# *Additions and Corrections*

**Oxazolidinone Protected 2-Amino-2-deoxy-D-glucose Derivatives as Versatile Intermediates in Stereoselective Oligosaccharide Synthesis and the Formation of α-Linked Glycosides** [*J. Am. Chem. Soc.* **2001**, *123* (38), 9461−9462]. KAMEL BENAKLI, CONGXIANG ZHA, AND ROBERT J. KERNS*

The following citation suggesting the use of C-2,C-3 bridging heterocycles in the synthesis of 2-amino-2-deoxy-D-hexopyranoses was inadvertently omitted: Miya, K.; Gross, P. H. Heterocyclic Aminosugar Derivatives. II. Preparation of D-glucopyranosido-[2.3:4′,5′]-2′-Oxazolidinones. *J. Org. Chem.* **1969**, *34* (6), 1638−1642.

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# *Book Reviews*

**Protein Structure, Stability, and Folding. Methods in Molecular Biology. Volume 168**. Edited by Kenneth P. Murphy (University of Iowa College of Medicine). Humana Press: Totowa, New Jersey. 2001. ix + 252 pp. $89.50. ISBN 0-89603-682-0.

Protein folding, its mechanism, and the forces that are responsible for guiding an unfolded polypeptide chain through the complex energy landscape leading to the native fold remain some of the key issues of modern molecular biology. The unfolded states of interest include the experimentally accessible denatured state and the nascent protein state that results as the sequence is synthesized in vivo. The protein-folding question was formulated in the 1950s with the discovery that denatured states can, indeed, find their way to the native fold without biological intervention and the theoretical considerations that led to the Levinthal paradox. The recent discoveries that misfolded proteins are vectors of human diseases and the need for methods to predict protein structures using sequences from genome elucidations have only increased the importance of both theoretical and experimental protein-folding studies.

Protein folding was last covered in this series in 1995. That volume, edited by B. A. Shirley, stressed experimental techniques for studying the stability and folding of proteins. The present volume has a more theoretical bent but does include updates on some experimental methods in the form of two chapters on amide hydrogen exchange methods and a chapter on laser T-jump methods for studying fast folding dynamics. A chapter on computer simulation of protein unfolding reveals that such in silico experiments can guide mutational studies of fold optimization. With its theoretical emphasis, this volume differs from most in the series. Typically the volumes provide technical methods and protocols in sufficient detail for implementation. In the present volume, this applies only to the chapters on experimental methods and to the description of the COREX algorithm for modeling native-state ensembles (Chapter 5). Over the entire volume, the citation of the original literature since 1997 is rather sparse, essentially limited in some chapters to the work of the chapter coauthors. Nonetheless, the basic coverage of the topics included is excellent, and this volume represents an entry into this field that is appropriate for chemistry and biochemistry graduate students.

In the first chapter, the editor provides an excellent introduction to the hydrophobic effect and the factors that stabilize protein folds and the opposing factor, configurational entropy. This chapter also provides the basic thermodynamic equation for protein unfolding. In Chapter 3, Freire expands on this by providing the linkage between the thermodynamic parameters for unfolding ($\Delta H$, $\Delta C_p$ and $\Delta S$) and structural features. This treatment employs the current paradigm, which stresses changes in the solvent-accessible surface area (ΔASA). These changes are generally available from models of the folded state if the unfolded state can be equated with full disorder. Residual structure in the unfolded state is not reviewed in this volume; this possibility is, unfortunately, only briefly considered in several chapters. The need to consider ΔASA changes for hydroxyls and apolar and polar atoms separately is presented here, and fortunately, the same classification schemes for these and solvation effects on $\Delta S$ are used throughout the volume. Conformational entropy, the primary drive for unfolding, is considered in both Chapters 5 and 6, with Chapter 5 providing a tabulation of the three distinct increases in entropy associated with unfolding to a fully disordered state for each amino acid residue. Chapter 6 provides excellent guidance for the computational estimation of the conformational entropy changes associated with the formation of secondary structures.

Chapter 2 provides a discussion of the effects of cosolvents, denaturants, and osmolytes on protein stability. Transfer Gibbs energies are explained, and the transfer model is employed, largely with the goal of understanding the features that result in protein stabilization by naturally occurring osmolytes. This chapter would be more useful if it included the transfer free energies and other parameters for amino acid residues that are required for calculations using this model.

Newer applications of amide H/D exchange for the determination of protein stability (Chapter 4) and unfolding rates under the EX1 exchange regime (Chapter 9) are handled very well in this volume. These two chapters are particularly up-to-date, with many references to work appearing in 1998 and 1999 and even a few references to publications appearing in 2000. In addition, the authors of both chapters provide specific protocols for H/D exchange experiments. These chapters are highly recommended.

In Chapter 5, "Modeling the Native State Ensemble", Hilser provides a description of the COREX algorithm. Although it is important for newcomers to protein folding to be introduced to the concept of the folded state as an ensemble rather than a single rigid structure, the "modeling method" presented does not provide structural insights. Rather, the algorithm provides a means for calculating residue-level stabilities (folded vs unfolded equilibrium constants) that are, theoretically, equivalent to H/D exchange protection factors. Comparisons to the experimental measures and the degree of correlation between calculated residue-level stabilities can provide insights into the cooperativity of sub-global unfolding events.

Chapter 7 provides an up-to-date discussion of the importance of turns in protein structures and the extent to which the formation of $\beta$ hairpins may be important in folding transition states. The authors mention several recent studies that reveal that such formations are driven by initial hydrophobic collapse to U-shaped structures that become H-bonded $\beta$ structures later in the folding pathway. This chapter provides references to literature accounts of the effects of mutations at or near turn loci on fold kinetics and fold stability and makes a strong argument for the value of further studies of this type, which the authors refer to as "turn scanning".

In the remaining chapter on experimental methods, the author focuses on laser temperature-jump apparatuses that can be used to determine microsecond and nanosecond folding/unfolding rates. The physical basis of the experiment and the problems presented by thermal lensing, cavitation, and photoacoustic waves are discussed. The instruments at the NIH, Los Alamos, and UI−Urbana are described in detail, which should provide the reader with a basis for evaluating the results that are now emerging. As the author notes, T-jump kinetics for transitions in secondary structures in designed peptides will undoubtedly provide insights into protein folding that would be difficult to obtain using native proteins.

In Chapter 10, Daggett demonstrates that it is now possible to use molecular dynamics simulations to elucidate protein-unfolding pathways. Multiple high temperature (498−600 K) trajectories are examined in order to define a transition-state region that is characterized by a substantial increase in enthalpy with only a modest increase in entropy. The MD unfolding simulation method presented is synergistic with experimental methods (Φ-value analysis from mutations and NMR studies of partially folded states), and in a number of cases, structuring indexes for transition-state models from the MD simulations correlate with experimental Φ values.

Overall, this volume realizes its goal. Even though the coverage of the most recent literature is weak in some chapters, the reader will gain an appreciation of the current theoretical paradigm for protein folding and the computational and experimental techniques that are used to study this important process. It is written at a level appropriate for a graduate student's first serious exposure to the subject and does not make inappropriate assumptions regarding the background material that such a reader would bring to the task.

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