Preface

Cage compounds have been known in biochemistry and physiology for more than two decades [1]. The past few years have witnessed a considerable increase in interest in caged derivatives because of their high degree of temporal and spatial controllability. Light-initiated cage release is now extensively employed to investigate molecular processes in biochemistry and biophysics as well as to initiate other physiological phenomena. More recently, these same approaches have been extended to the release of substances in building or isolating libraries in combinatorial chemistry, in photolithography, and in the photorelease of caged reagents in chemical transformations. In parallel with recent developments for biological and medicinal technological innovations, the miniaturization of devices for delivery of reagents in analysis and chemical processing and in real-time spectral and physical measurements is a rapidly developing technology. These developments have placed increased demands on the need for even greater spatial and temporal control on processes including chemical transformations. Consequently, the use of light-activated processes becomes much more appealing to those working in the life sciences [2].

As will be discussed in this volume, a very extensive range of substrates and reagents has been delivered by the photolysis of photoactivated protecting groups. This monograph both reviews the recent accomplishments in the field of caged compounds and also looks forward to future inroads into other fields.

Much of what is presented here, in fact, refers to processes in many other fields where the control of reagent or substrate delivery is a key element in a biological study. Initially in this field, only small, low-molecular-weight compounds were "releasable". Now, whole proteins and oligonucleotides are the object of "caging" applications that can range from molecular beacons to enzyme switches.

In spite of the increased interest, the number and range of useful and practical cages remains very limited, with less than a handful that have found sustained interest within the life sciences. In fact, over 80% of the published discoveries employing photoremovable protecting groups are based on a single photochemical process, the photoredox chemistry of the 2-nitrobenzyl chromophore [3]. While this photochemical reagent has proven to be versatile, robust, and generally efficient, it has well-documented limitations, such as the slow rate

Dynamic Studies in Biology. Edited by M. Goeldner, R. Givens

ISBN: 3-527-30783-4

of substrate release and generation of a reactive nitroso functionality, that significantly restrict its application in biological studies. These limitations have stimulated the design and development of cages, leading to an expansion in the availability of usable caging groups. Caging chromophores must have several key properties or attributes. Among these are a strong absorption in the near UV-vis region, an efficient photorelease process, a hypsochromic shift of the absorption spectrum due to the photoproduct, ease of attachment of the chromophore without introducing new added stereocenters, and a cage and photoproduct that are biologically inert. There are currently four principal chromophores, used in caged reactions, that are included in this monograph. These four are evaluated and their applications presented. The newer applications of multiphoton decaging have also been included. These have shown particular promise because of the improvement in spatial resolution for controlled release.

This monograph provides a timely assessment and overview of the state of the field and recent investigations of cage photorelease for a wide variety of applications. It remains to be discovered what new cages will replace or augment those chromophores now in use and what expanded repertoire of applications will emerge. Future research will undoubtedly extend both areas and require a reinvestigation of the accomplishments achieved with the aid of photoremovable protecting groups.

References

1 (a) Kaplan, J.H., Forbush, B.I., Hoffman, J.F., Rapid photolytic release of adenosine 5'-triphosphate from a protected analogue: Utilization by the Na:K pump of human red blood cell ghosts. *Biochemistry* **1978**, *17*, 1929–1935. (b) Engels, J., Schlaeger, E.-J., Synthesis, structure, and reactivity of adenosine cyclic 3',5'-phosphate benzyl triesters. *J. Med. Chem.* **1977**, *20*, 907–911.

2 G. Marriott, Ed. *Methods in Enzymology*, Vol. 291, Academic Press, San Diego, **1998**.

3 Walker, J.W., Reid, G.P., McCray, J.A., Trentham, D.R., 1-(2-Nitrophenyl)ethyl phosphate esters of adenine nucleotide analogues: Synthesis and mechanism of photolysis. *J. Am. Chem. Soc.* **1988**, *110*, 7170–7178.

Strasbourg, France, July 2004
Lawrence, Kansas, USA, July 2004

Maurice Goeldner
Rich Givens