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**FINAL REPORT 1992
STUDIES IN BIOORGANIC CHEMISTRY**

Jeffrey D. Winkler, PI

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Grant: N000014-91-J-1886

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STUDIES IN BIOORGANIC CHEMISTRY

Principal Investigator: Jeffrey D. Winkler

Department of Chemistry
The University of Pennsylvania
Philadelphia, PA 19104

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Accomplishments and Conclusions:

The grant addressed two issues of fundamental importance in biomimetic chemistry that had not been successfully imitated in a non-enzymatic system at the time at which this project started: the conformational flexibility of the enzyme active site and the consequences of such mobility for catalysis, and the stereoselective formation of carbon-carbon bonds using compounds that are based on the ubiquitous biological methylating agent S-adenosylmethionine.

The photodynamic macrocycles that were originally proposed are not only fascinating molecules because of their unique structural effects, but were designed to be useful in the active transport of both metals and organic molecules which would have obvious implications in processes like the extraction of metals and organic molecules from aqueous solutions. The mimics of S-adenosylmethionine that were proposed in the original contract were to be applied to a variety of alkylation reactions, and could ultimately be applied to the development of site-specific reagents for DNA functionalization, thereby providing an important control mechanism for gene expression.

During the grant award period, the effect of metal ions on the spiropyran=merocyanine interconversion has been studied. We have found that metal ions can be *reversibly* bound to suitably substituted spiropyrans (J. Winkler, K. Deshayes, B. Shao, "Photodynamic Systems for Metal Ion Transport," *J. Am. Chem. Soc.*, **1989**, *111*, 769) and that the piperinomethyl-substituted compounds are particularly selective for the transport of group IIb metal ions (Zn^{+2} , Cd^{+2}). By changing the metal ion binding group, ion-selective transport has been realized and, in unpublished work in our laboratory, the selective transport of Cu^{+2} has been achieved using spiropyrans that incorporate the 8-quinolinol moiety. Increasing the mechanical efficiency of the transport apparatus and coupling the metal transport to a proton pump has led to significant (10^3) increases in the rate of metal ion transport using these spiropyranindoline-based systems.

In the second area of research, the synthesis and study of sulfides and selenides that could lead to the catalytic transmethylation of carbon- and heteroatom nucleophiles has been examined. The first sulfonium and selenonium salt electrophiles that are reactive enough to methylate carbon nucleophiles at neutral pH in aqueous solvents (i.e., near physiological conditions) have been developed (J. Winkler, M. Finck-Estes, "Carbon-Carbon Bond Formation Under Aqueous Reaction Conditions Using Sulfonium and Selenonium Salt Electrophiles," *Tetrahedron Letters* **1989**, 7293). The application of this methodology to the development of a catalytic cycle for methylation has been explored, and the first example of catalytic transmethylation using this methodology has recently been achieved (J. Winkler, M. Finck-Estes, J. Stelmach, "Catalytic Carbon-Carbon Bond Formation via Transmethylation," manuscript in preparation). By decreasing the electrophilicity of the exogenous source of electrophilic methyl, i.e., going from dimethylsulfate to methyl tosylate, the efficiency of the catalytic cycle increases by an order of magnitude. Further efforts in both of these areas are currently underway in our laboratory.

Publications/Technical Reports During the Grant Period

1. J. Winkler, K. Deshayes, "Photodynamic Macrocycles," *J. Am. Chem. Soc.*, **1987**, *109*, 2190 (Technical Report #1).
2. J. Winkler, K. Deshayes, B. Shao, "Photodynamic Systems for Metal Ion Transport," *J. Am. Chem. Soc.*, **1989**, *111*, 769 (Technical Report #2).

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3. J. Winkler, M. Finck-Estes, "Carbon-Carbon Bond Formation Under Aqueous Reaction Conditions Using Sulfonium and Selenonium Salt Electrophiles." *Tetrahedron Letters* 1989, 7293 (Technical Report #3).
4. J. Winkler, K. Deshayes and Bin Shao, "Photochemical Binding, Release and Transport of Metal Ions." In *Bioorganic Photochemistry, Volume II*, H. Morrison, Ed., Wiley, New York (1993).

Personnel Participating in this Project

K. Deshayes, graduate student, University of Chicago (1983-1987)

M. Finck-Estes, graduate student, University of Chicago (1986-1990)

B. Shao, graduate student, University of Chicago/University of Pennsylvania (1987-1992)

J. Stelmach, graduate student, University of Pennsylvania (1991-present)

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