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## 1. ACCOMPLISHMENTS ON ONR CONTRACT N00014-88-K-0115

The primary objective of the ONR contract was to develop qualitative and, if possible, quantitative relationships between the molecular structural features of selected chiral macrocyclic hosts and chiral organic ammonium ion guests and the degree of chiral recognition shown by these host and guest species toward each other. This objective has been met to a large degree. The results of the research have led to important conclusions and several promising leads to future research have been opened. Details of specific aspects of the research can be found in the papers published and in press and in the Technical Reports to ONR, both of which are listed in this final report.

Two approaches were used in the initial phase of this contract. First, our experience led us to design and synthesize a number of chiral pyridine- and triazole-containing macrocycles with attached pendant substituents which we believed might have significant chiral recognition capabilities (see Technical Reports #3, 4, 5, 8, 9, and 14). Second, concurrently we collaborated through correspondence and personal visits with Professor S. Lifson of the Weizmann Institute in Israel to use a molecular mechanics (Empirical Force Field) approach to estimate the recognition capabilities of particular pyridine-containing macrocycles (see Technical Reports #7, 10, and 14). This work led to the identification of two substituents (*t*-butyl and phenyl) which should cause macrocycles into which they were incorporated to have superior chiral recognition capabilities. This collaboration has resulted in significant findings. The Empirical Force Field predictions of enantiomeric selectivity correlated well with the differences in free energy of activation values for chiral macrocycle-chiral ammonium ion interactions. Since our previous work showed that free energy of activation and  $\log K$  values correlate well with each other, the  $\log K$  values are also consistent with the Empirical Force Field results.

Chiral pyridine-containing macrocycles containing phenyl and *t*-butyl substituents were synthesized (see Technical Report #9). Chiral hosts containing these moieties have been found to be two to three times as effective as the best ligands that we had earlier in recognizing enantiomeric amines (see Technical Report #14). The effectiveness of the *t*-butyl and phenyl-substituted macrocycles is steric in nature. Stereoviews based on the calculations by Professor Lifson show the expected steric interactions of these groups with the guests (see Technical Reports #10 and 14).

Our need for accurate  $\log K$  data caused us to make a study of the accuracy of  $K$  values determined using  $^1\text{H}$  NMR. This was done by studying the same host-guest systems by titration calorimetry and  $^1\text{H}$  NMR using identical solvents (except that D was substituted for H in  $\text{CH}_3\text{OH}$ ) (see Technical Reports #11, 13, and 14). These results show that the  $\log K$  values determined by the two methods are in excellent agreement indicating that the direct  $^1\text{H}$  NMR method to determine  $\log K$  values is reliable for our use and it requires only mg amounts of these hard to prepare chiral ligands.

## 2. PUBLICATIONS RESULTING FROM ONR CONTRACT N00014-88-K-0115

1. J.S. Bradshaw, R.M. Izatt, J.J. Christensen, K.E. Krakowiak, B.J. Tarbet, R.L. Bruening and S. Lifson. "Stable Silica Gel-Bound Crown Ethers. Selective Separation of Metal Ions and Potential for Separations of Amine Enantiomers," J. Incl. Phenomena, 7, 127-136 (1989).
2. C.W. McDaniel, J.S. Bradshaw and R.M. Izatt, "Proton-Ionizable Crown Ethers. A Short Review," Heterocycles, 30, 665-706 (1990).
3. J.S. Bradshaw, P. Huszthy, C.W. McDaniel, C.Y. Zhu, N.K. Dalley, R.M. Izatt and S. Lifson, "Enantiomeric Recognition of Organic Ammonium Salts by Chiral Dialkyl-, Dialkenyl-, and Tetramethyl-Substituted Bis-Pyridino-18-Crown-6 Ligands: Comparison of the Temperature Dependent  $^1\text{H}$  NMR and the Empirical Force Field Techniques," J. Org. Chem., 55, 3129-3137 (1990).
4. J.S. Bradshaw, C.W. McDaniel, K.E. Krakowiak and R.M. Izatt, "Proton-Ionizable Crown Compounds. 19. The Synthesis of Chiral Dialkyl-substituted Triazolo-18-Crown-6 Macrocycles," J. Heterocyclic Chem., 27, 1477-1479 (1990).
5. C.Y. Zhu, J.S. Bradshaw, J.L. Oscarson and R.M. Izatt, "Evaluation of a Direct  $^1\text{H}$  NMR Method for Determining  $\log K$  and  $\Delta H$  Values for Crown Ether-Alkyl Ammonium Cation Complexation," J. Incl. Phenom., in press.
6. P. Huszthy, J.S. Bradshaw, C.Y. Zhu, R.M. Izatt and S. Lifson, "Recognition by Symmetrically Substituted Chiral Diphenyl- and Di-*t*-Butyl- and Asymmetrically Substituted Chiral Dimethylpyridino-18-Crown-6 Ligands of the Enantiomers of Various Organic Ammonium

Perchlorates," J. Org. Chem., in press.

7. J.S. Bradshaw, P. Huszthy, C.W. McDaniel, M. Oue, C.Y. Zhu, R.M. Izatt and S. Lifson, "Enantiomeric Recognition of Organic Ammonium Salts by Chiral Pyridino-18-Crown-6 Ligands: A Short Review," J. Coordination. Chem., Section B, in press.

3. TECHNICAL REPORTS EMANATING FROM ONR CONTRACT N00014-88-K-0115

1. C.W. McDaniel, J.S. Bradshaw and R.M. Izatt, "Proton-Ionizable Crown Ethers. A Short Review," Technical Report #1 to ONR, May 30, 1989.
2. J.S. Bradshaw, R.M. Izatt, J.J. Christensen, K.E. Krakowiak, B.J. Tarbet, R.L. Bruening and S. Lifson, "Stable Silica Gel-Bound Crown Ethers. Selective Separation of Metal Ions and a Potential for Separations of Amine Enantiomers," Technical Report #2 to ONR, June 10, 1989.
3. J.S. Bradshaw, P. Huszthy, C.W. McDaniel and R.M. Izatt, "Synthesis of Chiral Dialkyl-Substituted Pyridino-18-Crown-6 Ligands," Technical Report #3 to ONR, January 12, 1990.
4. J.S. Bradshaw, P. Huszthy, N.K. Dalley and R.M. Izatt, "Synthesis of Chiral Tetramethyl-Substituted Pyridino-18-Crown-6 and Bispyridino-18-Crown-6," Technical Report #4 to ONR, February 9, 1990.
5. J.S. Bradshaw, C.W. McDaniel, K.E. Krakowiak and R.M. Izatt, "Synthesis of Chiral Dialkyl-Substituted Triazolo-18-Crown-6 Ligands," Technical Report #5 to ONR, February 9, 1990.
6. J.S. Bradshaw, C.Y. Zhu and R.M. Izatt, "Enantiomeric Recognition of Organic Ammonium Salts by Chiral Dialkyl-, Dialkenyl- and Tetramethyl-Substituted Pyridino-18-Crown-6 Ligands," Technical Report #6 to ONR, February 20, 1990.
7. J.S. Bradshaw, C.Y. Zhu, S. Lifson and R.M. Izatt, "A Comparison of The Temperature Dependent <sup>1</sup>H NMR and Empirical Force Field Techniques in Determining Enantiomeric Recognition of Organic Ammonium Salts by Chiral Di- and Tetraalkyl-Substituted Pyridino-18-Crown-6 Ligands," Technical Report #7 to ONR, February 20, 1990.
8. J.S. Bradshaw, P. Huszthy and R.M. Izatt, "Preparation of Chiral Diamido-, Dithionoamido- and Azapyridino-18-Crown-6," Technical Report #8 to ONR, April 20, 1990.
9. J.S. Bradshaw, P. Huszthy, C.Y. Zhu and R.M. Izatt, "Preparation of

New Chiral Di-*t*-Butyl-, Diphenyl- and Dimethyl-Substituted Pyridino-18-Crown-6 Ligands," Technical Report #9 to ONR, April 18, 1990.

10. J.S. Bradshaw, P. Huszthy, C.W. McDaniel, C.Y. Zhu, N.K. Dalley, R.M. Izatt and S. Lifson, "Enantiomeric Recognition of Organic Ammonium Salts by Chiral Dialkyl-, Dialkenyl-, and Tetramethyl-Substituted Pyridino-18-Crown-6 and Tetramethyl-Substituted Bis-Pyridino-18-Crown-6 Ligands," Technical Report #10 to ONR, April 18, 1990.
  11. C.Y. Zhu, J.S. Bradshaw, J.L. Oscarson and R.M. Izatt, "An Evaluation of a Direct  $^1\text{H}$  NMR Method for Determining Log  $K$  and  $\Delta H$  Values for Crown Ether-Alkylammonium Cation Complexation," Technical Report #11 to ONR, April 17, 1990.
  12. J.S. Bradshaw, C.W. McDaniel, K.E. Krakowiak and R.M. Izatt, "Proton-Ionizable Compounds. 19. The Synthesis of Chiral Dialkyl Substituted Triazolo-18-Crown-6 Macrocycles," Technical Report #12 to ONR, October 23, 1990.
  13. C.Y. Zhu, J.S. Bradshaw, J.C. Oscarson and R.M. Izatt, "Evaluation of a Direct  $^1\text{H}$  NMR Method for Determining Log  $K$  and  $\Delta H$  Values for Crown Ether-Alkylammonium Cation Complexation," Technical Report #13 to ONR, October 24, 1990.
  14. J.S. Bradshaw, P. Huszthy, C.W. McDaniel, M. Oue, C.Y. Zhu, R.M. Izatt and S. Lifson, "Enantiomeric Recognition of Organic Ammonium Salts by Chiral Pyridino-18-Crown-6 Ligands: A Short Review," Technical Report #14 to ONR, October 24, 1990.
4. HONORS RECEIVED DURING 1988-1990
1. Jerald S. Bradshaw, Annual Sigma Xi Lecturer, BYU Chapter of Sigma Xi, March 17, 1988.
  2. Jerald S. Bradshaw was awarded the 1989 Utah Award of the American Chemical Society, sponsored by the Central Utah and Salt Lake Sections of the American Chemical Society, April 14, 1990.
  3. Reed M. Izatt received the 1990 Utah Governor's Medal in Science and Industry on April 6, 1990.

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government agencies. We greatly appreciate the financial help by ONR in our research efforts.

5. NAMES OF ALL GRADUATE AND POST-DOCTORAL STUDENTS WHO WORKED ON ONR CONTRACT N00014-88-0115

Haoyun An - Synthesis

J. Ty Redd - Synthesis

Christopher McDaniel (received Ph.D.) - Synthesis

Dr. Peter Huszthy - Synthesis

Dr. Masatoshi Oue - Synthesis

Chung Zhu (received Ph.D.) - NMR and calorimetry