THE BIOCHEMISTRY OF INORGANIC COMPOUNDS OF SULPHUR

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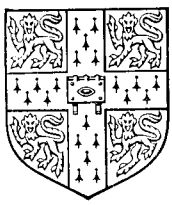

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PREFACE

The biochemistry of inorganic compounds of sulphur is an important topic which has many ramifications, the extent of which is only now being appreciated. Aside from their intrinsic academic interest, studies on the metabolism of inorganic sulphur compounds impinge directly upon such fields as the metabolism of steroids, diseases of the central nervous system, soil fertility, the corrosion of concrete, the origins of sulphide ore bodies and the early evolution of life.

These ramifications have provided a stimulus to research in the biochemistry of inorganic compounds of sulphur, a topic which might otherwise have suffered considerably in competition with the more fashionable fields of modern biology. As a result, the past decade or so has witnessed a remarkable increase in the published information on the metabolism of inorganic sulphur compounds. Several excellent reviews have, over the last few years, summarized various aspects of this subject but these have appeared in diverse medical, chemical, biological and industrial journals and we know of no recent publication embracing the broad field of the biochemistry of inorganic sulphur compounds.

The present monograph is an attempt to remedy this deficiency and to provide those with direct or fringe interests in sulphur biochemistry with a detailed account of the subject. Chapters on sulphur chemistry and methodology are included in the hope that the book may also prove to be a useful laboratory manual for research workers engaged in, and more particularly about to embark upon, experimental work in this field.

The book can conveniently be divided into four sections dealing with rather different aspects of the subject matter. After a general introduction, chapters 2 to 4 deal with the more chemical aspects of the subject; chapters 5 to 8 with investigations using more or less well characterized enzymes, chapters 9 to 11 with the metabolism of inorganic compounds of sulphur and finally chapters 12 and 13 consider what might be called the economic aspects of sulphur biochemistry.

Inorganic sulphur metabolism is, of course, intimately related to the metabolism of organic compounds of sulphur. The latter aspect, however, has been frequently discussed in general text books of biochemistry as well as in periodicals such as *Advances in Enzymology* and *Annual Reviews*. In this book, therefore, organic compounds of sulphur are largely ignored except in so far as is necessary for a full discussion of the metabolism of inorganic forms of the element.

We wish to thank our many friends and colleagues who have helped us in so many ways during the preparation of this book. In particular, Dr C. A. Appleby, Dr D. P. Kelly, Professor J. M. Swan and Dr A. E. R. Thomson deserve special mention for their most valuable criticisms of early drafts of several parts of the text. Dr R. G. Nicholls kindly helped us to prepare the subject index. We are also extremely grateful to Mrs E. Allen and Mrs L. Calis for their help, over several years, in ways too numerous to detail here, to Mrs A. Howard, Mrs V. Taylor and Mrs C. Pedersen for their skill in preparing the typescript, and to the latter and Miss A. Jerfy for their assistance with the onerous tasks of proof-reading and indexing. Without this assistance our book would certainly contain many more imperfections than those which, we fear, may still remain.

A.B.R.
P.A.T.

A NOTE ON THE NOMENCLATURE OF SULPHUR-CONTAINING COMPOUNDS

The naming of sulphur-containing organic compounds is complex and there was no internationally agreed system of nomenclature until the recent appearance of rulings on the subject (*Pure and Applied Chemistry*, **11**, 1965) from which this brief summary has been prepared. It provides only a guide to the nomenclature of the compounds whose biochemistry is to be discussed in this book and it is not a general summary of the subject.

The following list gives the chemical groupings with which we will be concerned together with the suffixes and prefixes to be used in forming the systematic names of compounds containing them.

Group	Suffix	Prefix
—SH	-thiol (or hydrosulphide)*	mercapto-
—S—SH	hydrodisulphide†	—
—S—S_n—SH	hydropolysulphide	—
—S—S—	disulphide	—
—S—S_n—S—	polysulphide	—
—SOH	-sulphenic acid	sulpheno-
—SO_2H	-sulphinic acid	sulphino-
—SO_3H	-sulphonic acid	sulpho-
—NH.SO_3^-	*N*- sulphamate	sulphoamino‡
—O.SO_3^-	sulphate	—
—S.SO_3^-	*S*- thiosulphate	*S*-sulpho-

In some cases another form of nomenclature is useful, particularly when it is wished to stress that a compound contains a chain of sulphur atoms as occurs, for instance, in some of the derivatives of the more complex sulphur acids. This nomenclature takes the sulphanes, HS.S_n.SH (disulphane, $n = 0$; trisulphane, $n = 1$; hexasulphane, $n = 4$; etc.) as

* The term thiophenol is permissible with derivatives of simple phenols.
† The term persulphide is frequently encountered in biochemical literature and will be used in this book.
‡ This name should strictly be applied only to the free acid and not to its salts.

the parent compounds and the more complex substances are named as derivatives of these. This nomenclature has been used in chapter 2 to stress the analogous reactions undergone by inorganic and organic compounds of sulphur, for example by disulphane and by alkyl disulphanes. (The latter compounds are usually called alkyl persulphides elsewhere in the text.) Examples of the use of this type of nomenclature are given in the following table.

$C_2H_5.S.SH$	Ethyl disulphane	Ethyl hydrosulphide
$C_6H_5.S.S_n.SH$	Phenyl polysulphane	Phenyl hydropolysulphide
$C_2H_5.S.S.C_2H_5$	Diethyl disulphane	Diethyl disulphide
$C_6H_5.S.S.S.C_6H_5$	Diphenyl trisulphane	Diphenyl trisulphide
$C_2H_5.S.SO_3^-$	Ethyl sulphosulphane	*S*-Ethyl thiosulphate
$C_6H_5.S.S.SO_3^-$	Phenyl sulphodisulphane	—

The last example, phenyl sulphodisulphane, may be given the alternative name of benzene sulphenyl thiosulphate. This is not a name recognized by the International Union of Pure and Applied Chemistry but nevertheless such nomenclature is sometimes useful. It can also be applied to thiosulphate esters to give the analogous term, sulphenyl sulphites.

This same 'sulphane' nomenclature can be used to name some inorganic compounds when it is again wished to stress that they contain a chain of sulphur atoms. For example:

$HO_3S.S.S.SO_3H$	Disulphodisulphane	Tetrathionic acid
$HO_3S.S.S.S.S.SO_3H$	Disulphotetrasulphane	Hexathionic acid

Unfortunately correct nomenclature has not been widely used in biochemical literature and if only the systematic names were used in this book then many of the compounds would appear in a most unfamiliar guise. Not many biochemists would at first sight recognize, for example, *S*-(2-amino-2-carboxyethyl) thiosulphate as *S*-sulphocysteine. In the following chapters of this book, therefore, the well-known trivial names have been used for many sulphur compounds (in a few instances more than one trivial name may have been used in different contexts) but the list at the end of this section will serve to provide the systematic names for these compounds. Other commonly used names, not necessarily adopted in this book, are also listed: in some cases these names are quite incorrect and if so, this is clearly indicated. It is to be hoped that in future works of this type it will be possible to use correct trivial names,

if not systematic names, for sulphur-containing compounds of biochemical interest.

Finally, the nomenclature of sulphate esters requires some comment. The term *O*-sulphate is frequently encountered in names such as choline *O*-sulphate (for choline sulphate ester) and serine *O*-sulphate (for serine 3-sulphate) to stress that these compounds contain the —O.SO_3^- grouping and are not to be confused with the corresponding salts of choline or of serine, nor with the sulphoamino derivative of the latter which contains the —NH.SO_3^- group. Undoubtedly the term *O*-sulphate is wrong and a more correct designation would seem to be *O*-sulphonate, as has been used to describe the appropriate derivatives of oximes which contain the grouping =N.O.SO_3^-, but this does not seem to be in accord with the recognized system of nomenclature. Likewise the term *N*-sulphate is incorrectly used to describe the sulphoamino group, —NH.SO_3^-. Unfortunately, however, these two terms appear to have become established in the biochemical literature and they have, where necessary, been used in this book. For example, they have been used to distinguish between the —O.SO_3^- and —NH.SO_3^- groups which occur in heparin.

The following list gives the systematic names of the sulphur-containing compounds of biochemical interest which are considered in subsequent chapters of this book. Those trivial names given in italics are those which have been used in subsequent discussions.

SYSTEMATIC NAME	TRIVIAL NAMES
Adenosine 3′-phosphate 5′-sulphatophosphate	*3′-Phosphoadenylyl sulphate* 3′-Phosphoadenosine 5′-phosphosulphate
Adenosine 5′-sulphatophosphate	*Adenylyl sulphate* Adenosine 5′-phosphosulphate
2-Amino-2-carboxyethanesulphenic acid	*Alanine 3-sulphenic acid* 3-Sulphenoalanine 3-Sulphenylalanine* Cysteine sulphenic acid*
2-Amino-2-carboxyethanesulphinic acid	*Alanine 3-sulphinic acid* 3-Sulphinoalanine 3-Sulphinylalanine* Cysteine sulphinic acid*
2-Amino-2-carboxyethanesulphonic acid	*Alanine 3-sulphonic acid* 3-Sulphoalanine 3-Sulphonylalanine* *Cysteic acid* Cysteine sulphonic acid*
2-Amino-2-carboxyethanethiosulphonic acid	*Alanine 3-thiosulphonic acid*

NOMENCLATURE OF SULPHUR-CONTAINING COMPOUNDS

SYSTEMATIC NAME	TRIVIAL NAMES
2-Amino-2-carboxyethyl hydrodisulphide	*Cysteine persulphide*†‡ Thiocysteine*
2-Amino-2-carboxyethyl sulphodisulphane	*Alanine sulphodisulphane* Cysteine sulphenyl thiosulphate*
S-(2-Amino-2-carboxyethyl) thiosulphate	*S-Sulphocysteine* Cysteine *S*-sulphonate*
Bis(2-Amino-2-carboxyethyl) trisulphide	*Thiocystine*†
2-Aminoethanesulphinic acid	*Hypotaurine*
2-Aminoethanesulphonic acid	*Taurine*
2-Aminoethanethiol	*Cysteamine*
2-Aminoethanethiosulphonic acid	*Thiotaurine*†
Bis(2-Aminoethyl) disulphide	*Cystamine*
2-Aminoethyl hydrodisulphide	*Cysteamine persulphide*†‡ Thiocysteamine*
2-Carboxy-2-oxoethanesulphinic acid	*3-Sulphinopyruvic acid* 3-Sulphinylpyruvic acid*
2-Hydroxyethanesulphonic acid	*Isethionic acid*

* These names are incorrect and should not be used.

† The use of these trivial names is not to be recommended. They have been adopted in the present instance because of the lack of any suitable alternatives.

‡ The corresponding derivatives of other thiols, such as glutathione and dihydrolipoic acid, are named analogously.

The anions of some oxy-acids of sulphur

SO_3^{2-}	sulphite
SO_4^{2-}	sulphate
$S_2O_2^{2-}$	thiosulphite
$S_2O_3^{2-}$	thiosulphate
$S_2O_4^{2-}$	dithionite (hydrosulphite)
$S_2O_5^{2-}$	metabisulphite
$S_2O_6^{2-}$	dithionate
$S_2O_7^{2-}$	pyrosulphate (disulphate)
$S_2O_8^{2-}$	persulphate
$S_3O_6^{2-}$	trithionate
$S_4O_6^{2-}$	tetrathionate
$S_5O_6^{2-}$	pentathionate
$S_6O_6^{2-}$	hexathionate

ABBREVIATIONS

ADP	Adenosine 5′-diphosphate
AMP	Adenosine 5′-phosphate, adenylic acid
APS	Adenylyl sulphate
APSe	Adenylyl selenate
APW	Adenylyl tungstate (hypothetical)
ATP	Adenosine 5′-triphosphate
BAL	2,3-Dimercaptopropanol
BVH	Reduced benzyl viologen
CTP	Cytidine triphosphate
DCIP	2′,6′-dichlorophenolindophenol
DNP	2,4-Dinitrophenol
EDTA	Ethylenediaminetetraacetate
FAD, $FADH_2$	Flavin-adenine dinucleotide (oxidized and reduced)
FMN, $FMNH_2$	Flavin mononucleotide (oxidized and reduced)
GSH, GSSG	Glutathione and oxidized glutathione
G-6-P	Glucose 6-phosphate
GTP	Guanosine triphosphate
MVH	Reduced methyl viologen
NAD^+, NADH	Nicotinamide-adenine dinucleotide (oxidized and reduced)
$NADP^+$, NADPH	Nicotinamide-adenine dinucleotide phosphate (oxidized and reduced)
NCS	Nitrocatechol sulphate
NEM	*N*-Ethylmaleimide
NP	*p*-Nitrophenol
NPS	*p*-Nitrophenyl sulphate
PAP	Adenosine 3′,5′-diphosphate
PAPS	3′-Phosphoadenylyl sulphate
PCMB	*p*-Chloromercuribenzoic acid
PMS	*N*-Methylphenazonium methosulphate
P_i	Orthophosphate ion
PP_i	Pyrophosphate ion
tris	2-Amino-2-hydroxymethyl-1,3-propanediol
UTP	Uridine triphosphate

LIST OF ENZYMES

The following list will serve to definitively identify most of the enzymes which are mentioned in the text. It cannot, however, detail all of them because some quite important enzymes (e.g. APS-reductase) have not been named by the Enzyme Commission. If, therefore, an enzyme is mentioned in the text but does not appear in the following list then it may be taken that it does not yet have a systematic name.

In the list are given the numbers assigned to the enzymes, their systematic names and some commonly used trivial names, the first of which is in each case that recommended by the Enzyme Commission. We have not adhered to this recommendation in all cases and the names used in this book are therefore given in italics.

Number	Systematic names	Trivial names
1.1.1.49	D-Glucose-6-phosphate: NADP oxidoreductase	*glucose-6-phosphate dehydrogenase*
1.2.1.12	D-Glyceraldehyde-3-phosphate: NAD oxidoreductase (phosphorylating)	*glyceraldehyde-3-phosphate dehydrogenase* triose phosphate dehydrogenase
1.6.4.2	Reduced-NAD(P): oxidized glutathione oxidoreductase	*glutathione reductase*
1.6.6.4	Reduced-NAD(P): nitrite oxidoreductase	*nitrite reductase**
1.6.99.2	Reduced-NAD(P): (acceptor) oxidoreductase	reduced NAD dehydrogenase *NADH oxidase*
1.7.99.1	Ammonia: (acceptor) oxidoreductase	*hydroxylamine reductase*
1.8.1.2	Hydrogen sulphide: NADP oxidoreductase	*sulphite reductase**
1.8.3.1	Sulphite: oxygen oxidoreductase	*sulphite oxidase**
1.9.3.1	Ferrocytochrome-*c*: oxygen oxidoreductase	*cytochrome oxidase*
1.9.6.1	Ferrocytochrome-*c*: nitrate oxidoreductase	nitrate reductase (cytochrome) *nitrate reductase*
1.12.1.1	Hydrogen: ferredoxin oxidoreductase	*hydrogenase*
2.7.1.25	ATP: adenylylsulphate 3′-phosphotransferase	adenylylsulphate kinase *APS-kinase* APS-phosphotransferase
2.7.4.3	ATP: AMP phosphotransferase	*adenylate kinase* myokinase
2.7.4.6	ATP: nucleosidediphosphate phosphotransferase	*nucleosidediphosphate kinase*
2.7.7.4	ATP: sulphate adenylyltransferase	sulphate adenylyltransferase *ATP-sulphurylase*

* These names are also used to describe enzymes which catalyse similar transformations of their substrates but which use electron acceptors or donors other than those listed here.

LIST OF ENZYMES

Number	Systematic names	Trivial names
2.7.7.5	ADP: sulphate adenylyltransferase	sulphate adenylyltransferase (ADP) *ADP-sulphurylase*
2.8.1.1	Thiosulphate: cyanide sulphurtransferase	thiosulphate sulphurtransferase *rhodanese*
2.8.1.2	3-Mercaptopyruvate: cyanide sulphurtransferase	*3-mercaptopyruvate sulphurtransferase*
2.8.2.1	3′-Phosphoadenylylsulphate: phenol sulphotransferase	aryl sulphotransferase *phenol sulphotransferase* phenol sulphokinase
2.8.2.2	3′-Phosphoadenylylsulphate: 3β-hydroxysteroid sulphotransferase	3β-hydroxysteroid sulphotransferase *steroid sulphotransferase* steroid sulphokinase
2.8.2.3	3′-Phosphoadenylylsulphate: arylamine sulphotransferase	*arylamine sulphotransferase* arylamine sulphokinase
2.8.2.4	3′-Phosphoadenylylsulphate: oestrone sulphotransferase	*oestrone sulphotransferase* oestrone sulphokinase
2.8.2.5	3′-Phosphoadenylylsulphate: chondroitin sulphotransferase	chondroitin sulphotransferase *mucopolysaccharide sulphotransferase*
3.1.3.5	5′-Ribonucleotide phosphohydrolase	*5′-nucleotidase*
3.1.3.6	3′-Ribonucleotide phosphohydrolase	*3′-nucleotidase*
3.1.6.1	Aryl-sulphate sulphohydrolase	*arylsulphatase* phenol sulphatase
3.1.6.2	Sterol-sulphate sulphohydrolase	sterol sulphatase *androstenolone sulphatase* steroid sulphatase 3β-steroid sulphatase
3.1.6.3	Sugar-sulphate sulphohydrolase	*glycosulphatase*
3.1.6.4	Chondroitin-sulphate sulphohydrolase	*chondrosulphatase*
3.1.6.6	choline-sulphate sulphohydrolase	*choline sulphatase*
3.1.6.7	Cellulose-sulphate sulphohydrolase	*cellulose sulphatase*
3.6.1.1	Pyrophosphate phosphohydrolase	inorganic pyrophosphatase *pyrophosphatase*
3.6.1.3	ATP phosphohydrolase	*ATPase*
4.1.1.12	L-Aspartate 4-carboxy-lyase	aspartate 4-decarboxylase *aspartate β-decarboxylase*
4.2.1.5	L-Homoserine hydro-lyase (deaminating)	homoserine dehydratase *cystathionase*
4.2.1.20	L-Serine hydro-lyase (adding indole)	*tryptophan synthase*
4.2.1.22	L-Serine hydro-lyase (adding hydrogen sulphide)	cysteine synthase *serine sulphhydrase*
4.2.99.6	Chondroitin-sulphate-lyase	chondroitin sulphate lyase *chondroitinase*
4.4.1.1	L-Cysteine hydrogensulphide-lyase (deaminating)	*cysteine desulphydrase* cysteine lyase