

Chemical Processes with Participation  
of Biological and Related Compounds

*Biophysical and Chemical Aspects of Porphyrins,  
Pigments, Drugs, Biodegradable Polymers  
and Nanofibers*

*Edited by*

T.N. Lomova & G.E. Zaikov

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*To learn anything without thinking is absolutely useless,  
Thinking about something without analysing and  
Studying the subject of thinking is dangerous*  
Confucius, 551–479 BC  
Ancient China

*Chemistry is a miracle, interest, delight,  
The future and basis of well-being of people*  
Yury M. Luzhkov  
Mayor of Moscow  
November 12, 2003

## Preface

Everything around us has been created by chemistry (glass, gas, medicines, food, metals, polymers, etc.). There is no pathos of “chemical” enthusiasm in this definition. Chemistry is the basis of everything, which life produces (microbes, plants, animals, human beings). Any living body is a giant chemical reactor with millions of coordinated chemical reactions proceeding in it. Molecular biology, molecular genetics and gene engineering, biotechnology and intellect – all this is chemistry.

Nobelist Prof. N.N. Semenov and his pupils (Profs. M.N. Emanuel, V.N. Kondratyev, V.I. Goldansky, A.L. Buchachenko, K.I. Zamoraev, Yu.B. Monakov) insisted on that. And we fully agree with them.

There is a certain shift in the world of chemistry from studies of more or less simple reactions to get, for example, sulfuric acid, ammonia, phenol and acetone to research into complicated biochemical and biological processes. This is required for solving medical problems, because medicine is our health and our good life. It is common knowledge that it is better to be healthy and rich than to be poor and sick.

Chemistry is more than a science. It is a festivity. This volume presents the reviews of chemists working in the field of biochemistry, biology and, in the final analysis, for medicine and health.

We look forward to readers’ comments, will be grateful for them and will definitely use them in our future research.

*Prof. Gennady E. Zaikov*  
Moscow, Russia  
*Prof. Tatyana N. Lomova*  
Ivanovo, Russia



*To propagate education is to extend prosperity.  
I mean the general prosperity but not one's private wealth.  
With extension of prosperity, part of evil disappears.*  
Alfred Nobel, Sweden

## Foreword

Research into the kinetics and thermodynamics of processes involving biologically active substances and multistage mechanisms of their interactions in living systems is of primary interest for modern science. Many problems arising in the course of the studies may be solved by investigating the reactivity of BAS in model systems and synthetic analogs of naturally occurring biomolecules with a complex and often unknown structure. The authors of this book have been for many years engaged in studies of the reactivity of BAS in various aggregate states and in relation to the molecular structures and supramolecular forms.

The book covers many aspects of the effects of relatively simple biomolecules as model enzymes, molecular receptors, photosensitizers, pharmacophores, and biopharmaceutical agents. The quantitative characteristics of the transitions of cations, anions and small organic molecules, enzymic catalysis, and diffusion of molecules through biological membranes are presented. The mechanisms of the processes are discussed. The biological activity of the compounds studied is assessed.

Hydrated porphyrin forms and their unique properties are of great interest. Chapter 1 deals with naturally occurring bacteriochlorins, their properties, isolation and chemical modifications. A separate part is concerned with synthetic bacteriochlorins; here, general and particular methods of production of these compounds, their spectral and physicochemical characteristics, are considered. Special consideration is given to the use of naturally occurring and synthetic bacteriochlorins in the production of new-generation photosensitizers for photomedicine.

Chapter 2 describes methods of synthesis of *meso*-mono-, di-, tri-, and tetraphenylporphyrins along with schemes of addition and modification of substituents in them. Approaches are shown to fine setting of the physicochemical properties of porphyrins obtained.

Chapter 3 represents the results of research into the catalytic activity of manganese(III)- and copper(II)-porphyrins alkyl- and phenyl-substituted in  $\beta$ - and *meso*-positions in the reaction of decomposition of hydrogen peroxide in the DMFA–KOH–H<sub>2</sub>O system. The ion-molecular mechanism of the decomposition with kinetically significant stages of

two-electron oxidation and subsequent partial reduction of metalporphyrin was determined as well as acid–basic equilibria of peroxide. It is shown that the efficient catalysis of decomposition of hydrogen peroxide is determined by the degree of binding of porphyrin in a complex with metal, by the structure of the mixed coordination sphere, and by the mutual influence of the ligands; the compounds under study behave as catalases in living systems.

Investigation of the interactions between porphyrin molecules and protein surroundings in biological systems is an important research area in modern biochemistry. These interactions may proceed in various ways, e.g., through the formation of covalent bonds, by ionic association, as donor–acceptor interactions, or through hydrogen bonds between separate covalent-bound fragments.

Chapter 4 gives a systemic description of complexation properties of porphyrins and their ability to discern charged particles and small organic molecules.

Depending on the molecular structure and medium, NH bonds of the coordination nucleus of porphyrins are considered as localized or partially localized ones. Their delocalization may be caused by internal molecular effects, such as polarization of the molecule by substituents or by specifically nonplanar conformations of the macrocycle during solvation in solvents containing electron–donor components, by polymerization, sorption or transition to the solid state. The activation of NH bonds in porphyrin molecules is associated with drastic changes in the coordination nucleus reactivity.

Chapter 5 makes an analysis of the causes and pathways of activation of NH bonds with regard to the classification of porphyrins by their capability for NH activating. Some reliable quantitative criteria for determining the degree of NH activity were suggested for porphyrins and their analogues. Activation of NH bonds may manifest itself not only in the reactivity of porphyrin coordination nuclei but may lead to the reorganization of the  $\pi$ -chromophore and reacting sites and to tautomeric processes. Products of this reorganization are good models of supramolecular biological systems. Chemical activation of porphyrins is considered separately as a potent tool of controlling the activity of molecules along with biological aspects.

Chapter 6 reviews the latest achievements in the chemistry of macroheterocyclic compounds – structural analogs of porphyrin and hexapyrins. The aromas of various macro-cyclic molecules and their fragments were investigated in accordance with the geometric (EN, GEO, and HOMA) and magnetic (NICS) criteria based on experimental data and results of DFT quantum-chemical calculations. The coordination and biological properties of macroheterocyclic compounds and their complexes with metal cations are considered.

Chapter 7 presents the results of studies on the kinetics of photochemical reactions of biologically active pigments and related compounds with molecular oxygen.

Chapter 8 is devoted to the search of correlations of thermodynamic characteristics (the Gibbs energy and enthalpy and entropy constituents of the Gibbs energy) of solvation of molecules of drugs prepared by traditional experimental methods and their diffusive properties and biopharmaceutically important properties.

Chapters 9–11 deal with biodamage of materials (adhesion of microorganisms on the surface of materials), aspects of controlled release from polymer films and transport of water as a structurally sensitive process that characterizes the morphology of biodegradable polymer systems.

Chapters 12–14 discuss the development of an image analysis based method (direct tracking) for measuring the diameter of electrospun fiber, consider new trends and developments in image analysis of pore size distribution and present a detailed review of different

aspects of electrospinning biodegradable and biocompatible natural nanofibers.

This collection of papers dealing with the results of studies on various classes of biologically active compounds will add to understanding the problems of their reactivity and the nature of processes occurring in living objects with their participation.

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# 1 Synthetic and Natural Bacteriochlorins: Synthesis, Properties and Applications

M.A. Grin and A.F. Mironov

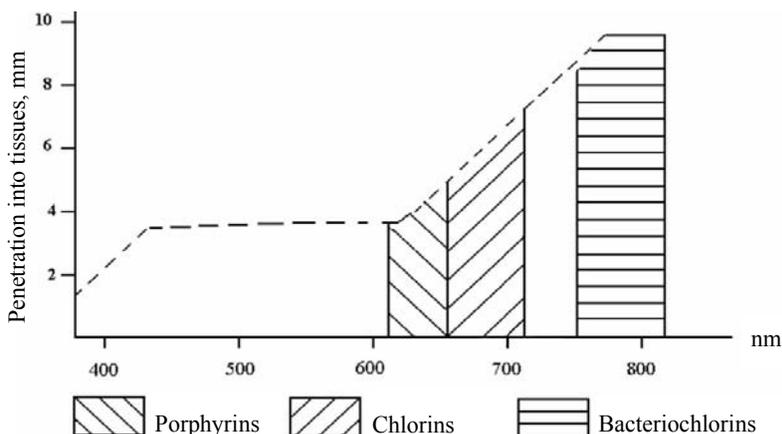
*Lomonosov Moscow State Academy of Fine Chemical Technology, 86 Vernadsky Prospekt, Moscow, 119571, Russia; email: [httos.mitht@g23.relcom.ru](mailto:httos.mitht@g23.relcom.ru)*

This chapter considers natural bacteriochlorins, their properties, isolation and chemical modifications. Part of the discussion is given to synthetic bacteriochlorins, with consideration of common and specific methods of producing these substances, their spectral and other physicochemical characteristics. Special attention is paid to the use of natural and synthetic bacteriochlorins in developing new-generation photosensitizers for photomedicine.

## Introduction

In the recent decade, attention of scientists, working in the field of developing new photosensitizers (PS) for photodynamic therapy (PDT) of cancer, has been focused on compounds with intensive absorption in the range of 770 up to 850 nm. The use of PS with this therapeutic window of absorption opens new possibilities for the diagnostics and treatment of malignant neoplasms. The light with these wavelengths scatters weakly and, therefore, can penetrate deeper into the tissue (Scheme 1) [1]. This is of special significance in pigmented tumors, for instance, melanoma. Besides, it is important that accessible and cheap semiconductor lasers can be used for this range.

Such compounds include derivatives of synthetic and natural bacteriochlorins. It is known that in porphyrin systems two peripheral double bonds in opposite pyrrole rings (B and D) are cross-conjugated, and their presence is not required for aromaticity to be preserved.



**Scheme 1** Dependence of the penetration of light into tissues on the wavelength.

In the reduction of one bond (dihydroporphyrins–chlorins) or both bonds (tetrahydroporphyrins–bacteriochlorins), aromaticity is preserved, and the change of symmetry leads to a bathochromic shift of the  $Q$  band. Figure 1 shows the real spectra of three compounds: porphyrin, chlorin and bacteriochlorin, which have the same *m*-hydroxyphenyl substituents in *meso*-positions of the macrocycle. Bacteriochlorins intensively absorb in the near IR region of the spectrum ( $\lambda_{\max} = 760\text{--}780\text{ nm}$ ,  $\epsilon = 4 \times 10^4\text{--}1 \times 10^5\text{ M}^{-1}\text{ cm}^{-1}$ ) [2] and, therefore, possess optimal properties for their use as photodynamic agents. Besides, they generate active oxygen species (AOS) with a high quantum yield, which depends on the nature of the central metal and peripheral substituents [3].

However, the macrocycle with two reduced double bonds is chemically unstable, therefore, derivatives of bacteriochlorophyll *a* are apt to be oxidized to respective chlorins and porphyrins. This fact largely restricts introduction of PS of bacteriochlorin series into clinical practice. A high hydrophobicity and related low solubility in polar solvents also complicate their use in medicine.

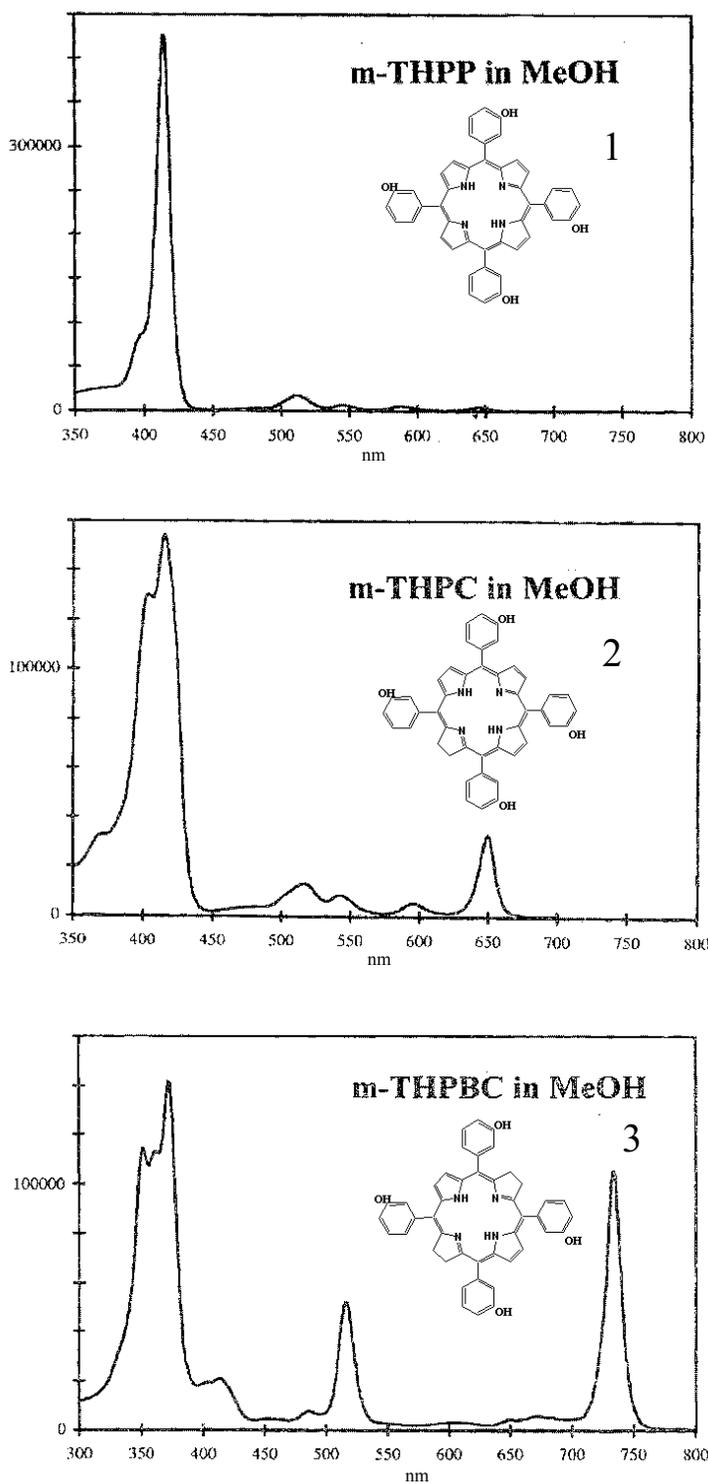
The main works on the chemical conversions of bacteriochlorophyll *a* (Bchl *a*) aim to increase the chemical stability and to develop water-soluble forms of bacteriochlorin photosensitizers.

Works on the chemical modification of bacteriochlorophyll *a* are comparatively a few. Major research in this field has been done at the Weizmann Institute of Science, Rehovot, Israel and Photodynamic Therapy Center, Roswell Park Cancer Institute, Buffalo, USA. Our group also does intensive research in this field, and major results will be presented in this review.

There are two approaches to production of bacteriochlorins. The synthetic way includes the reduction of double bonds in pyrrole rings B and D in porphyrins, and the semi-synthetic route is when bacteriochlorophylls isolated from natural sources are modified to increase their stability, improve the spectral characteristics and solubility in polar solvents.

## 1 Synthetic Bacteriochlorins

There are two approaches to the reduction of porphyrins to chlorins and bacteriochlorins. The first includes catalytic hydrogenation or treatment with metals in an alcohol medium



**Figure 1** Electronic spectra of porphyrin (1), chlorin (2) and bacteriochlorin (3).