.12. Found: C, 56.35; H, 5.83; N, 13.01.

Ethyl 2,6-dimethylnicotinate (6b). To a stirred suspension of ethyl 2,6-dimethyl-4-chloronicotinate (29g, 139mmol), triethylamine (46.8g, 450mmol), and palladium on charcoal (10%; 4g), was added formic acid (88%; 21g, 400mmol) dropwise while maintaining the
solution below 85°C. The mixture was then refluxed at 95°C; the time (ca. 6 days) was determined by monitoring (TLC) the loss of the starting ester \([R_f 0.83 \text{ (CH}_2\text{Cl}_2)\]). The cooled mixture was dissolved in \text{CH}_2\text{Cl}_2, filtered, washed with \text{H}_2\text{O}, and distilled \textit{in vacuo} to give the desired ester, 6b, as a colorless oil: 23.2g (95%); bp 74-75°C (0.5mm) \[\text{lit. 62 111-120}°\text{C (7mm)}\]; \(R_f=0.76\) (SiO\(_2\), \text{CH}_2\text{Cl}_2); \(^1\text{H NMR} \delta 1.39 \text{ (t, CH}_2\text{CH}_3, J=7.3Hz, 3H), 2.56 \text{ (s, 6-pyMe, 3H), 2.81 \text{ (s, 2-pyMe, 3H), 4.37 \text{ (q, CH}_2\text{CH}_3, J=7.3Hz, 2H), 7.05 \text{ (d, 5-pyH, J=7.9Hz, 1H), 8.09 \text{ (d, 4-pyH, J=7.9Hz, 1H); IR (neat) 1715 (C=O cm}^{-1}; \text{MS m/e 179 (M}^+, 44), 134 (\text{M}^+-\text{OEt, 100}); \text{Anal. Calcd. for C}_{10}\text{H}_{13}\text{NO}_2: C, 70.59; H, 7.84; N, 13.74. Found: C, 70.32; H, 7.66; N, 13.81.

A second product was isolated from the residue and shown to be the 4,4'-coupled product 9, as a white solid: 600 mg (3.5%); mp 168°C \[\text{CHCl}_3-\text{Et}_2\text{O}\]; \(^1\text{H NMR} \delta 1.33 \text{ (t, CH}_2\text{CH}_3, J=7.5Hz, 3H), 2.34 \text{ (s, 6-pyMe, 3H), 2.49 \text{ (s, 2-pyMe, 3H), 4.29 \text{ (q, CH}_2\text{CH}_3, J=7.5Hz, 2H), 6.33 \text{ (bs, 5-pyH, 1H); IR (KBr) 1705 (C=O cm}^{-1}; \text{MS m/e 195 (48), 149 (100); \text{Anal. Calcd. for C}_{20}\text{H}_{24}\text{N}_2\text{O}_4: C, 67.40; H, 6.79; N, 7.86. Found: C, 67.64; H, 6.61; N, 7.95.}

\text{Polyethereal bis-enamine Ila \[\sim 100\%; \text{\textit{1H NMR} \delta 1.20 \text{ (t, CH}_3, J=7.2Hz, 6H), 3.6 \text{ (m, OCH}_2\text{CH}_2, 16H), 4.03 \text{ (s, COCH}_2\text{O, J=7.4Hz, 4H), 4.06 \text{ (q, CH}_2\text{CH}_3, J=7.2Hz,}...}}]
2H), 4.44 (s, CH₂, 2H), 6.5 (bs, NH₂, 2H]) was prepared from the bis-ester 10a by reaction with anhydrous NH₃ in CH₂Cl₂. Upon evaporation, 11a was found to be a hygroscopic oil: ~100%; ¹H NMR δ 1.28 (t, OCH₂CH₃, J=7.0Hz, 3H), 1.28 (t, CO₂CH₂CH₃, J=7.0Hz, 3H), 3.52 (s, COCH₂CO, 2H), 3.56 (q, COCH₂CH₃, J=7.0Hz, 2H), 4.10 (s, OCH₂C=O, 2H), 4.20 (q, CO₂CH₂CH₃, J=7.1Hz, 2H)], which was in turn synthesized from ethyl 4-bromo-3-oxobutanoate by the method of Kellogg et al. for the synthesis of the polyethereal bis-β-ketoester: ca 50% (from bromide); mp 109.5°C; ¹H NMR (DMSO-d₆) δ 1.17 (t, CO₂CH₂CH₃, J=7.0Hz, 3H), 3.48 (q, COCH₂CH₃, J=7.0Hz, 2H), 3.72 (s, COCH₂, 2H), 4.00 (q, CO₂CH₂, J=7.0Hz, 2H), 4.87 (s, CH, 1H). Ester 11b readily polymerizes upon standing or attempted purification.

2-[3'-(2',6'-dimethylpyridyl)]-5,5-dimethylloxadiazoline (13). A stirred mixture of 2-amino-2-methylpropan-1-ol (40g, 449mmol), ethyl 2,6-dimethylnicotinate (20g, 112mmol), and P₂O₅ (15g), in anhydrous xylene (100 mL) was refluxed under nitrogen for 30 hrs. The
solution was cooled and carefully neutralized with aqueous 10% NaOH solution. The organic layer was decanted and the aqueous layer was extracted several times with CH₂Cl₂; then the combined organic extract was dried over anhydrous MgSO₄ and evaporated *in vacuo* to give a black viscous residue, which was distilled to afford oxazoline 13, as a colorless oil: 10.5 g (50%); bp 104°C (0.5mm); ¹H NMR δ 1.38 (s, diMe, 6H), 2.54 (s, 6-pyMe, 3H), 2.78 (s, 2-pyMe, 3H), 4.07 (s, 4-CH₂, 2H), 7.00 (d, 5-pyH, J=8.0Hz, 1H), 7.93 (d, 4-pyH, J=8.0Hz, 1H); IR (neat) 1635 (C=N), 1585, 1035 cm⁻¹; MS m/e 204 (M⁺, 100), 189 (M⁺-Me, 66), 161 (29), 149 (43), 134 (35), 133 (47); Anal. Calcd. for C₁₂H₁₆N₂O: C, 70.59; H, 7.84; N, 13.74. Found: C, 70.32; H, 7.66; N, 13.81.

The intermediate amide 14 can also be isolated under non-dehydrative conditions (no P₂O₅): mp 154-156°C; 21.5g (93%); ¹H NMR δ 1.41 (s, diMe, 6H), 2.53 (s, 6-pyMe, 3H), 2.62 (s, 2-pyMe, 3H), 3.67 (s, CH₂, 2H), 6.00 (s, OH, 1H), 6.98 (d, 5-pyH, J=7.8Hz, 1H), 7.53 (d, 4-pyH, J=7.8Hz, 1H); IR (KBr) 3200 (b, OH), 1660 (C=O), 1555, 1460, 1110, 1065 cm⁻¹; MS m/e 222 (M⁺, 0.1), 191 (M⁺-OCH₃, 9.7), 134 (100), 106 (21); Anal. Calcd. for C₁₂H₁₈N₂O₂: C, 64.86; H, 8.11; N, 12.61. Found: C, 64.69; H, 7.99; N, 12.69.

**Bromination of Oxazoline 13.** A stirred solution of oxazoline 13 (6g, 34mmol) and N-bromosuccinimide
(NBS; 17g, 98 mmol) in CH$_2$Cl$_2$ (400mL) was irradiated with a 150 watt light for 24 hours. The mixture was neutralized, then washed with 10% aqueous Na$_2$CO$_3$ (300mL). The organic layer was dried over anhydrous MgSO$_4$, filtered, and concentrated in vacuo to give a residue, which was chromatographed (column; SiO$_2$) eluting with CH$_2$Cl$_2$ to afford two main fractions:

**Fraction A** gave the desired symmetrical dibromide 15, as a colorless oil, which decomposes on standing to a glassy polymer: 2.94g (24%); $R_f$=0.23 (CH$_2$Cl$_2$); $^1$H NMR $\delta$ 1.35 (s, diMe, 6H), 4.06 (s, 4-CH$_2$, 2H), 4.48 (s, 6-pyCH$_2$, 2H), 5.08 (s, 2-pyCH$_2$, 2H), 7.37 (d, 5-pyH, J=7.8Hz, 1H), 8.09 (d, 4-pyH, J=7.8Hz, 1H); IR (KBr) 1715 (C=N), 1640, 1035 cm$^{-1}$; MS m/e 364 [M$^+$ (2$^8$Br), 55], 362 (M$^+$, 100), 360 [M$^+$ (2$^7$Br), 58]; Anal. Calcd. for C$_{12}$H$_{11}$N$_2$OBr$_2$: C, 39.78; H, 3.90; N, 7.73. Found: C, 39.51; H, 3.72; N, 7.59.

**Fraction B** gave the monobromide 16, as a crystalline solid: 3.82g (40%); bp 69°C; $R_f$ 0.10 (CH$_2$Cl$_2$); $^1$H NMR $\delta$ 1.41 (s, diMe, 6H), 2.57 (s, 6-pyMe, 3H), 4.11 (s, 4-CH$_2$, 2H), 5.12 (s, 2-pyCH$_2$, 2H), 7.12 (d, 5-pyH, J=8.2Hz, 1H), 8.02 (d, 4-pyH, J=8.2Hz, 1H); IR (Neat) 1700 (C=N), 1625, 1290, 1030 cm$^{-1}$; MS m/e 284 [M$^+$ (8$^1$Br), 63], 282 [M$^+$ (7$^9$Br), 71], 173 (81), 131 (100); Anal. Calcd. for C$_{12}$H$_{15}$N$_2$OBr: C, 50.87; H, 5.35; N, 9.89. Found: C, 50.73; H, 5.26; N, 9.75.
A fraction (Rf 0.3) gave a mixture of the monobromide 18 [\textsuperscript{\textit{5}}% (\textsuperscript{\textit{1}}H NMR \(\delta\) 2.87 (s, 3H)] and the geminal dibromide 17 [\textsuperscript{\textit{7}}% (\textsuperscript{\textit{1}}H NMR \(\delta\) 6.63 (s, 1H)]; further purification was not conducted.

**General Procedure for Macrocycle Preparation.**

**Reaction of 15 with pentaethylene glycol.** To a stirred suspension of NaH (oil-free; 150mg, 6.0mmol) in dry DME (450mL) at 60°C, pentaethylene glycol (710mg, 3mmol) was added, followed in 30 min. by 15 (985mg, 2.72mmol). The mixture was maintained for 2 hr, then cooled and carefully neutralized with aqueous (15\%) NH\textsubscript{4}Cl solution (10mL). The organic layer was separated and was made basic with 10\% aqueous Na\textsubscript{2}CO\textsubscript{3} (20mL) and extracted with CH\textsubscript{2}Cl\textsubscript{2}. The combined organic extract was concentrated in vacuo then chromatographed (ThLC, Al\textsubscript{2}O\textsubscript{3}) eluting with 5\% i-proH-CH\textsubscript{2}Cl\textsubscript{2} to give the desired macrocycle 19a, as a pale yellow oil: 560 mg (45\%); R\textsubscript{f}=0.28; \textsuperscript{\textit{1}}H NMR \(\delta\) 1.37 (s, diMe, 6H), 3.7 (m, \(\beta,\beta',\xi-\text{CH}_2\)), 4.08 (s, 4-CH\textsubscript{2}, 2H), 4.81 (s, \(\alpha'-\text{CH}_2\)), 5.05 (s, \(\alpha-\text{CH}_2\)), 7.39 (d, 5-pyH, J=7.8Hz, 1H), 8.10 (d, 4-pyH, J=7.8Hz, 1H); IR (neat) 1634 (C=N), 1581, 1425, 1340, 1290, 1100 cm\textsuperscript{-1}; MS m/e 438 (M\textsuperscript{+}, 11), 409 (31), 363 (22), 204 (100); Anal. Calcd. for C\textsubscript{22}H\textsubscript{34}N\textsubscript{2}O\textsubscript{7}: C, 60.24; H, 7.83; N, 6.39. Found: C, 60.11; H, 8.03; N, 6.25.

A second fraction afforded isomeric 2:2-macrocycles 20a, as an oil 587mg (48\%); R\textsubscript{f} 0.18; \textsuperscript{\textit{1}}H NMR \(\delta\) 1.39 (s,
diMe, 12H), -3.7 (m, β - β', ξ -CH₂, 40H), 4.10 (s, 4-CH₂, 4H), 4.73 (s, α'-CH₂, 4H), 4.97 (s, α -CH₂, 4H), 7.49 (d, 5-pyH, J=7.8Hz, 2H), 8.10 (d, 4-pyH, J=7.8Hz, 2H); IR (neat) identical to the 1:1-macrocycle; MS m/e 455 (13), 409 (20), 351 (35), 233 (73), 204 (100); Anal. Calcd. for C₄₄H₆₈N₂O₁₄: C, 60.24; H, 7.83; N, 6.39. Found: C, 60.31; H, 7.80; N, 6.36.

Reaction of 15 with hexaethylene glycol.

Macrocycles 19b and 20b. A mixture of 15 (1.43g, 3.95mmol), hexaethylene glycol (1.17g, 4.06mmol), and NaH (oil-free; 373mg, 8.7mmol) afforded, after standard workup, the 1:1-macrocycle 19b, as an oil: 879 mg (46%); Rf 0.30 (5% i-prOH-CH₂Cl₂); ¹H NMR δ 1.38 (s, diMe, 6H), 3.67 (m, β, β', ξ -CH₂, 2CH₂), 4.08 (s, 4-CH₂, 2H), 4.77 (s, α'-CH₂, 2H), 5.03 (s, α -CH₂, 2H), 7.42 (d, 5-pyH, J=7.8Hz, 1H), 8.10 (d, 4-pyH, J=7.8Hz, 1H); IR (neat) 1690 (C=N), 1585, 1455, 1342, 1102 cm⁻¹; MS m/e 482 (M⁺, 11), 395 (36), 233 (74), 219 (100), 204 (84); Anal. Calcd. for C₂₄H₃₈N₂O₈: C, 59.75; H, 7.95; N, 5.80. Found: C, 59.75; H, 8.11; N, 5.73.

The 2:2-macrocycle 20b was also isolated: oil; 823mg (43%); Rf 0.20; ¹H NMR δ 1.39 (s, diMe, 12H), -3.7 (m, β, β', ξ -CH₂, 48H), 4.10 (s, 4-CH₂, 4H), 4.73 (s, α'-CH₂, 4H), 4.98 (s, α -CH₂, 4H), 7.50 (d, 5-pyH, J=7.8Hz, 2H), 8.02 (d, 4-pyH, J=7.8Hz, 2H); IR (neat) identical to 1:1; MS m/e 499 (13), 219 (68), 204 (48),
Reaction of oxazoline 15 with the dibenzotetra-ethylene Glycol. A stirred mixture of dibromide 15 (500mg, 1.38mmol), benzoether 21 (400mg, 1.38mmol), and Cs₂CO₃ (992mg, 2.76mmol) in anhydrous DMF (200mL) was heated at 60°C for 14 hrs. The solution was cooled then concentrated in vacuo to give a white solid, which was in part dissolved in CH₂Cl₂ after filtration, the macrocycle, precipitated by trituration with MeOH, was recrystallized from EtOH-H₂O to give the desired 1:1-22, as a white powder: mp 149-150°C; 310mg (47%); 

³H NMR δ 1.38 (s, dMe, 6H), 3.83 (m, γ, γ'-CH₂, 4H), 4.08 (s, 4-CH₂, 2H), 4.14 (t, β'-CH₂, J=5.8Hz, 2H), 4.28 (t, β'-CH₂, J=5.8Hz, 2H) 5.31 (s, α'-CH₂, 2H), 5.63 (s, α'-CH₂, 2H), 6.9 (m, phH, 8H), 7.58 (d, 5-phH, J=7.8Hz, 1H), 8.19 (d, 4-pyH, J=7.8Hz, 1H); IR (KBr) 1645 (C=N), 1600, 1500, 1255, 1210, 1130 cm⁻¹; MS m/e 490 (M⁺, 28), 202 (100), 201 (77); Anal. Calcd. for C₃₈H₇₆N₄O₁₆: C, 68.54; H, 6.12; N, 5.71. Found: C, 68.60; H, 6.22; N, 5.74.

Bromination of ethyl 2,6-dimethylnicotinate. A stirred benzene solution (100mL) of ethyl 2,6-dimethylnicotinate (3.85g, 21.5mmol) was warmed to 70°C, then NBS (9.5g, 53mmol) and AIBN (50mg) were added in small
increments. The mixture was refluxed with illumination for 16 hrs. The resultant solution was cooled, washed with 10% aqueous Na₂CO₃, dried over anhydrous MgSO₄, and concentrated in vacuo to give a red oil, which was dissolved in a minimum volume of ether and allowed to stand at -10°C for several hours until the desired bis-bromemethyl ester 23 precipitated, as colorless crystals: 1.76g (25%); mp 51-52°C (ether); ¹H NMR δ 1.43 (t, CH₂CH₃, J=7.3Hz, 3H), 4.44 (q, CH₂CH₃, J=7.3Hz, 2H), 4.55 (s, α'-CH₂Br, 2H), 5.00 (s, α-CH₂Br, 2H), 7.49 (d, 5-pyH, J=8.5Hz, 1H), 6.28 (d, 4-pyH, J=8.5Hz, 1H); IR (KBr) 1720 (C=O), 1115 cm⁻¹; MS m/e 258 (93) 256 (M⁺⁻Br, 100); Anal. Calcd. for C₁₀H₁₁Br₂N₂O₂: C, 35.63; H, 3.29; N, 4.16. Found: C, 35.93; H, 3.53; N, 3.98.

Reaction of 23 with dibenzotetraethylene glycol

The reaction of 23 (624mg, 2.0mmol), dibenzopolyether 21 (540mg, 2.0mmol), and Cs₂CO₃ (1.24g, 4.0mmol) in anhydrous DMF (300mL) was conducted and worked up as described for 22 to give macrocycle 24, as colorless needles: 689 mg (76%); mp 124-125°C (EtOH-H₂O); ¹H NMR δ 1.40 (t, CH₂CH₃, J=7.3Hz, 3H), 3.85 (m, CH₂, 4H), 4.15 (t, γ-CH₂, J=5.2Hz, 2H), 4.31 (t, β-CH₂, J=4.7Hz, 2H), 4.39 (q, CH₂CH₃, J=7.3Hz, 2H), 5.38 (s, α'-CH₂, 2H), 5.60 (s, α-CH₂, 2H), 7.0 (m, phH, 8H), 7.65 (d, 5-pyH, J=8.2Hz, 1H), 8.32 (d, 4-pyH, J=8.2Hz, 1H); IR
(KBr) 1705 (C=O), 1585, 1495, 1245, 1200, 740 cm\(^{-1}\); MS m/e 465 (M\(^+\), 64), 121 (100); Anal. Calcd. for C\(_{26}\)H\(_{27}\)O\(_7\)N: C, 67.07; H, 5.86; N, 3.01. Found: C, 66.97; H, 6.08; N, 2.86.

**Reactions of 22 with ethylmagnesium bromide.** To a stirred solution of 22 (20mg, 0.04mmol) in anhydrous diethylether (5mL) at -70°C, ethylmagnesium bromide (400\(\mu\)L; 3M in ether, 1.2mmol) was slowly added under a nitrogen atmosphere. After 1 hr, the mixture was warmed to 25°C and poured into a saturated NH\(_4\)Cl solution. The ether was removed in vacuo and the residual aqueous phase was extracted with CH\(_2\)Cl\(_2\) (2 x 5mL). The combined extract was dried and concentrated in vacuo to give a mixture of 25 and 26 (ca. 1:1) \(^1\text{H NMR} \delta 5.16 (\alpha-\text{CH}_2)\) and 4.57 (\(\alpha'-\text{CH}_2\)), which was oxidized with chloranil (20mg) in toluene (10mL) for 2 hrs at 25°C. The toluene solution was extracted with aqueous (10%) NaOH, then dried over anhydrous MgSO\(_4\) and concentrate in vacuo. The residue was chromatographed (ThLC) eluting with CH\(_2\)Cl\(_2\)-MeOH (5%) to give 26, as solid: mp 42-44°C; R\(_f\) 0.45; 15mg (85%); \(^1\text{H NMR} \delta 1.26 (t, \text{CH}_2\text{CH}_3, J=7.4\text{Hz}, 3\text{H}), 1.40 (s, \text{diMe}, 6\text{H}), 2.77 (q, \text{CH}_2\text{CH}_3, J=7.4\text{Hz}, 2\text{H}), 3.6 (m, \beta', \gamma'-\text{CH}_2, 4\text{H}), 4.10 (s, 4-\text{CH}_2, 2\text{H}), 4.1 (m, \beta, \gamma'-\text{CH}_2, 4\text{H}), 6.9 (m, \text{phH}, 8\text{H}), 7.40 (s, 5-pyH, 1\text{H}); MS m/e 5.8 (M\(^+\), 2.1), 149 (100).

**General procedure for reaction of n-butyllithium**
with macrocycle 19a, 20a, and 22. To a stirred 0.1 molar THF solution of the macrocycle (0.05mmol) at -70°C, n-BuLi (0.25mmol) was added. In each case the reaction mixture became dark brown and upon standard work up as above the starting macrocycle and macrocyclic products were not detected.

**Reaction of macrocycles 27, 19a, and 20a with ethylmagnesium bromide.** The macrocycle (0.04mmol) in diethyl ether was stirred at -70°C then ethylmagnesium bromide (0.4mL, 3M ether, 1.2mmol) was added and stirred an additional 1 hr after which it was allowed to warm to 25°C. The reaction was worked as described above, with 27 only unchanged starting macrocycle 27 was (100%) recovered. Either macrocycle 10a or 20b (0.23mmol) in THF (5mL) treated similarly with excess ethylmagnesium bromide gave a yellowish precipitate. After standard work up each reaction also gave unchanged (100%) starting macrocycle.

**Reaction of 19a with potassium borohydride.** An anhydrous ethanol solution of 19a (40mg, 0.9mmol) and KBH₄ (100mg, 1.9mmol) was refluxed for 12 hrs under nitrogen. The solution was evaporated in vacuo to give a residue which was extracted with CHCl₃ to give, after concentration, a solid that was nearly identical to the starting material [¹H NMR δ 1.38 (s, diMe, 6H), 3.7 (m, OCH₂, 2H), 4.08 (s, 4-CH₂, 2H), 4.82 (s, α'-CH₂, 2H),...
5.12 (s, $\alpha$-CH$_2$, 2H), 7.30 (d, 4-pyH, $J=7.9$Hz, 1H), 8.12 (d, 5-pyH, $J=7.9$Hz, 1H). Treatment of the complex in acetonitrile with silver acetate (25mg) gave an immediate gray suspension. Filtration, evaporation, and dissolution of the residue in CH$_2$Cl$_2$ afforded a solution which was washed with water, dried, and concentrated to give (100%) 19a.

**Reaction of 22 with LiAlH$_4$.** Macrocycle 22 (40mg, 0.08mmol) in (5mL) was added to a stirred THF suspension of LiAlH$_4$ (38mg, 1mmol) then stirred at 25°C for 6 hrs. Upon standard work up, starting macrocycle (85%), oxazoline 13 (~15%), and glycol 21 (~15%) were isolated.

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For references herein: see General References
During the course of the research presented in the previous pages, some experimental details not within the scope of that particular publication had to be omitted. Some noteworthy details follow:

$^1$H NMR Investigation of Product Development in the Free Radical Bromination of 2-[[3'-{(2',6'-Dimethyl- pyridyl)}]-5,5-dimethyl-oxazoline 13.

The preparation of 15, because of the competing processes of geminal bromination and quaternary decomposition, required that 15 be formed in the highest yield possible. Therefore, optimization of the reaction conditions was of key interest. Under conditions prescribed by Vögtle $^{69}$ for the symmetrical bis-dibromination of 2,6-lutidine (20%) [NBS (1.2 eq) and AIBN (~50 mg), in refluxing benzene (100 mL) and irradiation (200 W incandescent) for 12 hrs.]; bromination of 13 lead to an abundance of the mono-bromination products 16 and 18 in 30 and 5% ($^1$H NMR) yields, respectively. The gem-dibromination product 17 was formed in 15% ($^1$H NMR), and the desired bis-dibromide 15 was observed in less than 10% ($^1$H NMR). A high degree of decomposition was also observed, due to the previously mentioned facile quaternization process which was accelerated by the relatively high temperature employed (benzene reflux). Subsequent work
by Vögtle shows a distinct relationship between solvent dipole moment, refractive index and product selectivity in NBS reactions on heteroaromatic systems. Vögtle found the most promising solvents for such selective NBS brominations to be those which have the combined properties of low refractive index and low boiling point. Unlike benzene \( n_D^{20}[\text{C}_6\text{H}_6] = 1.5011, \text{bp} = 80^\circ\text{C} \), \( \text{CH}_2\text{Cl}_2 \) effectively combines these two properties \( n_D^{20}[\text{CH}_2\text{Cl}_2] = 1.4242, \text{bp} = 39.8-40^\circ\text{C} \), hence, the solvent system chosen for the bromination of 13 was \( \text{CH}_2\text{Cl}_2 \). The employment of \( \text{CH}_2\text{Cl}_2 \) also presented other advantages over benzene in that the solubility of NBS as well as the products was somewhat improved.

The bromination of 13 in \( \text{CH}_2\text{Cl}_2 \) was monitored every 4 hrs. by removal of small (1ml) aliquots of reaction mixture, which were subjected to standard workup and analyzed by \(^1\text{H} \text{NMR} \). The reaction was performed as previously described; oxazoline 13 (34mmol), and NBS (98mmol), in \( \text{CH}_2\text{Cl}_2 \) (400 mL) were irradiation with 150 watt light for 24 hrs. The results are summarized in the following graph.
Bis-bromide 15 was monitored ($^1$H NMR) by the 5-pyridine proton resonance at $\delta$7.37; whereas the mono-bromide 16 was traced via its pyridyl methyl at $\delta$2.57, mono-bromide 18 by its methyl resonance at $\delta$2.87, and gem-bromide 17 by the methyne resonance at $\delta$6.63. From the appearance and disappearance of these resonances, a rationale can be given for product formation during the course of the reaction.

Starting oxazoline 13 is consumed quickly and converted almost entirely to mono-bromide 16 which in turn is converted to the desired bis-dibromide 15 or, to a lesser extent, the gem-dibromide 17. It also appears that the mono-bromide 18 is converted, to a
great extent, to the \textit{bis}-dibromide 15. At approximately 24 hours there is a maxima in the curve for \textit{bis}-bromide 15. Hence, reactions were allowed to run 24 hr under the prescribed conditions in order to obtain maximum yields of 15.
Chapter 2

NICOTINIC ACID LARIAT ETHERS: SYNTHESES, COMPLEXATION, REDUCTION, AND NADH MODEL REACTION

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NICOTINIC ACID LARIAT ETHERS: SYNTHESSES, COMPLEXATION, REDUCTION, AND NADH MODEL REACTION

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ABSTRACT

Chiral 6-methylnicotinic oxazoline (13), was converted to the 18-crown-6 and 15-crown-5 lariat ethers 22 and 24, via combination of 6-hydroxymethylnicotinic oxazoline (16) with monoaza lariat ethers 20 and 23, respectively. Chiral lariat ether 24b was converted to the corresponding enantiomerically enriched N-magnesio-1,4-dihydropyridine 26, by stereoselective metal directed addition of methylmagnesium bromide. N-Magnesio lariat 26 reduced \( \alpha, \alpha, \alpha \)-trifluoroacetophenone in an NADH model-like reduction to give the S-alcohol 32a in an enantiomeric excess of only 5%; whereas, the non-lariat analog 31 gave the S-32a enantiomer in 10.4% excess.
Metal ion participation in the stereospecific NADH mediated hydride reductions of carbonyl substrates in vivo has been well established. Likewise, by incorporation of various metal ions into "chiral models", dramatic enhancements in the stereospecificity of carbonyl reductions have been observed. A rationale for the improved selectivity of hydride reduction by chiral NADH models in the presence of magnesium ion has been forwarded by Ohno et al., in that he proposed the possible involvement of a three-step mechanism: (1) initial electron transfer; (2) proton transfer, and (3) electron transfer. This overall process can be mediated by a metal ion in an intermediate ternary sandwich-type tetradeutate charge transfer complex, as shown in structure 1. Recently, such a ternary complex was spectroscopically (UV) characterized by Fukuzumi et al. by monitoring of the reductions of p-benzoquinone derivatives with a NADH model. Fukuzumi reported a blue shift in the charge transfer band of +0.22 eV upon addition of Mg$^{2+}$, while Na$^+$ had no apparent effect. The existence of the ternary complex involving magnesium was further supported by a +0.2V shift in the oxidative peak potential by cyclic voltametry; whereas, there was no
By using models having a chiral center at the dihydropyridine 4-position and a carboxamide moiety, benzoylformates were reduced in optical yields greater than 95% in either enantiomer depending on the stereochemistry (1)\textsuperscript{72a} at the model's 4-position. The data gathered in that study strongly support Ohno's proposed mechanism, involving initial electron transfer, followed by generation of an electronically and sterically favorable configuration in which the substrate carbonyl-oxygen points toward the ring-nitrogen with the most electronegative substituent in the ketone facing the carboxamide group, prior to the slow proton transfer step. Therefore, the stereochemical integrity of the reduction is controlled by the thermodynamic stability of the intermediary charge transfer complex.

Several examples of N-metallo-1,4-dihydropyridines
capable of transferring hydride to suitable electrophilic centers, such as carbonyl compounds, have been reported.\textsuperscript{43} Like classical "model reactions" (e.g. with N-alkyl-1,4-dihydropyridines), reductions by N-metallo-1,4-dihydropyridine derivatives can be envisioned to occur \textit{via} an analogous type mechanism in which the metal mediates the approach and juxtaposition of the carbonyl substrate prior to hydride transfer. Thus, the degree of stereoselectivity depends upon the thermodynamic stability of the N-metallo-dihydropyridine ketone coordination complex 2.

The proposed mechanism involving complex 2 can be envisioned as a vinylogous analog of the cyclic hydride transfer proposed for the Meerwein-Ponndorf-Verley reduction (i),\textsuperscript{48} the reduction of ketones by Grignard reagents with \(\beta\)-hydrogens (ii),\textsuperscript{46} and the addition of Grignard reagents to ketones (iii)\textsuperscript{47}. 
Since the reaction of ketones with organometallics is an exothermic process, the stereochemical outcome of the reduction in 2 is most likely "steric approach" controlled, and should be predictable, if the model is asymmetric, by evoking Cram's rule. However, the findings of Ohno suggest the possibility of "anti-Cram" reduction in the case where the ketones most electronegative group happens to be the bulkiest group. Such "anti-Cram" behavior can be rationalized by the Karabutsos modification of Cram's rule which takes into account conformational restrictions due to metal coordination (i.e. coordinative bridging of the model's amide to the ketone's most electronegative group through a metal ion). In substrate reductions by $\text{N-metallo-1,4-dihydropyridines}$, such coordination-control of stereoselectivity should be most predominant if a "single electron transfer" (SET) mechanism is operative, as in the three-step process proposed for $\text{N-alkyl model reactions}$. Such a SET mechanism has been reported for the 8-center reductions of aryl ketones by unsubstituted
N-amino-1,4-dihydro pyridines.

With a transition state model 2 as a guide, we designed NADH mimics which incorporate a crown ether to stabilize the intermediary N-metallated species as well as catalyze preferential 1,4 over 1,2 reductive addition of metal hydrides or organometallics to the pyridine precursors. Further modification of these general models by introduction of chiral centers at the dihydropyridine 4-position and/or carboxamide moiety should produce a fascinating new series of stereoselective NADH mimics.

Earlier, Newkome, et al. described the syntheses and reactions of 2,6-bridged nicotinic acid crown ethers, incorporating either ether (3), or methylene linkages (4).

\[
\begin{align*}
\text{a (R=CO}_2\text{H)} \\
\text{b (R=CONMe}_2) \\
\text{c (R=CO}_2\text{Me)} \\
\text{d (R=CN)} \\
\end{align*}
\]

\[
\begin{align*}
\text{a (R=)} \\
\text{b (R=CO}_2\text{Et)} \\
\text{c (R=oxaz., dibenzo-fB-crown-6)} \\
\end{align*}
\]
Of these previously studied crowns, only the oxazolyl 3-pyridine macrocycle 4c smoothly underwent chemical reduction to generate products which support the desired N-metallo-dihydropyridine intermediate. Treatment of 4c with ethylmagnesium bromide, followed by hydrolysis, gave dihydropyridine 5, which readily oxidized to 6.

In contrast, under identical conditions the "more flexible" non-benzo crown ether derivatives afforded primarily starting macrocycle. It is conceivable that the primary difference in the reducability of the benzo and non-benzo crowns is due to steric interactions between the oxazoline and the bridging $\alpha$-methylene group, thus inhibiting coplanarity of the oxazoline and pyridine ring, so necessary for metal directed
Such a conformation is apparently more favored in the "rigid" dibenzo compound than in the "floppier" and larger macrocyclic ring systems of the non-dibenzo derivatives.\textsuperscript{76}

In order to continue our studies toward a more effective and representative "NADH model", a new series of "lariat ether" nicotinic acid macrocycles was prepared, bearing chiral oxazoline moieties and eliminating the steric congestion caused by the 2-substituent on the pyridine; thus circumventing the obvious detrimental interaction present in structure 7.

This preliminary study describes the synthesis of chiral lariat N-metallodihydronicotinic acid derivatives and the reduction of $\alpha, \alpha, \alpha$-trifluoroacetophenone by
this new sub-class of NADH model.

RESULTS AND DISCUSSION

1. Syntheses of chiral nicotino-"lariat ether" macrocycles. Two general procedures to these "lariat ethers" 8 were envisioned: (I) nucleophilic substitution of a N-2-ethanolmonoaza crown ether alkoxide on nicotinic acid derivatives possessing a good leaving 6-methyl group, and (II) the converse, a pyridine carbinol salt reacting with an azacrown ether possessing an appropriate leaving group.

Recent work, from the Meyers' group, shows the chiral nicotinic oxazolines (Scheme I) undergo regional facial selective ring addition by "metal direction" of selected alkyl and aryl Grignard and organolithium reagents. The "trapping" of the intermediate metallated adduct by methyl chloroformate, affords N-methoxy-carbonyl-4-alkyl(or aryl)dihydropyridine products in S/R
enantiomeric ratios, at the dihydropyridine 4 position, as high as 97:3!

Scheme I

Thus, the use of this chiral oxazoline directing group in our model would provide a convenient way to produce a chiral center in the dihydropyridine 4-position with a high degree of stereospecificity.

Utilization of the intermediary chiral metallated adduct (Scheme I) with only a single "transferable" hydrogen\textsuperscript{25,72a} may provide more detailed information about the credibility of the proposed transition state (array 2) [as in Ohno's model] which invokes a hydride source possessing a preferred face capable of approach by an electrophile. Thus, Meyers\textsuperscript{45g,h} chiral oxazoline 13 (Scheme II) was an excellent starting point for both proposed synthetic routes; however Meyers' procedure was modified in the oxidation of the 1,2-dihydropyridine 11 to alkylpyridine 12, in that KMnO\textsubscript{4} acetone rather than DDQ/toluene was more advantageous.
Attempted α-halogenation 13 via free radical procedures gave numerous products, including the worthless halooxazolines; therefore, functionalization of the 6-methyl substituent was accomplished via the traditional Boekelheide N-oxide rearrangement.77 Picoline 13 was selectively N-oxidized to pyridine N-oxide 14 with m-chloroperoxybenzoic acid78 in chloroform at 0°C. Formation of 14 was substantiated (1H NMR) by the 0.25 and 0.38 ppm upfield shift in the pyridine H-6 and H-4 signals, respectively, as well as the lesser (0.06 ppm) upfield shift of the 2-methyl singlet. N-Oxide 14 was treated with refluxing acetic anhydride to give (80%) the desired ester 15, which was spectroscopically characterized (1H NMR) by the singlets at δ 2.18 and δ 5.28 for the acetate methyl and α-methylene groups, respectively52a; however, 15 was not
isolated in an analytically pure form because of its tendency to decompose when subjected to chromatographic procedures. Ester 15 was rapidly transesterified in ethanol with anhydrous potassium carbonate to give (68.8% from 14) the target alcohol 16.

Alcohol 16 was characterized (1H NMR) by the disappearance of the acetate singlet at δ 2.18, an upfield (Δδ 0.47) shift of the α-methylene singlet to 4.81, and the appearance of a broad singlet at δ 3.9 for the hydroxyl proton. Attempts to generate the corresponding chloromethyl derivative by treatment of 16 with SOCl₂ gave a complex mixture of water soluble decomposition products. Subsequent to concentration of the halogenated "free base" under workup conditions, the resulting residue could not be redissolved in chloroform, and was presumed to be quaternary polymers. In an attempt to retard quaternization, mesylation of alcohol 16 was attempted. Spectral (1H NMR) data of freshly generated mesylate showed singlets at δ 3.0 and 5.1 possibly corresponding to mesyl-methyl and α-methylene groups, respectively; however, the mesylate likewise
rapidly decomposed to generate a chloroform-insoluble residue. Numerous modifications of these procedures failed to circumvent the problems. Hence, Route I to the desired lariat models was rejected.

The $\mathbf{N}$-2-ethanol azacrown ether derivatives 17 were obtained via three related procedures. First, treatment of the azacrown ethers with 2-bromoethanol (DMF/$\mathrm{K}_2\mathrm{CO}_3$) generated (ca 40-50%) the desired sidearm alcohols; however, subsequent chromatography (ThLC, column) proved difficult due to the highly polar character of the products as well as their poor visualization by UV detection. Second, an alternate approach was employed in an attempt to circumvent purification problems associated with the presence of the hydroxyl group. This method employed the tetrahydropyranyl ether (THP) of 2-bromoethanol (prepared by treatment of 2-bromoethanol with dihydropyran in the presence of a catalytic amount of p-toluenesulfonic acid). The THP protected $\mathbf{N}$-2-ethanol azacrown 18 was prepared (62.4%) in a similar fashion to that of 17. As predicted the incorporation of the tetrahydropyranyl moiety greatly enhanced the ease of purification by column chromatography ($\mathrm{Al}_2\mathrm{O}_3$/EtOAc/CHCl$_3$). The purified THP derivative 18 was deprotected upon treatment with HCl/MeOH, followed by neutralization and extraction ($\mathrm{CH}_2\mathrm{Cl}_2$) to generate (87%) the desired alcohol 17, which
required no further purification. Lastly, our preferred method entails a 3-step process involving nucleophilic substitution of diethanolamine on THF protected 2-bromoethanol to give (88%) 19. Cyclization of 19 was accomplished by treatment of the corresponding disodium alkoxide with an appropriate ditosylated polyethylene glycols at 25°C to give (>45%) the desired 1:1 macrocycles 18. As previously noted such cyclizations also afford the corresponding undesired 2:2 macrocycles, as well as oligomers, which were minimized in the workup by using an ether extraction.

The desired 1:1 isomers 18 were easily purified by chromatography (ThLC; Al₂O₃, 5% MeOH/CHCl₃). Their ^1H
NMR spectra display three distinct multiplets at δ 1.37-1.70, δ 3.4-3.9, and δ 4.58, which correspond to the pyranyl ring methylene protons, the remaining O-methylene protons, and the methyne proton, respectively. The integration ratios were indicative of the merging of 19 and the ditosylated glycols; this is supportive but not definitive proof of the assigned structure. Both crown derivatives 18 gave two well-defined triplets for the two non-equivalent N-methylenes at δ 2.80 (arm) and 2.84 (crown). Merger is further evidenced in that the mass spectral analyses of 18 display the "typical" N-methylazacrown ether cation (unambiguously identified by Mass Spectroscopy; 210°, EI, 70EV, 10KRP) as the most abundant fragment, however, neither show "parent ions".

The THP ethers 18 were smoothly deprotected by standard treatment with alcoholic HCl. The hydrophilic nature of ethers 17 is evidenced by reduced spectral resolution in their 1H NMR spectra in the presence of a trace of water; thus resolved spectra were only realized under strictly anhydrous conditions.
At the outset of this study, only the 12-crown-4 analog of 17 was known. Recently, however, two other methods for synthesis of 17 have been reported, in which the azacrown and either 2-chloroethanol or ethylene oxide were used. All physical data herein reported for 17 are in complete agreement with literature.

Alcohols 17 were transformed to 20 by refluxing in freshly purified SOCl₂. These N-2-chloroethyl derivatives 20 rapidly decomposed in solution within a few hours at 25°C or a few days at -15°C. Therefore, to circumvent the instability of amines 20, their stable hydrochloride salts 21 were generated and used without further purification.

Formation of the target lariat models 22 (a: 5%; b: 7%) was accomplished (Route II) through the combination of alcohol 16 and the N-2-chloroethyl azacrown ethers 21 (1.5 eq.) in THF at 55-60°C with NaH and N,N,N',N'-tetramethylethylenediamine (TMEDA) in two-fold excess.
The low yields of 22 are attributed to the diminished nucleophilicity of the alkoxide due, in part, to intramolecular chelative stabilization of the oxygen metallated species. This complexation can be partially retarded by the introduction of TMEDA as a competing ligand. Additionally, the competing self-quaternization of 20 generates quaternary decomposition products through facile inter- and intra-molecular processes. The lariat models 22 were characterized (\(^1\)H NMR) by the appearance of the multiplets at \(\delta\) 2.41-2.96 and 3.53-3.75 for the N- and O-methylene protons, respectively, as well as a 0.08 ppm upfield shift (4.73) of the singlet for the pyridine-\(\alpha\)-methylene and a 0.13 ppm downfield shift in the pyridine 3-proton signal.

Mass spectral analyses for 22 revealed no "parent ion"; however, the N-methylazacrown ether cation (v) was again the most abundant fragment in both cases. Further, the corresponding pyridine methoxy ether cation (vi) was visible (m/e 311: 22a 8.5%, 22b 9.0%) as well as a predominant fraction with a mass of 339 (22a 48.5%, 22b 49.5%), whose origin will be discussed later.
Repeated attempts at generating "models" 22 in higher yields were unsuccessful; thus, another method was envisioned for the construction of a related lariat, which utilized an amide linkage of the crown to the pyridine nucleus. This pivot would circumvent the Lewis Base character of these aza crowns and, therefore, retard the degradative quaternization. Synthesis of the chloro-acetamide crowns 23 (a: 92.5%, b: 89.9%) was achieved by treatment of the azacrown ether with chloroacetyl chloride in Na$_2$CO$_3$/acetone. In their $^1$H NMR, these amides display a broad multiplet (δ 3.50-3.75) for the Q-α-methylene protons ($^{23a}$: 24H, $^{23b}$ 20H) and a two-proton singlet (ca. δ 4.20) for the two α-chloromethylene protons.
The amide lariat ethers 24 were synthesized (24a: 84.5%; 24b: 79.8%) by treatment of a mixture of alcohol 16 and 23, with NaH and TMEDA in THF at 55-60°C for 1 hr. The $^1$H NMR spectra of 24 are nearly superimposable, except for the magnitude of the polyethylene bridge multiplet. In addition, new singlets at $\delta$ 4.39 and 4.80 correspond to the $\beta$ and $\alpha$ protons, respectively, and the doublet for the pyridine 3-proton is shifted downfield (0.09 ppm) from that of 19 to $\delta$ 7.63. Both amide derivatives exhibited "parent ions" in their mass spectrum [24a: m/e 601 (0.7); 24b: m/e 557 (0.6)] and the previously mentioned prominent fragment at m/e 339 was observed (24a: 100; 24b: 86), as in the case of 19. The fragment m/e 339 (viii) can be envisioned to arise from the 5-centered fragmentation process depicted in Scheme III,

**Scheme III**

![Diagram](image-url)
since, regardless of the identity of vii, fragment viii (m/e 339) is prevalent.

The magnesium bromide complex of 24 was generated by refluxing 24b and MgBr₂ in acetonitrile followed by concentration in vacuo. The ¹H NMR spectra of the magnesium-bromide "complex" of 24c displayed a dramatic downfield shift (Δ δ 0.50 and Δ δ 0.43) for the β and α protons, respectively, indicative of increased rigidity caused by the strong encapsulation of the magnesium ion. However, there are only slight up-(Δ δ 0.04) and down-(Δ δ 0.14) field shifts for the 4- and 3-pyridine protons, respectively, and essentially no shift in the pyridine 2-proton signal indicating that there is probably little participation by the pyridine nitrogen in CDCl₃. In addition, the chemical shift values of the oxazoline protons remains invariant suggesting that Mg²⁺ does not coordinate with this portion of the molecule in CDCl₃.

Similarly, treatment of 24b with KI gave 24c which exhibited a ¹H NMR spectra indistinguishable from that of 24b except for a slight broadening of the signals for
the crown methylenes and the oxazoline phenyl protons. These results indicate that the lariat moiety of 24b may have a weaker affinity for potassium than for magnesium; however, the oxazoline does show a preference for the alkali metal.

Amide 24b was converted (55%) to the stable dihydropyridine 29 with stereospecific\textsuperscript{45g,h} metal directed nucleophilic addition of methylmagnesium bromide (2 eq.) at 0°C in THF. Hence, 24b was employed in the preliminary reductive studies of carbonyls to evaluate these lariats as possible NADH models. Attempted reduction of the amide lariat 24b with LiAlH\textsubscript{4} afforded the amine derivative 22b in very low yield (ca. 5%).

2: Synthesis of chiral lariat

N-metallo-1,4-dihydropyridine derivatives and their reductions of \(\alpha,\alpha,\alpha\)-trifluoroacetophenone. Macrocycle 24 was reacted with 2 equivalents of methylmagnesium bromide at 0°C in THF (10\textsuperscript{-2}\text{M}) to generate a solution of metallated adduct 26, which was either hydrolyzed to 27, trapped with methyl chloroformate to give 29, or treated with \(\alpha,\alpha,\alpha\)-trifluoroacetophenone (TFA) to give 28 along with the TFA alcohol reduction product.
Hydrolysis of adduct 26 gave the dihydropyridine 27 (55%, \( ^1H \) NMR), which quickly air oxidized to the corresponding 4-methylpyridine 28. The \( ^1H \) NMR of the freshly prepared 27 exhibited a broad singlet at \( \delta 7.13 \) and a doublet at \( \delta 1.18 \) (J=6.4Hz) for the DHP-6-proton and DHP-4-methyl, respectively, as well as new singlets at \( \delta 3.99 \) and 4.22 for the lariat \( \beta \) and \( \alpha \) methylene, respectively. The 4-methylnicotinic oxazoline derivative 28, obtained from the air oxidation of 27, was characterized by the disappearance of the 4-pyridine proton observed in 24b (\( \delta 8.31 \)) and appearance of a singlet at \( \delta 2.65 \) for the 4-pyridine methyl.

The stable methyl chloroformate "trapped" dihydropyridine 29 was characterized (\( ^1H \) NMR) by: (1) a singlet at \( \delta 3.40 \) for the new urethane methyl protons;
(2) an upfield shift (Δ 0.27) of the oxazoline methoxy ether protons (3); new lariat bridge methylene signals at 4.19 and 3.89 for α and β protons respectively; and (4) a doublet at 1.36 corresponding to the dihydropyridine 4-methyl protons. HPLC (C6H12/EtOAc, SiO2) analysis of 29 gave two fractions [MS; m/e = 631 (M+; corresponding to the parent mass for 29)] in a ratio of 90:10, by integration of chromatographic peak areas. The fractions were identified as the two diastereomers of 29 (90% S, 10% R) based upon the earlier work of Meyers,45g,h dealing with the non-lariat oxazoline 30.

The reduction of TFA was initially conducted using the simple non-lariat N-metallo dihydropyridine 31, which was previously reported by Meyers.45g,h Stereoselective addition of methylmagnesium bromide (2 eq.) to the corresponding nicotinic oxazoline 30 gave 31 quantitatively (>91:9 S to R diastereomeric ratio with respect to the stereochemistry at the dihydropyridine 4-position, according to Meyers). TFA (2 eq) was allowed to react with 31 (6 hr; 55°C) yielding the alcohol 32a as a mixture of S and R enantiomers with an enantiomeric ratio of 54.5:45.5 ([α]D25 = +1.39, c = 1.80, benzene)76 which was in agreement with the enantioselective preference predicted by the ternary complex transition state array 34a.72 Further, the
4-methylnicotinic oxazoline 33 was generated in a nearly quantitative yield from 31 as was as the methyl adduct of TFA 32b.

Two equivalents of Grignard rather than 1 equivalent, as reported by Meyers, were utilized for comparison purposes since the lariat analogue requires at least 2 equivalents for sufficient conversion to the dihydroadduct 28. The resulting mixture was a 1:1 mixture of 31 and Grignard reagent. Hence, two equivalents of TFA were reacted with the above mixture to yield S and R 32a and the methyl adduct 32b in nearly
Under identical conditions, the reduction of TFA with 26 was conducted using the lariat ether $N$-metalldihydropyridine 26 (55% yield, diastereomeric ratio 90:10, HPLC $SiO_2$ EtOAc/$C_6H_{12}$, absolute configuration at py-4 assumed predominantly $S^{45f,h}$) to render the predicted $S$ enantiomeric preference in the TFA reduction product (32a) with an enantiomeric $S$ to $R$ ratio of 52.5:47.5 ($[\alpha]_{25}^{D} = +0.67$, $c = 1.54$, benzene, $\%ee = 5$). Under these conditions the lariat ether "model" 26 reduced TFA with an enantioselectivity somewhat less than that of the non-lariat version 31. The apparent lack of positive influence on the stereochemical outcome of the "model reduction" under these conditions, by the lariat ether appendage was unexpected and deserves further scrutiny.

It is conceivable that a strongly competing acyclic mechanism may be operative in the reduction of TFA by the
magnesio-adduct 26, as a result of an extremely strong crown ether complex which would diminish its coordinating ability towards the carbonyl oxygen of the substrate.

Work is underway to further refine these lariat model systems. By employment of various metal hydrides and organometallics in the formation of model N-metallo derivatives, as well as the introduction of chiral centers at strategic loci on the lariat ether appendage, we hope to obtain more information about their performance as enantioselective reducing agents.

EXPERIMENTAL

General Comments. All melting points were taken in capillary tubes with a Thomas-Hoover Uni-Melt apparatus and are uncorrected. $^1$H and $^{13}$C NMR spectra were determined on an IBM-Bruker NR-80 NMR Spectrometer using CDCl$_3$, as solvent, except where noted, with Me$_4$Si, as the internal standard. IR spectra were recorded on a Perkin-Elmer 621 grating-IR spectrometer. Mass spectral (MS) data (70ev) (herein noted as: assignment, relative intensity) were determined by Mr. D. Patterson on a Hewlett-Packard HP-5985 GC/mass spectrometer. High resolution mass spectral data (210°C, EI, 70 eV) were determined by the Mass Spectral Laboratory at Florida State University, Tallahassee, FL. CD/ORD measurements
were made on a Jasco model J-20 spectropolarimeter. Reported \( R_f \) values were ascertained by a standardized TLC procedure: Baker-Flex\(^\text{®}\) silica gel IB2-F plates eluting with the stipulated solvent system. For preparative thick-layer chromatography (ThLC), 2-mm silica gel PF-254-366 plates were used. Elemental analyses were performed by MicAnal Laboratories in Tucson, Arizona.

**Preparation of oxazoline 13.** Oxazoline 13 was prepared by a known 5-step route.\(^{45g,h}\)

**Step 1:** To a stirred solution of oxazoline alcohol (20.0g, 0.19mol) and anh. EtOH (13.3g, 0.28mol), in anh. \( \text{CH}_2\text{Cl}_2 \) (200mL) at 0°C, was passed a stream of anh. HCl for 1 hr. After standing 6 hr., anh. HCl was again passed through the solution for an additional 1 hr., followed in ~45 min by evaporation in vacuo below 30°C, to give. Hygroscopic white solid imidate 9, utilized directly in Step 2.

**Step 2:** A solution of imidate 9 (42.18g, 0.19mmol), \( \text{CH}_2\text{Cl}_2 \) (150mL), \( \text{Et}_3\text{N} \) (38.9g, 0.38mol), and (1S 2S)-(+-)2-amino-1-phenyl-1,3-propanediol\(^87\) (37.9g, 0.19mol) was stirred for 17 hr., then washed with aq. NaHCO\(_3\) (10%), dried over anh. MgSO\(_4\), filtered, and evaporated in vacuo to give a solid, which was
recrystallized (C₆H₁₂) to give oxazoline 10 (48%):
23.16g; mp 125°C [Lit. 45g mp 124-125°C (Et₂O)]; ¹H NMR δ 2.9 (bs, OH, 1H), 3.7-4.4 (m, CH₂O, 4-CH, 3H), 5.60 (d, 5-CH, J=7.7Hz, 1H), 7.35 (m, 5-pyH, phH, 6H), 8.22 (dt, 4-pyH, J₅,₄=8.1Hz, J₂,₄=1.8 Hz, 1H), 8.69 (dd, 6-pyH, J₅,₆=4.9Hz, J₄,₆=1.8Hz, 1H), 9.22 (dd, 2-pyH, J₄,₂=1.8Hz, J₅,₂=0.55Hz, 1H).

Step 3: To a stirred solution of oxazoline 10 (10g, 39.4mmol) in dimethoxyethane (400mL) at 0°C, was added MeLi (2 eq, 2.5 M/ether). The solution was stirred for 1 hr, then hydrolyzed (H₂O, 20 ml), and then the DME was evaporated in vacuo. The residue was dissolved in CH₂Cl₂, washed with eq. NaHCO₃ (10%), dried over anh. MgSO₄, filtered, and evaporated to give dihydropyridine 11, as a yellow oil (10.53g)

Step 4: The mixture of dihydropyridine 11 (8.00g, ~29.7mmol) was dissolved in acetone (100mL) to which saturated KMnO₄/acetone (~100mL) was added dropwise at 0°C. Progress of the oxidation was monitored by TLC until the starting dihydropyridines were no longer apparent (DHP, are highly fluorescent under UV light), after which the suspension was filtered, evaporated to give a residue [1,2- and 1,4-dihydropyridines ~80:20 ¹H NMR by methyl singlets at δ 2.59(2-py) and δ 2.55 (4-py)], which was recrystallized (C₆H₁₂) to give (61%) 12, as a solid: 6.43g; mp 116-117°C [Lit. 45g mp 117-118°C] ¹H NMR δ
2.59 (s, 2-pyCH₃, 3H), 3.2-3.5 (bs, OH, 1H) 3.4-3.6 (m, 4-CH, CH₂O, 3H), 5.59 (d, 5-CH, J=7.3Hz, 1H), 7.16 (d, 3-pyH, J=8.3Hz, 1H), 7.36 (s, phH, 5H), 8.08 (dd, 4-pyH, J₃,₄=8.3Hz, J₆,₄=2.0Hz, 1H), 9.10 (d, 6-pyH, J₆,₄=2.0Hz, 1H).

**Step 5:** To a stirred solution of oxazoline alcohol 12 (5.01g, 18.7mmol) in THF at 25°C, was added i-BuOK (2.51g, 22.4mmol) in one portion, followed by dropwise addition of MeI (2.92g mmol in 20mL THF). The solution was stirred an additional 6hr., then evaporated in vacuo, dissolved in CH₂Cl₂, washed with aq. NaHCO₃ (10%), dried over anh. MgSO₄, evaporated in vacuo, and chromatographed (column) to give (74%) 3, as an oil: 3.90g; R₉ 0.6 (CHCl₃); ¹H NMR δ 2.64 (s, 3-pyCH₃, 3H), 3.46 (s, OCH₃, 3H), 3.55-3.75 (m, CH₂OCH₃, 2H), 4.10-4.24 (m, 4-CH, 1H), 5.02 (d, 5-CH, J=7.2Hz, 1H), 7.22 (d, 3-pyH, J=8.1Hz, 1H), 7.34 (s, phH, 5H), 8.18 (dd, 4-pyH, J₃,₄=8.1Hz, J₆,₄=2.2Hz, 1H) [Lit. ¹H NMR δ 8.12 (4-pyH dd)], 9.12 (d, 3-pyH, J=2.2Hz, 1H); MS m/e 282 (M⁺, 4), 237 (M⁺-CH₂OCH₃), 119 (100).

Reaction of 2-methyl-5-oxazolinylpyridine 13 with N-bromosuccinimide (NBS), 2-Chloromethy-5-oxazolinylpyridine. A stirred solution of 13 (500mg, 1.8mmol) and NBS (624mg, 3.2mmol) in CH₂Cl₂ (200mL) was irradiated with an 150W light for 24hr. The mixture was neutralized by washing with 10% aq. Na₂CO₃ (100mL). The organic
layer was dried over anh. MgSO₄, filtered, and concentrated in vacuo to yield a residue (780mg), which was a complex mixture of bromination products, which was not further separated. ¹H NMR of this mixture exhibited no resonances for the 4 and 5-CH protons of the oxazoline, nor a resonance characteristic of pyCH₂Br. In addition, a prominent resonance corresponding to pyCH₃ (δ 2.65) remained.

Chiral 5-oxazolinylpyridine N-oxide (14). To a stirred solution of 2-methyl-5-oxazolinylpyridine 13 (3.5g, 12.4mmol) in CHCl₃ (75mL) at 0°C, was added MCPBA (80-85%, 3.2g, ~1.2 eq.) in small portions over 10 minutes. The solution was allowed to warm to 25°C and stirred for an additional 1.5 hr. The mixture was washed with 10% eq. NaHCO₃ (50mL), followed by H₂O, dried over anh. MgSO₄, filtered, and chromatographed (column, SiO₂) eluting with CH₂Cl₂/5% MeOH to give (94%) the N-oxide 14, as an oil: 3.48g, Rf 0.30; ¹H NMR δ 2.56 (s, 2-pyMe, 3H), 3.44 (s, OMe, 3H), 3.7 (m, CH₂OMe, 2H), 4.3 (m, 4-CH, 1H), 5.52 (d, 5-CH, J=7.1Hz, 1H), 7.35 (bs, phH, 5-pyH, 6H), 7.78 (dd, 4-pyH, J₄₃=8.1 Hz, J₆₄=1.5 Hz, 1H), 8.85 (d, 6-pyH, J=1.5 Hz, 1H); IR (neat) 3055, 2925, 1650, 1610, 1375, 1225 cm⁻¹; MS m/e 298 (M⁺, 10.4), 253 (M⁺-OMe, 23.7), 237 (31.0), 119 (100); Anal. Calc. for C₁₇H₁₈N₂O₃: C, 68.43; H, 6.09; N, 9.39. Found: C, 68.34; H, 6.07; N, 9.15.
Chiral 2-acetoxyethyl-5-oxazolinylpyridine (15).
N-Oxide 14 (3g, 10.1mmol) was dissolved in AcO₂ (25mL) at 0°C, then the solution was refluxed for 15 minutes, after which the AcO₂ was evaporated in vacuo. The dark brown residue was dissolved in CHCl₃ (50mL) and washed with aq. Na₂CO₃ (10%; 40mL). The organic layer was dried over anh. MgSO₄, evaporated in vacuo, and decolorized by ether elution through a silica gel pad (15g) to give (80%; ¹H NMR) the crude ester (2.8g). Further attempts to purify 15 by ThLC resulted in mild decomposition: Rₐf 0.43 (CHCl₃/5% MeOH); ¹H NMR δ 2.18 (s, COMe, 3H), 3.41 (s, OMe, 3H), 3.6 (m, CH₂OMe, 2H), 4.3 (m, 4-CH, 1H), 5.28 (s, α-CH₂, 2H), 5.37 (d, 5-CH, 1H), 7.35 (bs, PhH, 5-pyH, 6H), 8.31 (dd, 4-pyH, J₄,₃=8.2 Hz, J₆,₄=2.1Hz, 1H), 9.20 (d, 6-pyH, J=2.1Hz, 1H).

Chiral 2-hydroxyethyl-5-oxazolinylpyridine (16).
A mixture of crude 15 (3.3g) in absolute EtOH (50mL), and excess anh. K₂CO₃ (5g, 36.2mmol) was stirred for 2hr. at 25°C. The suspension was partially dissolved in CHCl₃ (50mL) to precipitate the K₂CO₃, then filtered through Celite®. The filtrate was evaporated in vacuo, and chromatography (ThLC, SiO₂, CHCl₃/5% MeOH, Rₐf 0.19) to give (68% from N-oxide) the desired alcohol 16, as a colorless oil: 2.37g; ¹H NMR δ 3.43 (s, OMe, 3H), 3.7 (m, CH₂OMe, 1H), 3.9 (bs, OH, 1H), 4.3 (m, 4-CH, 1H), 4.81 (s, α-CH₂, 2H), 5.51 (d, 5-CH, J=7.1Hz, 1H), 7.35
(s, phH, 5H), 7.41 (d, 3-pyH, J3,4=8.1Hz, 1H), 8.29 (dd, 4-pyH, J4,3=8.1Hz, J6,4=2.0Hz, 1H); IR (neat) 3275, 3100, 2905, 1640, 1495, 1380, 750, 705 cm⁻¹; MS m/e 298 (M⁺, 2.5), 253 (M⁺-OMe, 100), 161 (47), 119 (91.7), 91 (73); Anal. Calcd. for C₁₇H₁₈N₂O₃: C, 68.43; H, 6.09; N, 9.39. Found: C, 68.19; H, 6.18; N, 9.21.

**Reaction of 2-hydroxymethyl-5-oxazolinylpyridine 16 with SOCl₂.** Attempted preparation of 2-chloromethyl-5-oxazolinylpyridine analogue of 16. A stirred solution of 16 (100mg, 0.34mmol) and cold freshly distilled SOCl₂ (5mL) was refluxed for 15 minutes. The SOCl₂ was removed in vacuo and the residue neutralized with aq. Na₂CO₃ (10%; 20mL) and extracted with CH₂Cl₂. The organic layer was dried over anh. MgSO₄, filtered, and evaporated in vacuo to give a colored residue (78mg), which after concentration could not be redissolved in CH₂Cl₂.

**Reaction of 16 with mesyl chloride.** To a stirred solution of 16 (100mg, 0.34mmol) in Et₃N (10mL) at 0°C, mesyl chloride (78mg, 0.68mmol) was carefully added. After 30 minutes, the Et₃N was removed in vacuo and the residue neutralized with aq. Na₂CO₃ (10%, 50mL), extracted with CH₂Cl₂, dried over anh. MgSO₄, filtered, and evaporated in vacuo to give a complex mixture, whose ¹H NMR exhibited peaks at 8 3.0 and 8 5.1 attributed to mesyl-methyl and py-α-methylene, respectively. However, the mesylate compound also decomposed in
solution in a matter of hours evidenced by the disappearance of the peaks at 83.0 and 5.1 and darkening of the solution.

Tetrahydropyranyl ether of 2-bromoethanol. To a stirred solution of dihydropyran (8.4g, 100mmol) at 0°C, was added dropwise a mixture of 2-bromoethanol (6.25g, 50 mmol) and p-toluenesulfonic acid (75mg) The solution was stirred an additional 12 hrs., after which aq. NaHCO₃ (10%, 100mL) was added. The resulting mixture was extracted with CH₂Cl₂, dried over anh. MgSO₄, evaporated in vacuo, and distilled (91%) to give the protected alcohol, as an oil: 9.51 g; bp 75°C (1mm) [Lit. 81b bp 94°C (14mm)]; ¹H NMR δ 1.6 (m, CH₂, 6H), 3.35-4.1 (m, CH₂, 6H), 4.6 (br, s, CH, 1H); IR (neat) 1124 cm⁻¹.

Mono-tetrahydropyranyl triethanolmine (19). A solution of THP protected bromoethanol (6.00g, 28.7mmol), diethanolamine (3.02g, 28.7mmol) and anh. K₂CO₃, (4.76g, 34.4mmol) in anh. DMF (50 mL), and anh. K₂CO₃, (4.76g, 34.4mmol) was stirred at 25°C for 24 hr. after which the DMF was removed in vacuo to give a solid mass, which was re-suspended in CH₂Cl₂, filtered, evaporated in vacuo, and distilled [bp 150°C (2mm)] to give (88%) 19, as a colorless oil: 5.90g; ¹H NMR δ 1.4-1.9 (m, pyrCH₂, 6H), 2.55-2.85 (m, NCH₂, 6H), 3.2-4.0 (m, OH, OCH₂, 10H), 4.45-4.58 (m, CH, 1H); IR (neat) 3400, 2900, 2750, 1735, 1660cm⁻¹; MS m/e 132 (M⁺-C₅H₉O₂, 6.4), 118 (M⁺-C₆H₁₁O₂,
100), 85 (49.7), 74 (27.2); Exact mass calcd. for 
C$_6$H$_{14}$N$_2$O$_2$: 132.1025 (M$^+$-C$_5$H$_9$O$_2$). Found: 132.1027.

**General procedure for preparation of the THP protected N-2-ethanol azacrown ethers. Reaction of 19 with triethylene glycol ditosylate.** To a stirred 
suspension of NaH (oil-free; 970mg, 40.4mmol) in dry THF 
(300mL) at 25°C under N$_2$, diol 19 (3.94g, 16.9mmol) was 
added, followed in 30 minutes by triethylene glycol ditosylate\textsuperscript{82} (mp 78-79°C, 7.34g, 16.9mmol). The mixture 
was stirred for 72 hr., then neutralized with aq. NH$_4$Cl 
(15%, 20mL), evaporated in vacuo, dissolved with Et$_2$O, 
and washed with water. The combined organic extract was 
concentrated in vacuo, then chromatographed (column, 
Al$_2$O$_3$) eluting with 5% MeOH/CHCl$_3$ to give (44.4%) the 
desired azacrown ether 18b, as a colorless oil: 2.60g; 
R$_f$ 0.56; $^1$H NMR $\delta$ 1.4-1.7 (brm, CH$_2$, 6H), 2.80 (t, NCH$_2$, 
J=6.2Hz, 2H), 2.84 (t, NCH$_2$, J=6.0Hz, 4H), 3.4-3.9 (m, 
OCH$_2$, 20H), 4.58 (brm, CH, 1H); IR (neat) 2915, 2855, 
1455, 1355, 1115, 1035 cm$^{-1}$; MS m/e 262 (M$^+$-C$_5$H$_9$O, 0.5), 
246 (M$^+$-C$_5$H$_9$O$_2$, 3.6), 232 (M$^+$-C$_6$H$_{11}$O$_2$, 100); Exact mass 
calcld. for C$_{12}$H$_{24}$NO$_4$: 246.1706 (M$^+$-C$_5$H$_9$O$_2$). Found: 
246.1727.

**Reaction of 19 with tetraethylene glycol 
ditosylate.** A mixture of 19 (3.66g, 15.7mmol), 
tetraethylene glycol ditosylate\textsuperscript{82} (7.89g, 15.7mmol), and 
NaH (oil-free; 900mg, 37.5mmol) afforded (56.8%) after
standard workup the azacrown ether 18a, as an oil: 3.49g; Rf 0.56 (Al₂O₃, 5% MeOH/CHCl₃); ¹H NMR identical to 18b; MS m/e 306 (M⁺-C₅H₉O, 0.4), 276 (M⁺-C₅H₉O₂, 4.3), 290 (M⁺-C₆H₁₁O₂, 100); Exact mass calcd. for C₁₄H₂₈N₀₅ 290.1973 (M⁺-C₅H₉O₂): Found: 290.1951.

Preparation of 18b by reaction of aza-15-crown-5 with THP-2-bromoethanol. A mixture of THP-2-bromoethanol (543mg, 2.6mmol), aza-15-crown-5 (750mg, 2.6mmol), and anh. K₂CO₃ (1.0g, 7.2mmol) in anh. DMF (35mL) was stirred under N₂ for 12hr. The solution was concentrated in vacuo, dissolved in CH₂Cl₂, filtered, concentrated, and chromatographed [Al₂O₃, 5% MeOH/CH₂Cl₂] to yield 18b, which was previously described: 556mg (62.4%).

Acid-catalyzed deprotection of tetrhydropyranyl crown ethers 18a. A solution of crown ether 18a (2.9g, 5mmol), aq. HCl (6M, 4mL), and MeOH (16mL) was maintained at 25°C for 1.5hr, then solid Na₂CO₃ (10g) was added carefully, followed by concentration in vacuo, dissolution in H₂O, and extraction with CH₂Cl₂. The combined organic layer was dried over anh. MgSO₄ and concentrated to give (86.6%) 14a, as an oil: 1.33g; ¹H NMR δ 2.52 (t, NCH₂, J=4.8Hz, 2H), 2.74 (t, NCH₂, J=5.2Hz, 4H), 3.5-3.8 (brm, OCH₂CH₂O, OH, 23H); IR (neat) 3375, 2910, 2850, 1450, 1110 cm⁻¹; MS m/e 276 (M⁺-CH₂OH), 100); Exact mass calcd. for C₁₃H₂₆NO₅ 276.1812 (M⁺-CH₂OH). Found: 276.1812.
Acid-catalyzed deprotection of tetrahydropyranyl crown ether 18b. A solution of crown ether 15b (2.0 g, 6 mmol), aq. HCl (6 M, 4 mL), and MeOH (16 mL) was maintained at 25°C for 1.5 hr. After standard workup (see above), the residue gave (94.2%) 17b, as an oil: 1.59 g; $^1$H NMR identical to 17a except δ 3.5-3.8 (brm, OCH$_2$, OH, 19H); IR (neat) 3300, 2900, 1450, 1360, 1110 cm$^{-1}$; Exact mass calcd. for C$_{11}$H$_{22}$NO$_4$: 232.1550 (M$^+$-CH$_2$OH). Found 232.1544.

Reaction of 17a with SOCl$_2$. A solution of azacrown ether 17a (500 mg, 1.6 mmol) in cold SOCl$_2$ (25 mL) was refluxed for 1 hr, after which the SOCl$_2$ was removed in vacuo to give the intermediary hydrochloride salt, as a hygroscopic oil: (21a; 580 mg).

A portion of the crude salt 21a (100 mg - 0.3 mmol) was dissolved in H$_2$O (250 mL), then solid Na$_2$CO$_3$ (1.5 g) was carefully added. The mixture was extracted with CH$_2$Cl$_2$, dried over anh. MgSO$_4$, filtered, and evaporated in vacuo to give (92%) the free chloride 20a, as an oil, which rapidly decomposed on standing: 826 mg; $^1$H NMR δ 2.7-3.1 (m, NCH$_2$, 6H), 3.4-3.8 (m, OCH$_2$CH$_2$O, CH$_2$Cl, 22H).

Reaction of 17b with SOCl$_2$. The treatment of 17b (600 mg, 2.3 mmol) with SOCl$_2$ (30 mL) was conducted and worked up, as described above for 17a, to give 20b, as a hygroscopic oil (720 mg), which was utilized in the following reactions without additional purification.
Reaction of N-2-chloroethyl azacrown ether hydrochloride salt 21a with alcohol 16. Alcohol 16 (328mg, 1.1mmol) was added to a stirred suspension of NaH (oil-free; 75mg, 3.0mmol) and TMEDA (250mg, 2eq) in dry THF (50mL) at 55°C under N₂, followed by dropwise addition of the crude 21a (637mg, ca. 1.6 eq) in THF (20mL) over 1 hr. The mixture was allowed to cool to 25°C and neutralized with 10% aq. NH₄Cl solution and the THF removed in vacuo. The concentrate was dissolved in 10% aq. Na₂CO₃ and extracted with CH₂Cl₂. The combined organic layer was dried over anh. MgSO₄ and chromatographed (ThLC, Al₂O₃, CHCl₃/MeOH 5%) to give (5%) 22a, as an oil: 32mg; Rₙ 0.20; ¹H NMR δ 2.44-2.96 (m, NCH₂, 6H), 3.45 (s, OMe, 3H), 3.53-3.75 (m, OCH₂CH₂O, CH₂OMe, NCH₂CH₂, 24H), 4.35 (m, 5-CH, 1H), 4.73 (s, pyCH₂, 2H), 5.51 (d, 4-CH, J=7.1Hz, 1H), 7.36 (s, phH, 5H), 7.54 (d, 3-pyH, J=8.1Hz, 1H), 8.24 (d, 4-pyH, Jₙ₃=8.1Hz, J₆,₄×=2.1Hz, 1H), 9.16 (d, 6-pyH, J=2.1Hz, 1H); IR (neat) 3050, 2915, 1650, 1590, 1350, 1115 cm⁻¹; MS m/e 339 (48.5), 276 (100); Anal. Calcd. for C₁₃H₄₅N₃O₇: C, 63.34; H, 7.72; N, 7.15. Found: C, 63.76; H, 7.64; N, 7.22.

Reaction of N-2-chloroethyl azacrown ether hydrochloride salt 21b with alcohol 16. A mixture of alcohol 16 (300mg, 1.0mmol), salt 21b (579mg, 1.6mmol), oil-free NaH (75mg, 3.0mmol), and TMEDA (250mg) in THF
(100mL) was treated as above, after standard workup, gave (7%) lariat ether 22b, as an oil: 38 mg; \( R_f \) 0.23 (5% MeOH/CHCl\(_3\)); \(^1\)H NMR identical to 22a except: \( \delta \) 3.53-3.75 (m, OCH\(_2\)CH\(_2\)O, CH\(_2\)OMe, NCH\(_2\)CH\(_2\), 28H); IR (neat) identical to 22a; MS m/e 339 (49.5), 232 (100); Anal. Calcd. for C\(_{29}\)H\(_{41}\)N\(_3\)O\(_7\): C, 64.07; H, 7.62; N, 7.23. Found: C, 63.71; H, 7.35; N, 7.01.

**Reaction of aza-18-crown-6 with chloroacetyl chloride.** A stirred mixture of aza 18-crown-6 \(^{82}\) (1.56g, 5.9mmol), chloroacetyl chloride (780mg, 7.1mmol), and Na\(_2\)CO\(_3\) (1.80g, 17.0mmol) in dry acetone (50mL) was maintained under N\(_2\) at 25°C for 8 hr. after which MeOH (2mL) was added. The suspension was stirred an additional 30 min. after which the solvent was evaporated in vacuo and the solid residue was dissolved in dilute aq. HCl (50mL) then extracted with CH\(_2\)Cl\(_2\), dried over anh. MgSO\(_4\), concentrated in vacuo, and chromatographed (Al\(_2\)O\(_3\), 5% MeOH/CHCl\(_3\), \( R_f \) 0.46) to give (93%) 23a, as an oil: 1.85g; \(^1\)H NMR \( \delta \) 3.5-3.75 (m, OCH\(_2\)CH\(_2\)O, NCH\(_2\)CH\(_2\), 24 H), 4.19 (s, ClCH\(_2\)CO, 2H); IR (neat) 2920, 1720, 1635, 1125 cm\(^{-1}\); MS m/e 304 (M\(^+\)-Cl, 7.2), 262 (M\(^+\)-COCH\(_2\)Cl, 14.6), 120 (74.2), 89 (100); Anal. Calcd. for C\(_{14}\)H\(_{26}\)N\(_2\)O\(_6\)Cl: C, 49.48; H, 7.71; N, 4.12. Found: C, 49.15; H, 7.51; N, 4.10.

**Reaction of aza-15-crown-5 with chloroacetyl chloride.** A solution of monoaza 15-crown-5 (2.00g,
9.1 mmol), chloroacetyl chloride (1.34 g, 11.9 mmol), and Na₂CO₃ (3.20 g, 30 mmol) in acetone (50 mL) was treated as above for 23a. After standard workup, 23b was isolated as an oil: 2.42 g (89.8%); Rf 0.42; ¹H NMR identical to 23a except multiplet in 3.5-3.75 ppm; IR (neat) identical to 23a; MS m/z 295 (M⁺, 0.7), 260 (M⁺-Cl, 9.6), 218 (M⁺-COCH₂Cl, 16.6), 120 (99.2), 89 (100); Anal. Calcd. for C₁₂H₂₂N₅O₅Cl: C, 48.73; H, 7.50; N, 4.74. Found: C, 48.46; H, 7.46; N, 4.75.

Reaction of alcohol 16 with chloroacetamide crown ether 23a. To a stirred suspension of alcohol 16 (250 mg, 0.8 mmol), NaH (oil-free; 36 mg, 1.5 mmol), and TMEDA (232 mg, 2.0 mmol) in dry THF (50 mL) at 55-60°C, crown ether 23a (272 mg, 0.8 mmol) in THF (20 mL) was added in one portion. The mixture was stirred for an additional 45 minutes, then cooled to 25°C, neutralized with a minimum volume of 10% aq. NH₄Cl, evaporated to dryness and chromatographed (ThLc, SiO₂, 5% MeOH/CH₂Cl₂) to give (84.5%) 24a, as an oil: 407 mg; Rf 0.17; ¹H NMR at 3.44 (s, OM, 3H), 3.40-3.70 (m, CH₂CH₂O, CH₂OMe, 26H), 4.35 (m, 4-CH, 1H), 4.39 (s, CH₂CO, 2H), 4.80 (s, α-CH₂, 2H), 5.50 (d, 3-CH, J=7.1 Hz, 1H), 7.35 (s, pHH, 5H), 7.63 (d, 5-pyH, J=8.2 Hz, 1H), 8.31 (dd, 4-pyH, J₂₃=8.2 Hz, J₄₆=2.0 Hz, 1H), 9.15 (d, 6-pyH, J=2.0 Hz, 1H); IR (neat) 3040, 3890, 1725, 1640, 1120 cm⁻¹; MS m/z 601 (M⁺, 0.7), 556 (M⁺-CH₃OCH₂, 0.6), 339 (100); Anal. Calcd. for
$C_{31}H_{43}N_3O_9$: C, 61.88; H, 7.20; N, 6.98. Found: C, 61.62; H, 7.05; N, 6.86.

Reaction of alcohol 16 with chloroacetamide crown ether 23b. 24b was prepared under similar reaction conditions as above for alcohol 16 (400mg, 1.49mmol), NaH (100mg, 4.2mmol), TMEDA (300mg, 2.58mmol), and chloroacetamide crown ether 23b (441mg, 1.49mmol), THF (100ml) at 45-55°C gave (80%) 24b, as an oil: 662mg; Rf 0.16; $^1H$ NMR identical to 24a except $\delta$ 3.40 - 3.70 (m, CH$_2$CH$_2$O, CH$_2$OMe, 22H); IR (neat) identical to 24a; MS m/e 557 (M$^+$, 0.6), 512 (M$^+$-CH$_2$C=OCH$_3$, 0.8), 339 (100); Anal. Calcd. for C$_{29}$H$_{39}$N$_3$O$_8$: C, 62.47; H, 7.05; N, 7.54. Found: C, 62.32; H, 6.96; N, 7.05.

$^1H$ NMR Analyses of 24b in the presence of magnesium chloride. To a stirred solution of 24b (50mg, 0.09mmol) in anh. CH$_3$CN (2mL), MgCl$_2$ (38mg, 0.40mmol) was added the refluxed for 30 min. The solution was evaporated in vacuo and the residue was dissolved in CDCl$_3$ (0.5mL), filtered, and analyzed by $^1H$ NMR: $\delta$ 3.44 (s, OMe, 3H), 3.40-3.70 (m, CH$_2$CH$_2$O, CH$_2$OMe, 22H), 4.35 (m, 4-CH, 1H), 4.92 (s, CH$_2$CO, 2H), 5.23 (s, a-CH$_2$ 2H), 5.50 (d, 5-CH, J=7.1Hz, 1H), 7.35 (s, phH, 5H), 7.73 (d, 3-pyH, J=8.1Hz, 1H), 8.27 (dd, 4pyH, J$_{4,3}$=8.1Hz, J$_{4,6}$=1.8 Hz, 1H), 9.11 (d, 6-pyH, J=1.8Hz, 1H).

$^1H$ NMR Analyses of 24b in the presence of potassium iodide. To a stirred solution of 24b (50mg, 0.09mmol)
in CH$_3$CN (2mL), KCl (30mg, 0.40mmol) was added and refluxed for 30 min. After standard workup (described above) the $^1$H NMR (CDCl$_3$) spectra of the residue was identical to that of 24b except for broadening of the crown methylenes $\delta$3.38-3.80 (m, CH$_2$CH$_2$O, CH$_2$OMe, 22H) and a broadening of the phenyl singlet $\delta$7.30-7.41 (brs, phH, 5H).

**Reaction of 24b with methylmagnesium bromide.** To a stirred solution of 24b (600mg, 1.08mmol) in THF (20mL) at 0°C, methylmagnesium bromide (2.16mmol, 0.75mL, 2.8 M/ether) was added in one portion under N$_2$ stirring was continued for an additional 30 min. The resulting dark orange solution of 26 was used in the following reactions.

**Hydrolysis of 26.** A portion (2mL) of the THF solution of 26 was hydrolyzed by addition of H$_2$O (5mL) and then extracted with CH$_2$Cl$_2$ (15mL). The organic layer was dried over anh. MgSO$_4$, filtered, and evaporated in vacuo to give a mixture of 24b (~45%, $^1$H NMR), dihydropyridine 27 (~50%, $^1$H NMR), and the 4-methylpyridine derivative 25 (~5%, $^1$H NMR). The dihydropyridine 27 could not be isolated pure due to its tendency to spontaneously oxidize to pyridine 28; however, several $^1$H NMR signals could be assigned from the mixture: $\delta$ 1.18 (d, 4-CH$_3$, J=6.4Hz), 3.99 (s, NCOCH$_2$), 4.22 (s, $\alpha$-CH$_2$), 7.13 (d, 2-diH pyH, J=6.1Hz).
The mixture was dissolved in CHCl₃ (100mL) and was oxidized by slowly bubbling air into the solution for 2 days, periodically replenishing the evaporating solvent, only 24b (previously described) and 28 were detected by ¹H NMR in 45% and 55%, respectively. The 4-methylpyridine 28 was isolated by chromatography (ThLC; SiO₂, CHCl₃/MeOH 10%) as an oil: 22mg; Rᵣ 0.20; (~35% yield); ¹H NMR δ 2.65 (s, pyCH₃, 3H), 3.45 (s, OCH₃, 3H), 3.3-3.8 (m, XCH₂CH₂X, CH₂OMe, 22H), 4.35 (m, 4-CH, 1H), 4.40 (s, COCH₂, 2H), 4.77 (s, α-pyCH₂, 2H), 5.48 (d, 5-CH, J=7.2Hz, 1H), 7.35 (s, phH, 5H), 7.58 (s, 3-pyH, 1H), 9.0 (s, 6-pyH, 1H); IR (neat) 3045, 3890, 1730 cm⁻¹; MS m/e 571 (M⁺, 0.8), 526 (M⁺-CH₂OCH₃, 0.6), 353 (100); Anal. Calcd. for C₃₂H₄₅N₃O₉: C, 67.72; H, 7.93; N, 7.35. Found: C, 67.51; H, 8.18; N, 7.16.

Reaction of 26b with methyl chloroformate. A portion (2mL) of the stirred THF solution of 26b was treated with a solution of methyl chloroformate (100mg, 1.1 mmol) in dry THF (5mL) at 25° under N₂. The solution was stirred for an additional 15 minutes, after which the solvent and excess methyl chloroformate were evaporated in vacuo. The residue was treated with aq. Na₂CO₃ (10%; 15mL), then extracted with CH₂Cl₂. The organic layer was dried over anh. MgSO₄, filtered, evaporated in vacuo and chromatographed (ThLC, SiO₂, CHCl₃/MeOH 5%; Rᵣ 0.24) and 29 was isolated, as an orange oil: 29 mg (~43%); ¹H NMR δ
1.36 (d, 4-diHPyCH₃, J=6.7Hz, 3H), 3.40 (s, CO₂Me, 3H), 3.3-3.75 (m, XCH₂CH₂X, 4-diHPyH, CH₂OMe, 23H), 3.71 (s, CO₂Me, 3H), 3.89 (s, COCH₂, 2H), 4.19 (s, pyCH₂, 2H), 4.20 (m, 4-CH, 1H), 4.75 (d, 5-diHPyH, J=6.5Hz, 1H), 5.37 (d, 5-CH, J=5.9Hz, 1H), 7.31 (s, ph-H, 5H), 7.60 (s, 6-diHPyH, 1H); IR (neat) 1730, 1670, 1635, 1450, 1125 cm⁻¹; MS m/e 631 (M⁺, 0.4), 585 (M⁺-CH₂OCH₃, 0.8) 218 (100); Anal. Calcd. for C₃₂H₄₅N₃O₉: C, 60.84; H, 7.18; N, 6.65. Found: C, 61.06; H, 7.05; N, 6.47.

3-Oxazolinylpyridine 30. As previously reported⁴⁵g to a stirred solution of 10 (5.00g, 19.7mmol) in THF (50mL), t-BuOK (2.43g, 21.7mmol) was added, followed by MeI (2.92g, 19.7mmol) in THF (10mL) at 25⁰C. The mixture was stirred for 6 hr., followed by evaporation in vacuo. The residue was dissolved in CH₂Cl₂, washed with aq. NaHCO₃ (10%), dried over anh. MgSO₄, evaporated in vacuo, and chromatographed (EtOAc/C₆H₁₂) to give (95%) 30, as an oil: 5.28g; ¹H NMR δ 3.44 (s, OCH₃, 3H), 3.67 (m, 4-CH₂, 2H), 4.34 (m, 4-CH, 1H), 5.52 (d, 5-CH, 1H), (m, 5-pyH, 1H), (s, phH, 5H), 8.30 (ddd, 4-pyH, J₄,₅=7.8Hz, J₄,₂+ J₄,₆=2.0Hz, 1H), 8.73 (dd, 6-pyH, J₆,₁=4.6Hz, J₂,₄=2Hz, 1H), 9.24 (dd, 2-pyH, J₂,₄=2.0Hz, J₂,₅=1.4Hz, 1H).

Reduction of α,α,α-trifluoroacetophenone with N-metallo-1,4-dihydropyridine 31. As described by Meyers,⁴⁵h to a stirred solution of 30 (268mg, 1.0mmol)
was added in THF (10mL), MeMgBr (0.4mL, 2.5M, 1.0mmol) and stirred an additional 30 min. [conditions under which Meyers generated the S (91%) enantiomer at the dihydropyridine 4-position with quantitative conversion of 30 to 31], to which a second equivalent of MeMgBr (0.40mL, 2.5M, 1.0mmol) was added (in order to more closely emulate the reductive conditions employed in the reaction involving the lariat analog 26). To that solution TFA (2 eq., 0.2mmol) in THF (3mL) was added in one portion at 0°C, then slow warming to 55°C. The temperature was held at 55°C for an additional 6 hr. The mixture was hydrolyzed by addition of H₂O (1mL). The mixture was concentrated in vacuo, dissolved in CH₂Cl₂ (20mL), washed with aq. NaHCO₃ (10%, 10mL), dried over anh. MgSO₄, filtered, and evaporated in vacuo to give a residue, which was chromatographed (column, EtOAc/C₆H₁₂) to give two fractions A and B.

Fraction A was a mixture of two compounds and further chromatographed (ThLC, benzene to give two additional fractions. Fraction 1: 32a, to hydride reduction product alcohol (93% with respect to precursor 30) as an oil: 164 mg, bp 93°C (15mm) [Lit. bp 99-105°C (17mm)]; [α]D²⁰ +13.4° (c=0.91, benzene)]; ¹H NMR δ 2.45 (brs, OH, 1H), 4.93 (q, CH, JHF=6.8Hz, 1H), 7.25-7.50 (m, phH, 5H). Alcohol 32 was analyzed by polarimetry: [α]D²⁵ = +1.39 (c = 1.80, benzene)
corresponding to an enantiomeric bias of 54.5:45.5 S/R (%ee = 10.4), and Fraction 2: 33, The methyl adduct (99%, with respect to 1 eq. Grignard regent) characterized by $^1$H NMR: S 1.79 (q, CH$_3$, J$_{HF}$=1.5Hz, 3H), 2.71 (brs, OH), 7.4-7.6 (m, phH, 5H).

Fraction B gave (95%) the 4-methylpyridine 34 as an oil: 268mg; $^1$H NMR S 2.62 (2, pyCH$_3$, 3H), 3.42 (s, OCH$_3$, 3H), 3.68 (m, CH$_2$, 2H), 4.30 (m, 4-CH, 1H), 5.48 (d, 5-CH, J=6.4Hz), 7.16 (d, 5-pyH, J=5.0Hz, 1H) 8.91 (d, 6-pyH, J=5.0 Hz, 1H) 8.98 (s, 2-pyH, 1H).

Reduction of 23b with LiAlH$_4$. To a stirred solution of 23b (100mg, 0.18mmol) in THF at 25°C, LiAlH$_4$ (100mg) was added. The solution was warmed to 60-65°C, then stirred an additional 24h. The mixture was
hydrolyzed by addition of H$_2$O/THF (50:50, 10mL). The THF was evaporated in vacuo and the residue was treated with aq. NaHCO$_3$ (10%, 20mL), extracted with CH$_2$Cl$_2$, dried over anh. MgSO$_4$, concentrated in vacuo, and chromatographed (ThLC, CHCl$_3$/EtOH) to give the desired product 22b (previously characterized); 5 mg (−5%); starting 24b 25mg (26%) and numerous unidentified decomposition products.

Acknowledgments. We acknowledge the National Institute of Health and the National Science Foundation for funds to purchase the NMR instrumentation.

For references herein: see GENERAL REFERENCES.
Chapter 3

γ-RAY INDUCED HOMOLYTIC ALKYLATION OF METHYL NICOTINATE BY 1,3 DIOXOLANE

\[
\begin{align*}
\text{O} & \text{Me} \\
\text{O} & \text{Me}
\end{align*}
\]

\[
\begin{array}{c}
\text{Co-60} \\
\gamma-hv
\end{array}
\]

To be submitted to *J. Org. Chem.* as a "Note"
**γ-RAY INDUCED HOMOLYTIC ALKYULATION OF METHYL NICOTINATE BY 1,3-DIOXOLANE**

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There have been few reports which have dealt specifically with radiation-induced alkylations and α-hydroxyalkylations of the biologically important pyridinecarboxylic acid derivatives. The nucleophilic character of alkyl radicals, particularly radicals with α-heteroatoms, readily permits the homolytic alkylation of protonated heteroaromatic bases (Fig. I).

Recent developments in homolytic substitution reactions induced by chemical and photochemical methods have opened up new, simple synthetic avenues for rapid and clean substitution of heterocycles.

During our investigation of the new methods for
preparation of functionalized 6-methylnicotonic acid
derivatives, specifically methyl 6-formylnicotinate (1).
We attempted the direct transformation of methyl
nicotinate to acetal 2 by a γ-ray induced alkylation
procedure. We report here the methylation of protonated
methyl nicotinate via γ-ray induced homolytic
substitution by 1,3-dioxolane.

Figure II

Our reactions were conducted by subjecting a
deareated solution of methyl nicotinate, sulfuric acid,
and dioxolane to ⁶⁰Co γ-irradiation (6 x 10⁵ rad h⁻¹)
with an overall dose of 1.0 x 10⁷ rad. The resulting
mixture gave (21%) only methyl 6-methylnicotinate⁹⁵ (3)
and methyl 4,6-dimethylnicotinate\textsuperscript{89} (45\%) with the remaining portion being unchanged starting ester (71\%). In contrast, analogous reactions, which were chemically induced\textsuperscript{92,93}, gave exclusively the expected acetal products. The formation of 3 and 4 under these conditions was not unexpected, based upon the work of Sugimori\textsuperscript{89} in which protonated methyl nicotinate was $\gamma$-irradiated in the presence of various alcohols to give a mixture of both alkylation (A) and $\alpha$-hydroxyalkylation products (B), with alkylation being the major product (Fig. III).

Figure III

With these results, it was, however, unexpected that there would be found no trace of acetal 2. Apparently, under the harsh conditions of "mega dose" $\gamma$-irradiation and with a readily available source of hydrogen atoms\textsuperscript{89} the intermediary acetal 2 undergoes a facile "double"
homolytic cleavage\textsuperscript{96} to give the methyl substituted products exclusively (Fig. IV).

Figure IV

$$\text{OMe}_2\text{H}^+$$

We are currently investigating analogous reactions on a variety of heteroaromatic bases to ascertain the scope and application of this general methodology.

**EXPERIMENTAL SECTION**

Irradiation was performed at the Louisiana State University Nuclear Science Center employing a 60Co source ($6 \times 10^5$ rad h$^{-1}$). $^1$H NMR spectra used in comparison with literature spectra were recorded with an IBM NR-80 spectrometer. Unless specified otherwise, reagent grade reactants and solvents were obtained from chemical suppliers and used as received.

\textit{\textgamma-}Irradiation of Protonated Methyl Nicotinate and 1,3-Dioxolane. To a solution of methyl nicotinate (4.1g,
30 mmol) in dioxolane (100mL) was added sulfuric acid (4.9g, 50mmol) after which the solution was deaerated by bubbling nitrogen gas for 20 min. The solution was sealed in a glass stoppered Pyrex® flask and placed in an aluminum bell-jar (10cmID, 50mm Wall), which was lowered into the radiation source (\(^{60}\)Co-\(\gamma\), \(6 \times 10^5\) rad H\(^{-1}\)). After 7 days (\(1.0 \times 10^7\) rad), the solution was removed from the source, the excess dioxolane removed in vacuo, and the residue neutralized by aq. \(\text{Na}_2\text{CO}_3\) (10%). The aqueous layer was extracted with \(\text{CH}_2\text{Cl}_2\), dried over anh. \(\text{MgSO}_4\), and chromatographed (ThLC \(\text{C}_6\text{H}_{12}/\text{EtOAc}\)) to give unchanged starting compound (methyl nicotinate; 2.91g, 71%), 3 (methyl 6-methyl nicotinate; 0.95g, 21%)\(^95\), and 4 (methyl 4,6-dimethylnicotinate; 0.25g, 5%)\(^89\) each characterized by \(^1\)H NMR comparison with literature spectra.

**Acknowledgments**

We acknowledge Dr. Edward N. Lambremont Director of the Nuclear Science Center at Louisiana State University, for his assistance.

For references herein: see GENERAL REFERENCES
Chapter 4

N-ALKYL LARIAT ETHER NADH MODEL SYSTEM

"Bird On A Nest"
Crown ether or cryptand stabilization of a metal ion involved in a the biomimetic reduction of ketone by "classical" asymmetric NADH model systems has been shown to enhance stereospecificity. Hence, incorporation of a multidentate ligand into the molecular architecture of an asymmetric model, as an apoenzyme mimic, may further enhance the stereospecificity of carbonyl reductions by effectively increasing the "local concentration" of the crown/cryptand species. In addition, incorporation of such a ligand may present a means by which "biologically important" metals other than magnesium (i.e. Na⁺, K⁺, Zn²⁺, etc.) can be utilized in stereospecific NADH model reductions. A model was envisioned in which a crown ether would be bridged to a nicotinamide moiety via an one-carbon bridge, through the pyridine nitrogen (Fig. 1).

Figure 1

Being a "classical" N-alkyl model, the reduced (NADH) form should be easily produced by treatment of the
corresponding pyridinium salt with $\text{Na}_2\text{S}_2\text{O}_4$ under alkaline conditions.

Reduction of ketones by this model is envisioned to proceed via a ternary charge transfer complex similar to that proposed by Ohno\textsuperscript{15} in the pyridine nitrogen, crown ether oxygens, and substrate carbonyl, jointly encapsulate the metal ion through which the electrons flow. By the use of CPK models, this transition state could be likened to a "bird on a nest" standing watch over it's precious egg (Fig. 2) and waiting for a juicy insect to come within range of her beak.

Figure 2

Interestingly, this class of NADH model could be modified by the introduction of a chirally substituted crown ether, thus, eliminating the necessity of chirality at the amide functional group, creating a more representative NADH analogue (46). This approach is
very similar to the binding of NADH models to protein backbones, however, without the inherent complexities associated with such complex structures (i.e. separation and characterization).

Like other "classical" NADH models, the "bird on a nest" heteroatom can be envisioned bound to polymer frameworks, micelles or other solid supports such as silica gel in an attempt to give an easily regeneratable stereospecific reducing agent (Fig. 3), which could possibly be utilized in industrial batch processes.

Figure 3
In addition, if a model of this type could be bound to an electrode surface, it may be possible to achieve the first example of an electrochemically activated stereoselctive NADH reduction promoted by stabilization of the charge transfer intermediate by encapsulated metal ion (Fig. 4).  

The following was conducted in an effort to establish the potential of such a model and explore its possible applications.

RESULTS AND DISCUSSION

For this preliminary study, the NADH mimic 20a, investigated at length by Inouye et al., was chosen as a reactivity reference for the "bird on a nest". Accordingly, the S-prolinamide 48 served as the starting point and was easily prepared by a prescribed method (Scheme I) via condensation of 3-pyridinecarboxylic acid chloride with L-proline ethyl ester. Ester 47 was
subsequently transaminated via treatment with anhydrous NH$_3$ in methanol to give the desired S-prolinamide 48.

Nicotinamides 47 and 48 were envisioned to undergo quaternization with an electrophilic methyl-15-crown-5 to give NAD$^+$ models 49 and 50, respectively.

The tosyl derivative of hydroxymethyl-15-crown-5 (54) was selected as the electrophile and was prepared via the method of Gokel$^{102}$ (Scheme II) from 3-(benzyloxy)propylene-1,2-oxide (51). Benzyl glycol$^{103}$ 51 was cyclized by treatment with NaH then ditosyltetraethyleneglycol to give crown ether 52 (39%), which was converted (98%) to the alcohol 53 via
debenzylation with H₂ and Pd/C. The desired tosylate (54) was then formed by treatment of 53 with p-toluenesulfonyl chloride in pyridine under standard conditions.

**Scheme II**

Ultimately, NAD⁺ models 49 and 50 were prepared by treatment of 47 and 48 with 54 in DMSO at 100°C for 24 hrs to give 49 (55%) and 50 (50%), respectively, as hygroscopic oils. The coupling of 47 and 54 was evidenced spectroscopically ¹H NMR, DMSO D₆) by the upfield shifts in the two nonequivalent aryl proton signals of p-toluenesulfonyl moiety from δ 7.33 and 7.85 to δ 7.07 and 7.46, respectively, and downfield shifts in the 6 and 2-pyridine proton signals from δ 8.67 and 8.82
in 47 to 8.872 and 9.01 in 49, respectively. The coupling is further verified, in that the tosylate (anion) can be exchanged with chloride on an ion exchange resin. Similar spectral (1H NMR) characteristics were seen with amide 50. The 6 and 2 protons shifted downfield from 8.870 and 8.87 in 48 to 8.874 and 9.03, respectively. The spectral pattern of the corresponding tosylate was identical to that in 49.

Ester 49 and amide 50 were reduced to the 1,4-dihydropyridine via Na2S2O4, under standard conditions in low yields as monitored by (1H NMR). Nevertheless, the 1H NMR spectra of the unstable CH2Cl2 soluble extract from the attempted reductions of both 49 and 50 exhibited an ill-defined resonance at 5.75 reminiscent of the resonance for H-6 in the simple N-benzyl-1,4-dihydro derivatives, reported by Inouye. The rationale for the apparent deactivation of the pyridinium salts 49 and 50 toward reduction by Na2S2O4 is not yet known.

**Experimental**

**Ethyl N-nicotinoyl-(S)-proline (47)** was prepared by the method of Inouye. To a stirred solution of nicotinoyl chloride hydrochloride (3.8g, 21mmol) and pyridine (10mL) in benzene (200mL), ethyl L-prolinate (3.0g, 21mmol) was added. The solution was refluxed 6 hr., cooled, washed with aq. Na2CO3 (10%; 100mL), dried
over MgSO₄, filtered, evaporated in vacuo, and chromatographed (column, C₆H₁₂/EtOAc) to give (58%) 47, as a colorless oil: 3.02g; ¹H NMR δ 1.26 (t, CH₃, J=7.1Hz, 3H), 1.70-2.40 (m, CH₂, 4H), 3.48-3.75 (m, CH₂, 2H), 4.24 (q, OCH₂, J=7.1Hz, 2H), 4.5-4.75 (m, CH, 1H), 6.34 (dd, 5-pyH, J₅,₄=7.3Hz, J₅,₆=4.2Hz, 1H), 7.90 (ddd, 4-pyH, J₄,₅=7.3Hz, J₄,₆=1.7Hz, J₄,₂=1.4Hz, 1H), 8.67 (dd, 6-pyH, J₆,₅=4.2Hz, J₆,₄=1.7Hz, 1H), 8.82 (bd, 2-pyH, J₂,₄=1.4Hz, 1H). ¹H NMR was identical to literature.

N-Nicotinoyl-(S)-prolinamide 48. Into a solution of ester 47 (2.5g, 10mmol) in MeOH (anh., 50mL) anh. NH₃ was bubbled at -5°C for 30 min. after which the vessel was sealed and placed into a 45°C oven for 15 days. The solvent was removed in vacuo and the residue recrystallized (CHCl₃/Et₂O) to give (83%) 48, as colorless crystals: mp 87-88°C [Lit. mp 87-88°C]; 1.82g; ¹H NMR δ 1.70-1.90 (m, CH₂, 4H), 3.45-3.70 (m, CH₂, 2H), 3.80 (s, NH₂, 2H), 4.55-4.75 (m, CH, 1H), 7.32 (dd, 5-pyH, J₅,₄=7.2Hz, J₅,₆=4.3Hz, 1H), 7.81 (brd, 4-pyH, J=7.2Hz, 1H), 8.70 (brd, 6-pyH, J=4.5Hz, 1H), 8.87 (brs, 2-pyH, 1H).

2-[(Benzzyloxy)methyl]-15-crown-5 (52). To a stirred suspension of 3-(benzzyloxy)propylene-1,2-oxide 51 (9.10g, 50mmol) and oil-free NaH (2.64g, 110mmol) in THF (50mL), tetraethylene glycol ditosylate (25.1g, 50mmol) was added in one portion, then refluxed for 24
hr. After cooling, the THF was removed in vacuo. The residue was taken up in H₂O (300mL) and extracted with CH₂Cl₂ (3 x 150mL). The combined organic extract was dried over anh. MgSO₄ and filtered. The CH₂Cl₂ was evaporated in vacuo and the residue chromatographed (column, EtOAc/C₆H₁₂) and distilled (Kugelrohr) to give (39%) 52, as an oil: 8.03g; bp 170-176°C (0.1mm)
[lit.¹⁰² bp 164-166°C (0.02mm)]; ¹H NMR δ 3.5-4.0 (m, CH₂CH₂X, CH₂, 21H), 4.5 (s, phCH₂, 2H), 7.25 (s, phH, 5H); IR (neat) 3060, 3030, 2980-2800, 1450, 1155cm⁻¹.

2-[(Hydroxymethyl)-15-crown-5] (53). A Parr® bottle was charged with ether 52 (7.5g, 18mmol), abs. EtOH (absolute, 100mL), and 10% Pd/C catalyst (200mg). The mixture was shaken for 24 hr at 25°C under H₂ (60psi), filtered through Celite and the ethanol evaporated to give (98%) 53, as an oil, which needed no further purification: 4.77g; ¹H NMR δ 2.6 (brt, CH, 1H), 3.63 (brs, 21H); IR (neat) 3500-3100, 1450, 1350, 1290, 1250, 1150-1020 cm⁻¹ (both ¹H NMR and IR are in agreement with literature values¹⁰²).

2-[(Tosyloxy)methyl]-15-crown-5 (54). To a stirred mixture of pyridine (5mL) and p-TsCl (3.14g, 16.5mmol) at 0°C, alcohol 53 (3.75g, 15mmol) in pyridine (2mL) was added. The mixture was refrigerated at 0°C for 24hr, after which the mixture was poured into ice cold dil. HCl (50mL) and extracted with CH₂Cl₂ (3 x 50mL). The
combined organic extract was washed with H$_2$O (20mL),
dried over anh. MgSO$_4$, filtered, and evaporated to give
(86%) tosylate 54, as a pale yellow oil: 4.57g; $^1$H NMR 8
2.45 (s, CH, 1H), 3.64 (m, XCH$_2$CH$_2$X, 19H), 4.15 (m, CH$_2$,
2H), 7.33 (d, phH, J=8.1Hz, 2H), 7.85 (d, phH, J=8.1Hz,
2H) ($^1$H NMR identical to literature$^{102}$).

Pyridinium lariat-ether model ester 49. A DMSO
(2mL) solution of ester 47 (1.0g, 4.0mmol) and
tosyl-crown 54 (1.6g, 4.0mmol) was heated at 100°C and
maintained for 24hr. after which the solvent was removed
in vacuo. The residue was dissolved in H$_2$O (25mL) and
filtered through Celite. The filtrate was extracted
once with CH$_2$Cl$_2$ (5mL) to remove unchanged starting
material and the aqueous phase was evaporated in vacuo to
give (1.44g) 49, as a hygroscopic oil: 55%; $^1$H NMR
(DMSO-D$_6$) 8 1.2-1.4 (brt, CH$_3$, J=7.0Hz, 3H), 1.6-2.3
(brm. CH$_2$, 4H), 2.25 (s, CH$_3$, 3H) 3.1-3.8 (brm, CH$_2$,
25H), 4.0-4.4 (brq, OCH$_2$, J=7.0Hz, 2H), 4.5-4.8 (brm, CH,
1H), 7.07 (d, phH, J=8.0Hz, 2H), 7.46 (d, phH, J=8.0Hz,
2H), 7.4-7.6 (brm, 5-pyH, 1H), 8.0-8.3 (brm, 4-pyH, 1H),
8.72 (brd, 6-pyH, 1H), 9.01 (brs, 2-pyH, 1H); Anal.
Calcd. for C$_{31}$H$_{44}$N$_2$O$_{11}$S: C, 57.03; H, 6.81; N, 4.29.
Found: C, 57.38; H, 6.49; N, 4.08 [corrected for water
absorption (MicAnal)].

Pyridinium lariat-ether model amide 50. A DMSO
(2mL) solution of amide 48 (1.0g, 4.6mmol) and
tosyl-crown 54 (1.82g, 4.6mmol) was heated to 100°C for 24 hrs. After workup as above, 50 was obtained (50%), as a hygroscopic oil: 1.43g; $^1$H NMR (DMSO D$_6$) the ill-defined spectra was identical to 49 except for the absence of the ester resonances (8, 1.2-1.4 and 4.0-4.4); Anal. Calc. for C$_{29}$H$_{31}$N$_3$O$_{10}$S; C, 55.83; H, 6.64; N, 6.74. Found: C 55.41; H, 6.34; N 6.59. [corrected for water absorption (MicAnal)].

Attempted reductions of 49 with Na$_2$S$_2$O$_4$. To a stirred solution of pyridinium salt 49 (1.0g, 1.5mmol) in a CO$_2$ saturated solution of NaHCO$_3$ (3g) in H$_2$O (50mL), Na$_2$S$_2$O$_4$ (8.5g) was added. After foaming had stopped additional H$_2$O (50mL) was added, followed by Na$_2$CO$_3$ (15g) and CH$_2$Cl$_2$ (100mL). Stirring was continued for 5 hr. at 25°C in the dark. The CH$_2$Cl$_2$ layer was washed with H$_2$O and dried over anh. MgSO$_4$, filtered, and concentrated in vacuo to give a dark residue (20mg), whose $^1$H NMR exhibited only traces of dihydropyridine as evidenced by a poorly defined bump at $\delta$ 5.75 (~5 mole%) characteristic of the dihydro derivatives 6-proton$^{25}$. The remainder of the resonances was characteristic of the precursors 47 and 54 (~45 mole%) and unchanged pyridinium salt 49 (~50 mole%). Attempts to further reduce 49 were unsuccessful. The unstable dihydropyridone was not isolated due to its tendency to decompose quickly.

Attempted Reduction of 50 with Na$_2$S$_2$O$_4$. Under
identical conditions as above, pyridinium salt 50 (1.0g, 1.6mmol) was treated with Na₂S₂O₄ (8g) to give after workup as above, only 30 mg (CH₂Cl₂ soluble residue) of a mixture of precursors 48 and 54 (~90 mole%) and the starting pyridinium salt 50 (~40 mole%). However, as in the case of 49, a poorly defined resonance (as seen by Inouye²⁵) was observed at δ 5.75 (~10 mole%) possibly arising from the desired dihydropyridones's 6-proton. Likewise, the reduction product could not be isolated free of decomposition products.
Chapter 5

N-ALKYL LARIAT ETHER NADH FUNCTIONALIZED ELECTRODE

"Bird On A Nest"
DISCUSSION

It is well known that highly specialized electrodes can be prepared by immobilization of organic or organometallic reagents on an electrode surface.\textsuperscript{104} Thus, electrodes can be designed which are highly specific red-ox electrocatalysts by incorporation of well characterized electroactive species on the electrode surface. Such functionalization of electrodes is commonly accomplished via a polymer coating or by direct covalent bonding. The attached molecule acts as a fast electron transfer mediator\textsuperscript{105} for a substrate dissolved in the contacting solution and making direct reduction of the substrate by the naked electrode (Figure 1), a minor process.

Figure 1

Preparative scale reductions by NADH chemically modified electrodes have not been reported. The absence of such may be due to the fact that the usual mode of electrochemical reduction gives inactive
Nevertheless, similar selective reductions by chirally functionalized electrode surfaces have been reported. It is our hope that introduction of the multidentate ligand may promote 1,4-isomer formation. Herein is reported the attempted stereoselective reduction of 4-acetylpypyridine by a "Bird on the Nest" functionalized carbon electrode.

**EXPERIMENTAL**

**General Comments:** Electrochemical reductions were performed on a Printon Applied Research Model 370 Electrochemistry System. For other comments applicable here, see the General Comments in Chapter 2.

**Attempted preparation of a chirally functionalized (NADH model) electrode.** Functionalization of a spectroscopic grade graphic electrode (1 x 4 x 0.2 cm) was attempted by the following 5-step process. (1) The carbon electrode was thermally oxidized by oven baking in air at 160°C for 36 hr. inducing acid groups;
(2) the acid groups were converted to their acyl chloride derivatives via treatment with refluxing \( \text{SOCl}_2 \) (3mL) in dry benzene (10mL), for 72 hr; and (3) the electrode was then treated with a solution \( N,N' \)-dimethylhexanediamine (0.1M in benzene 10mL) at 75° for 48 hr. Upon cooling, a small amount of floculant precipitate (HCl salt) was present, which was indicative that the acyl chloride surface was present and that the condensation was successful:

\[ \begin{align*}
\text{O} & \quad 2 \quad \text{SOCl}_2 \\
\text{HO} & \quad \text{3} \\
\text{H} & \quad \text{N} \\
\text{N} & \quad \text{CH}_3 \\
\text{N} & \quad \text{CH}_3 \\
\end{align*} \]

(4) The electrode was then treated with (S)-proline ester 47 (0.1M in benzene, 10mL) and a catalyst, \( t\)-BuOK (50mg) under reflux for 48 hr, and finally;

\[ \begin{align*}
\text{O} & \quad 4 \\
\text{47} & \quad \text{OC}_2\text{H}_5 \\
\end{align*} \]

(5) the electrode was treated with tosylmethyl 15-crown-5
The reduction of 4-acetylpyridine (55) was chosen for initial study because it reduces at a relatively positive potential$^{109} (-0.95 \text{V vs. SCE})$ well suited for redox coupling with NADH analogues generally having reduction potentials of approx. $-1.15 \text{V}^{100}$ vs. SCE. The electrochemical reduction of 55 was performed under $N_2$ at $-1.5 \text{V vs. SCE}$ in a two-compartment cell (Pt auxiliary electrode), and the catholyte (100mL) was a 1:1 mixture of 0.5M sodium acetate aq. buffer and ethanol. When the electrode was used as a cathode, addition of 55 (0.5mL, 4.5mmol) caused an increase in current from 6 to 16 mA. The current decayed to 8 mA after 6hr. after which, the catholyte was reduced to 40 mL volume in vacuo and made basic with solid Na$_2$CO$_3$, then extracted with ether. The extract was washed with a sat. aqueous NaCl solution and dried over anh. MgSO$_4$ to give a mixture of 55 and 56$^{110}$.
(0.5g) in a 54 and 46% (\textsuperscript{1}H NMR), respectively, which were separated chromatographically (ThLC, benzene). The electrolysis product 56 (0.2g) was polarographically inactive (c = 3, CHCl\textsubscript{3}) and taken to be a racemic modification.

Remarks

The inability of the electrode to reduce the substrate stereoselectively is a strong indication that functionalization had not occurred (i.e. Step 4 in which the chiral moiety was introduced). It has been shown that electrodes functionalized by chiral "non-electroactive" species, such as amino acids, are capable of stereoselective reduction of 4-acetylpyridine\textsuperscript{107} and, similarly, it is known that optically active alkaloids in the electrolytic solution can lead to asymmetric reduction.\textsuperscript{111} Therefore, if a chiral moiety were bound to the electrode surface in a significant population the reduced substrate would be expected to be enantiomerically enriched.

Further study in the area of electrochemically induced NADH model reductions by functionalization with "Bird on the Nest" compounds on a variety of electrolytes and with various metal salts may provide some insight into the redox activity of the actual enzyme NADH. The
crown ether more closely models the apoenzymatic portion of the enzyme than the simple N-benzyl substituent utilized in previous examples, since the multidentate crown ether can be more closely likened the multidentate apoenzymatic portion of NADH itself (Fig. 2).

Figure 2
CONCLUSION

In recent years, a primary research goal of Newkome's group was to fabricate "finely tuned" ion (or molecule) specific complexes which would be capable of distinguishing a specific cation or molecule ultimately from a mixture of all other cations or molecules. In this effort, the Newkome group has pioneered an exciting new area of crown ether chemistry by incorporating sub-heterocyclic rings, particularly pyridine and polypyridines, into a variety of macrocyclic frameworks. It was found that the replacement of crown ether or cryptand oxygen ligands by the heteroatom of a sub-heterocyclic moiety, gave a new ligand with markedly different cation affinity. Naturally, the mode and extent of complexation by the newly included heteroatom with the cationic species became of prime importance when setting about the task of designing new macrocycles.

Early works showed that in the case of 2,6-oxy-bridged pyridino crowns, the participation of the pyridine nitrogen, as an active ligating center, is seriously impaired due to deleterious conformational restraints. In circumvention of such interference, a series of methylene-bridged 2,6-pyridino crown ethers was prepared in which the participation of the pyridine nitrogen in cation binding has been well established.
Hence, a methylene-brided-2,6-pyridino crown complex was envisioned in which the fittedness of the encapsulated metal ion and electronic interaction of the pyridine nitrogen with the included cation would be so "finely tuned" as to impart "pyridinium-like" character to the pyridine sub-ring. That is, the ligating nitrogen would attain a substantial positive charge buildup. It was further envisioned that the complexed pyridine (pseudo pyridinium) could be involved in reactions characteristic, heretofore, only of pyridinium salts. One such characteristic reaction is the addition of nucleophiles under relatively mild conditions to give dihydropyridines, which is a particularly facile process with pyridinium salts "activated" by electron withdrawing groups in the 3 and/or 5-position(s). The long-range goal of the research presented herein, was to synthesize N-metallo-1,4-dihydropyridines via reductive mettallation of a pyridine sub-ring incorporated within a macrocyclic structure; in realization of the above envisioned (pseudopyridinium) process. With recent strides in NADH modeling chemistry, the significance and application of our nicotinic acid crown ethers, are immediately obvious as evidenced by the many short range goals accomplished in the quest for an ideal NADH model.

The most important goals accomplished here were:

(1) The synthesis of the first asymmetrically
substituted 2,6-methylene-bridged pyridino crown ethers.

(2) In the investigation of their application as N-metallo-NADH models, it was found that only the 18-crown-6-dibenzo crown ether 22 underwent facile addition of organometallic reagent (EtMgBr) to give the model N-metallo-1,4-dihydro derivative.

(3) A series of novel lariat ethers was synthesized to circumvent possible steric restraint by the 2,3-substituent interaction, on the 1,4-reductive metallation of such models. This series possesses a "lariat" ether side-chain bridged through the pyridine position and incorporating a chiral oxazoline moiety.

(4) The chiral lariat biomimetic reductant N-metallo-1,4-dihydropyridine 26 was synthesized.

(5) The first stereospecific reductions by N-metallo-1,4-dihydropyridines were performed, in that the chiral N-metallo-1,4-dihydro-pyridine-3-oxazoline 26, along with the nonlariat analog 31, was used in the biomimetic reduction of α,α,α-trifluoroacetophenone to give the corresponding S alcohol in ~5 and ~10% enantiomeric excesses (ee's), respectively.

(6) New N-alkyl NADH models were synthesized. Preliminary investigation of their reactivity as both "free" and "bound" species, was performed.

During the course of these investigations several variations of the theme of N-metallo NADH models were
conceived, some of which are directly related to the models presented here. The ultimate N-metallo or N-alkyl NADH model should have a high degree of asymmetry yet with the more representative simple (CONH₂) amide moiety rather than the usual chirally modified amide. Thus, chirality should be imparted to the multidentate appendage in mimicry of the parent enzymes' asymmetric apoenzymic structure. In addition, the encapsulated metal ion must have a high affinity for carbonyl oxygen and be capable of stabilizing one electron transfer intermediates.

A new series of models which satisfies these prerequisites, can be envisioned utilizing specialized transition metal complexes.
Most recently the Newkome group has been involved in the synthesis and characterization of a number of such pyridine and polypyridine complexes, however, lacking the 3-carboxamide and chiral functionalities. Therefore, with the application of the technology perfected in these "preliminary" studies, an interesting new series of NADH-like reductants could be created.

Also, presented here are preliminary details in an attempt to incorporate appendage crown ethers into "classical-type" N-alkyl NADH model. Similar directions in molecular architecture of this class of model are also envisioned.

The work presented herein is an excellent starting point into the investigation of the synthesis, structure, reactivity, mechanism, and application of NADH-like biomimetic reductants.
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VITA

Charles R. Marston was born on November 25, 1955 in Lexington, Kentucky. Charles grew up in Southern Michigan where his father, Rev. Robert V. Marston, pastored at Free Methodist Churches first in Garden City, in Battle Creek, and in Jackson.

Charles entered Spring Arbor Free Methodist College in September, 1974, married Carol L. Jacobson in June, 1976, and was awarded his Bachelor of Arts degree in May, 1978. He immediately entered the graduate program at Louisiana State University in Baton Rouge under the supervision of Dr. George R. Newkome. For the six years of his graduate study, he was employed as a graduate teaching assistant, teaching laboratory courses in General Chemistry, Qualitative and Quantitative Analysis, Instrumental Analysis, and Organic Chemistry. He is currently a candidate for the degree of Doctor of Philosophy at Louisiana State University.
EXAMINATION AND THESIS REPORT

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Major Field: Organic

Title of Thesis: Nicotinic Acid Crown Ethers; Syntheses, Characterization, Complexation, and NADH Model Reaction

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