THE AMIDE LINKAGE

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SELECTED STRUCTURAL ASPECTS IN CHEMISTRY, BIOCHEMISTRY, AND MATERIALS SCIENCE

Editors

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A JOHN WILEY & SONS, INC., PUBLICATION

New York / Chichester / Weinheim / Brisbane / Singapore / Toronto

This book is printed on acid-free paper. ♾

Library of Congress Cataloging-in-Publication Data:

The amide linkage : selected structural aspects in chemistry,
biochemistry, and materials science / editors, Arthur Greenberg,
Curt M. Breneman, and Joel F. Liebman.
p. cm.
Includes index.
ISBN 0-471-35893-2 (alk. paper)
1. Amides. I. Greenberg, Arthur. II. Breneman, Curt M.
III. Liebman, Joel F.
QD305.A7A35 2000 99-15235
547'.042–dc21

Printed in the United States of America.

10 9 8 7 6 5 4 3 2 1

DEDICATION AND DESIDERATA

Amour	Chimie	Joie
Sustenance	Reading	Friendship
Generosity	Writing	Creativity

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PREFACE

The amide linkage is a common and very important functional group which contributes to the special properties of peptides, proteins, beta-lactam antibiotics, and numerous synthetic polymers. The discovery of its rigid planarity and propensity for hydrogen bonding sped Linus Pauling's discovery of the alpha-helix and now offers a template for the design of exotic new materials. The present book presents many diverse aspects of the structure, bonding, and dynamics of amides and their influences on chemical, physical, biological, and material properties. It emphasizes a structural, energetics, and bonding perspective with a view toward understanding physical and chemical properties. The approach is also pedagogical in nature—its eighteen chapters provide background and context for the non-expert before going into depth in a particular area. This book is meant to be complementary to Zabicky's classic *The Chemistry of Amides* in the Patai series published in 1970, in that it is broader in scope and places less emphasis on the synthesis and reactions of amides. The Zabicky book continues to provide a great deal of useful background information for readers of the present book.

The amide linkage is undergoing a renaissance of interest at the start of the twenty-first century. When amide planarity and rigidity was discovered by Pauling and co-workers in the 1930s, this important attribute was rationalized by resonance theory—one of the widely accepted canons of modern chemistry. However, theories and ''accepted knowledge'' are challenged every generation and the first two chapters, by Breneman and then Wiberg, apply molecular orbital (MO) theory, density functional theory (DFT), and Bader's Atoms in Molecules (AIM) approach to achieve new levels of understanding of the structures and dynamics of amides. Chapter 3, by Greenberg, uses the more traditional resonance canon to understand the effects of distortion on the ligand properties (e.g., the site of protonation) of amides. Chapter 4 by Brown details the very subtle physical organic chemistry investigations of the minute details of acid- and base-catalyzed hydrolysis of lactams (cyclic amides). Although amides and lactams are normally stable to hydrolysis around neutral pH, he describes the kinetics and mechanistic details for highly distorted lactams that react under these conditions. Liebman, Afeefy, and Slayden (Chapter 5) summarize the thermochemical data for amides. As valuable as this information is for practical problems in engineering and for understanding structure and bonding, there is surprisingly little published data. Chapter 6 (Hoffman) and Chapter 7 (Bose,

Manhas, Banik, and Srirajan) treat selected aspects of the stereoselective synthesis of alpha-lactams and beta-lactams. Chapter 7 also provides very interesting historical perspective on the role of serendipity in the discovery of penicillin and related antibiotics. In Chapter 8, Yamada explores the structural, spectroscopic, and chemical properties of acyclic amides twisted by virtue of steric repulsion. Rademacher (Chapter 9) explores the use of UV photoelectron spectroscopy (PES) as a means of understanding the nature of chemical bonding in planar and distorted amides and lactams.

Starting with Chapter 10 (Palmore and MacDonald), the emphasis switches towards larger amide-containing molecules. Palmore and MacDonald use hydrogen bonding, so vital to the structures of alpha-, beta- and other protein structures, to design new materials in which the sum of numerous weak-moderate H-bonds acting in concert more than equals the strength of attachment due to covalent bonds. Boyd's Chapter 11 nicely describes the role of the ab initio MO theory in the exploration of beta-lactam antibiotics. It provides additional perspective to this interesting history and leads into Chapter 12 (Bohacek and Shakespeare) which describes the design of new enzyme inhibitors as potential pharmaceutical agents. In Chapter 13, Perczel and Csizmadia explore the current limits of computing full conformational energy surfaces (Ramachandran plots) for peptides and proteins at accessible ab initio levels. Cassady (Chapter 14) explores the interactions of peptides and proteins with ions in order to elucidate both proton affinity and structural information. The idea of obtaining mass spectra of proteins seemed to be heretical until recently. In Chapter 15, Maitra and Nowick consider the interactions between beta-sheet proteins in order to gain important insights into molecular recognition. Chapter 16, by Spatola and Romanovskis, describes the generation of cyclic peptide libraries for use in the exploding field of combinatorial chemistry. Chapter 17 (Cieplak) and Chapter 18 (Kallenbach, Bell, and Spek) explore some of the myriad complexities in understanding the subtleties of protein folding that is so vital to our understanding of the biosynthesis and functioning of proteins including enzymes.

We hope that readers will find this book valuable, and will be encouraged to seek as yet unknown applications and understanding for the ubiquitous amide group.

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