Dimethyl Sulfoxide

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DEDICATION

To the many scientists from all over the world whose names appear on references relating to DMSO and who actually made this text possible.

Preface

Rapid accumulation of scientific articles on the clinical usefulness of DMSO following Jacob and Herschler's original publications led the authors to believe that it might be well to have current basic science thinking of DMSO under one cover.

The editors attempted to choose chapter authors that had qualifications for critical scientific evaluation of the literature in their specialties as well as being able to devote the time necessary to produce such a chapter. We are indeed grateful to those men who dedicated their efforts in the preparation of this book.

This text has been a continuous process for the past 2 years. We have maintained a constant check of the literature and believe that it is essentially current as of May 1969. It is inevitable that with such a massive literature some articles were missed and as these are called to our attention they will be added to subsequent printings.

We are aware of important clinical articles which will be summarized later in a sequel to this volume.

We are particularly indebted to Dr. Chauncey Leake and Dr. D.W.E. Baird, Dean emeritus of the University of Oregon Medical School, who stood steadfastly by us in the darkest hours when world opinion seemed to be against DMSO. We are also grateful to Dr. Gerhard Laudahn, of the Schering A.G. Corporation, who stimulated interest in research of this drug amongst European scientists even when it appeared that the drug might not be of any commercial value because of suspected "toxicity."

We will be ever grateful to the New York Academy of Sciences for its persistence in sponsoring a clinical conference on DMSO in March 1966 when political and social pressures would have made it much simpler for them to have abandoned the project. Instead, they used only

one criterion in deciding to sponsor an international symposium on DMSO after the drug had been declared "toxic" in humans; *let scientific facts speak for themselves.*

Without the help of these men and the Academy, clinical use of DMSO might have died in its infancy.

As the work on this volume draws to a close, we are receiving reports of research on DMSO in iron curtain countries. These studies have not been completely translated yet and will have to await future revisions of this volume. We are also aware of current unpublished research by other scientists throughout the world that therefore cannot be included in the initial publication.

The publishers have been extremely patient with us. We acknowledge with gratitude their foresight and stimulus in encouraging us to proceed with this endeavor.

Finally, our most heartfelt thanks to the many secretaries, typists, librarians, and scientists who so faithfully helped with the preparation of final copy—thank you each one.

S.W.J.
E.E.R.
D.C.W.

Foreword

Dimethyl sulfoxide, DMSO, is a remarkably versatile chemical compound, especially in its wide range of applicability to many major biological problems, involving both plants and animals, and importantly, humans as well. Its basic physico-chemical properties make possible its broad applications. Especially significant are its solvent properties. Its capacity to bind water led to its early use in preserving animal and human tissues and cells. Its radioprotective effect on living material was also quickly noted and its penetrating power led to its agricultural use in control of plant diseases, and in aiding nutritive element transport in plants.

Although prepared by Alexander Saytzeff in 1866, DMSO attracted little biological attention, except as a tissue preservative, until the discovery was reported in early 1964 by Stanley Jacob and Robert Herschler of its wide range of primary pharmacologic actions and unique tissue penetrability in plants and animals. This suggested many possible clinical applications. Among other things it was used to dissolve chemicals for direct application and absorption through the skin. Clinical studies showed that DMSO itself could relieve the pain and inflammation of musculoskeletal injuries. DMSO was made available to drug manufacturers through the Crown Zellerbach Corporation, which holds a process patent on making the compound from lignin. Clinical investigation was progressing routinely when a report was made that DMSO produced disturbances of the lens of the eye in experimental animals. The U.S. Food and Drug Administration then halted further clinical study on the drug.

Following two large conferences, one arranged by the New York Academy of Sciences in New York City, the other by Schering A.G. at the University of Vienna Medical School, it was apparent by 1967 that

allegations of toxicity from clinical use of DMSO were exaggerated. By that time many thousands of patients treated by DMSO for a variety of skin and musculoskeletal conditions had shown enough significant improvements to justify continuing clinical evaluation. Many careful clinical reports now testify to its relatively high clinical effectiveness and safety. Administrative roadblocks in the United States unfortunately still hamper appropriate use of DMSO in our country. On the other hand, it is now employed clinically in Europe, with much apparent satisfaction.

It is appropriate that Stanley Jacob, who so modestly, steadily, and effectively continued to study DMSO after he had first called attention to its potential usefulness in medicine, should bring together and edit for publication with two able colleagues, Edward E. Rosenbaum and Don C. Wood, reliable scientific information on the wide usefulness of this very interesting compound. This monograph should long serve as a basic reference source for information about DMSO. Impressive indeed are the vast numbers of publications on DMSO to which reference is made. It is likely that stimulus to further investigation of the remarkable physico-chemical properties of DMSO will result in ever more beneficial applications. It is hoped that this monograph may provide such stimulus.

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Chapter 1

Chemistry of DMSO

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I. INTRODUCTION

Excellent reviews dealing with the chemistry of dimethyl sulfoxide (DMSO) have appeared during the past decade *(1–13)*. The extraordinary interest in DMSO can be traced to a combination of the following factors:

(1) DMSO is one of the most prominent members of the family of polar but aprotic solvents *(14–18)* that have become widely available since World War II and which also include *N,N*-dimethylformamide (DMF), *N,N*-dimethylacetamide (DMA), *N*-methylpyrrolidone, sulfolane or tetramethylene sulfone (TMS), acetonitrile (AN), ethylene and propylene carbonates, and hexamethylphosphorotriamide (HMPT). Many of the traditional concepts of the role of solvent molecules in chemical processes were evolved by considering the existence of two opposite classes of solvents, the nonpolar and the polar. The latter, historically speaking, always belonged to the protic kind (water, the lower alcohols, acetic acid, and so forth), with the result that subconsciously the behavior of polar solvents became synonymous with that of the protic solvents. With the advent of the polar, aprotic solvents a better understanding was attained of the effects caused by specific solvation of the reacting species, and these specific solvation effects began to be distinguished from effects previously attributed to changes in the dielectric constant of the reaction medium.

(2) More so than any other member of the polar, aprotic solvent family, DMSO is also an extremely versatile reagent because it can act as a nucleophilic reagent at either the oxygen or the sulfur terminal of the sulfoxide function, behaving therefore either as a "hard" or "soft" base *(19)*, respectively. In addition, it is capable of being either an oxidizing or a reducing agent. Furthermore, the hydrogen atoms are capable of being ionized in the presence of strong bases, thus opening the way to a broad, new field of synthetic applications utilizing the anion of DMSO ("dimsyl"). At the same time, DMSO contains an excellent "leaving" group in the form of the methanesulfinate anion $(CH_3SO)^-$, and this gives rise to a series of interesting consequences in the chemistry of the dimsyl ion.

(3) Last but not least is the discovery of the exceptional biological properties of DMSO that have led to some immediate applications in medicine *(20)* and have aroused worldwide interest in its chemistry.

The remaining chapters of this monograph are dedicated to the biological aspects of DMSO and thus it is appropriate that this chapter attempts to bring to light those physical and chemical characteristics of DMSO that may have a direct bearing on its biological properties. The latter hinge, to a great degree, on the unique ability of DMSO to penetrate and diffuse through living tissues, a property most likely related to the structure and thermodynamics of molecular complexes formed by DMSO with water, protein, lipids, salts, and a host of other substances.