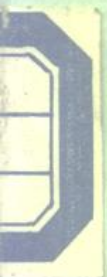
Chemical Sensors

edited by
T.E. EDMONDS



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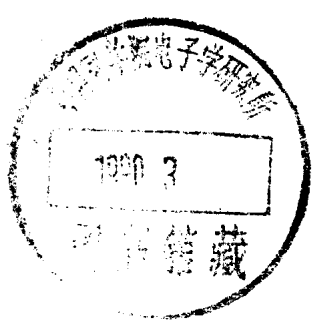

Blackie
Glasgow and London

Published in the USA by
Chapman and Hall
New York

Blackie and Son Ltd.
Bishopbriggs, Glasgow G64 2NZ
7 Leicester Place, London WC2H 7BP

Published in the USA by
Chapman and Hall
in association with Methuen, Inc.
29 West 35th Street, New York, NY 10001–2291

First published 1988

British Library Cataloguing in Publication Data

Chemical sensors.
1. Chemical detectors
I. Edmonds, T.E.
543 TP159.C46

ISBN 0–216–92255–0

Library of Congress Cataloging-in-Publication Data

Chemical sensors.

Includes bibliographies and index.
1. Chemical detectors. I: Edmonds, T.E.
TP159.C46C48 1987 660.2'8'00287 87–17841
ISBN 0–412–01601–X

Phototypeset at Thomson Press (India) Limited, New Delhi
Printed in Great Britain by Bell and Bain Ltd., Glasgow.

Preface

At the beginning of this book, and in the absence of guidance from IUPAC, it is appropriate to clarify the term 'chemical sensor'. A chemical sensor may be defined as a simple-to-use, robust device that is capable of reliable quantitative or qualitative recognition of atomic, molecular or ionic species. It is hard to imagine a field of applied chemistry in which a significant impact could not be made by such a device. Undoubtedly, it is this potential that has fuelled the contemporary preoccupation with chemical sensors. An unfortunate side-effect of this otherwise welcome interest is the use of the term 'chemical sensor' to add the chemical equivalent of a 'High-Tech gloss' to a rather ordinary device, publication, conference or research group. This loose usage of terminology is responsible in part for the ambiguity that surrounds many chemists' concepts of the form and function of chemical sensors. Further ambiguity arises from the extravagant claims that have been made for some sensors, and the impression that has been given of much 'verging-on-a-breakthrough' research. The research chemist engaged in sensor development should be mindful of the fact that the ultimate target for these devices is the real world, and that a successful laboratory device operating under well-defined conditions and careful calibration does not constitute a chemical sensor.

Research into chemical sensors is not a recent phenomenon; it has been under way for over 80 years. Indeed, two of the most successful devices, the glass pH electrode, and the non-dispersive infrared system, have been in routine use since the 1930s. Current research activity in sensors is more clearly identifiable, mainly because it is organized into coherent programmes, but the essential structure of a chemical sensor and the problems to be solved in developing one remain the same. A chemical sensor consists of two parts, a zone of selective chemistry, and a more or less non-specific transducer. The selective chemistry provides an interface between the transducer and a specific chemical parameter (usually concentration) of the target analyte. The function of this interface is twofold. Firstly, it must *selectively* interact with the target. Secondly, it must *transform* the desired chemical parameter into a chemical or physical signal to which the transducer responds. Clearly, the behaviour of the chemistry in this interface zone is of crucial importance to the overall performance of the sensor. Accordingly, the two major problems to be solved

in sensor research concern the development of the interface chemistry, and the localization of this chemistry in or on an appropriate transducer.

The layout of this book reflects the nature of the problems mentioned in the previous paragraph. Species recognition lies at the heart of chemical sensing, and fundamental approaches to this process are discussed in the first two sections. Molecular and ionic recognition is a primary biological process, and not surprisingly there is a range of chemistries that can be exploited for sensing: Part 1 deals with these. Part 2 consists of a review of the efforts of synthetic organic chemists to produce structures which react in a highly specific way with target species. The material of Part 3 takes up the themes of the previous chapters, but with a more practical emphasis. The chapters in this section are written by authors experienced in the application of specific chemistry. Each chapter reflects the contributor's knowledge of the realities of implementing their specialist chemistry, often coupled with their vision for its future development. The final two parts of the book deal with transducers: an arbitrary division has been made between electrochemical and other transducers. Although some of the chapters in these sections contain appropriate reviews of current applications of the subject transducer in chemical sensing, this is by no means the primary aim of the contribution. In each case the authors have attempted to give fundamental information relating to the *modus operandi* of the transducer; information that is intended to help the newcomer in assessing the applicability of a transducer to a particular sensing problem.

This book is intended to be a handbook, giving practical information to its readers, as well as supplying ideas for future use. A broad range of chemistries are drawn together in this volume, the chapters of which are written by authors from industrial, academic, clinical and government laboratories. It is not an up-to-the-minute review of every piece of chemical sensor research; that is a job best left to the specialist journals. Well-trodden paths have been deliberately avoided, as has the tendency to dwell on 'Friday afternoon laboratory curiosities' that work at the end of the week but fail on Monday. Finally, this book is a team effort, and I am grateful to all the contributors for their work, and to the publishers for their forbearance during the long gestation period. From a personal standpoint I am happy to acknowledge the help and guidance I have had from Professor T.S. West under whose supervision I embarked upon chemical sensor research in 1973. In the early stages of this book discussions with Dr J.F. Alder helped to sharpen my ideas on the objectives. His clarity of thought and his candour were most welcome. My family have supported me admirably during this time, and since in many respects the greatest beneficiaries of sensor research should be people like them who will experience improved health care and a cleaner and safer environment, I dedicate this book to Diana, Thomas and Matthew.

TEE

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1 MOLECULAR AND IONIC RECOGNITION BY BIOLOGICAL SYSTEMS

1 Molecular and ionic recognition by biological systems

L.J. KRICKA

1.1 Introduction

Recognition of a molecule by another molecule or group of molecules is a fundamental process of vital importance in all biological systems. Nature has evolved a vast array of biomolecules and biomolecular structures which exhibit an exquisite specificity in their molecular recognition properties.

Molecular recognition underlies many essential biological processes. For example, resistance to disease relies on the presence of antibody molecules which recognize and combine with specific molecules on the surface of an invading organism. Tissue is recognized by the immune system as compatible or incompatible (foreign) via tissue proteins coded by the genes of the Major Histocompatibility System. Olfaction and taste depend on the interaction of molecules with specific chemoreceptors and the subsequent neural coding of this information (1). Such biological systems provide the analyst with a rich source of molecules with specific binding properties, and some examples are listed in Table 1.1. By far the most important and versatile source are the immunoglobulins produced by the immune system, because it is possible to induce the production of specific immunoglobulins which will bind to a particular substance by immunizing animals with that substance. Many hundreds of different immunoglobulin molecules with diverse binding specificities have been produced in this way, and the technique has been refined through the development of monoclonal antibody technology (see section 1.3.1).

An effective sensor requires a molecular recognition component which is

Table 1.1 Range of molecules with molecular recognition properties and their specificities

Binder	Substance(s) bound
Immunoglobulins	Wide range of small and large molecules
Enzymes	Wide range of molecules
Lectins	Oligosaccharides
Receptors	Hormones
Avidin	Biotin
DNA	DNA, RNA
Protein A	IgG, IgM, IgA

capable of recognizing and binding one particular molecule amongst a mixture of molecules. The objective of this chapter is to survey the range of binding specificities of biomolecules and biomolecular structures (receptors) which may be useful as the molecular recognition component of a chemical sensor.

1.2 Characteristics of molecular recognition systems

1.2.1 *Specificity*

Ideally a molecular recognition system should exhibit specificity, i.e. it should only bind one particular molecule and not bind other types of molecules to any appreciable extent. This ideal is rarely achieved, and, in general, molecular recognition systems will bind a range of molecules; albeit to differing extents. For example, the enzyme glucose oxidase (EC 1.1.3.4) has specificity for beta-D-glucose which it binds and transforms to gluconolactone. However the enzyme will also bind other related substances such as 2-deoxy-D-glucose, 6-deoxy-6-fluoro-D-glucose, 6-methyl-D-glucose, and 4,6-dimethyl glucose (2). Characterization of the specificity of a particular binding system is an important prerequisite before it is used analytically. For the binding of antigens to immunoglobulins the degree of non-specificity in binding is measured by the 'cross-reactivity' of the immunoglobulin. Cross-reactivity is determined from results of competitive immunoassay standard curves obtained by incubating a limited amount of immunoglobulin and a fixed amount of labelled antigen with increasing amounts of the antigen or increasing amounts of the possible cross-reacting substance (3). Cross-reaction is then defined as the ratio of the weight of cross-reactant which reduces the binding of labelled antigen to 50% of the value in the absence of antigen (expressed as a percentage).

1.2.2 *Binding constants*

Interaction between a molecule (M) and a substance (B) with binding properties for that molecule can be described by the equation:

$$M + B \underset{k_2}{\overset{k_1}{\rightleftharpoons}} M{:}B$$

(k_1, rate of association; k_2, rate of dissociation). The affinity of the binder for the molecule is described by a binding constant (K) where:

$$K = [M{:}B]/[M][B] = k_2/k_1$$

For multivalent interactions (e.g. of antibodies with antigens) the term *avidity* has been introduced in order to emphasize the stabilization of complexes by

the multiple binding interactions. Binding constants vary widely, from 10^3 L M^{-1} for lectins, up to 10^{15} L M^{-1} for the avidin–biotin system.

1.2.3 *Chemical basis of binding*

Hydrophilic, hydrophobic and hydrogen bond interactions are all involved to varying extents in biomolecular binding reactions. The majority of work in this area has centred on the interaction of enzymes with their substrates and the binding of protein antigens to antibodies. Catalytically important amino acid residues in the active site have been determined for several enzymes (e.g. thermolysin) and enzyme–substrate binding interactions have been studied using molecular modelling systems (4, 5). X-ray analysis of several enzymes has revealed the presence of a cleft, crevice or depression in the globular protein structure. This is the site of the active centre of the enzyme which binds the substrate and mediates the metabolic transformation. Figure 1.1 illustrates structural data for the zinc metallo-enzyme carboxypeptidase A and shows the location of the key residuals Tyr 248, Glu 270, and Arg 145 in the active site.

The identification of which part of the surface of a protein (antigenic site, antigenic determinant or epitope) is in contact with the binding site of an antibody has received considerable attention. The antigenic site may be a continuous segment of polypeptide chain or may consist of two or more segments brought together in the tertiary structure of the protein. This latter type of antigenic site has been variously named as a neotope, topographical, conformation-dependent, or discontinuous determinant (6). Antigenic sites usually contain charged and polar amino acid residues (7, 8) although hydrophobic interactions also play a role in the binding reaction. Antigenically reactive regions of a protein are usually small, typically 6–7 amino acid residues. Binding to antibody is primarily via ionic reactions involving charged amino acids, with non-polar amino acids providing a stabilizing effect via hydrophobic interactions (7). Hydrophilic segments appear to be important in a wide range of protein macromolecule interactions (8); for example, complement binds to the most hydrophilic region of the Fc portion of an immunoglobulin (9), and DNA polymerase II binds to nucleic acids via its most hydrophilic segment (10).

1.3 Selected molecular and ionic recognition systems

1.3.1 *Antibodies*

The immune system is a highly developed and efficient molecular recognition system which has been extensively exploited for the production of antibodies with specific binding properties. *In vivo* a foreign molecule (an immunogen) induces B lymphocytes to proliferate and differentiate into plasma cells which

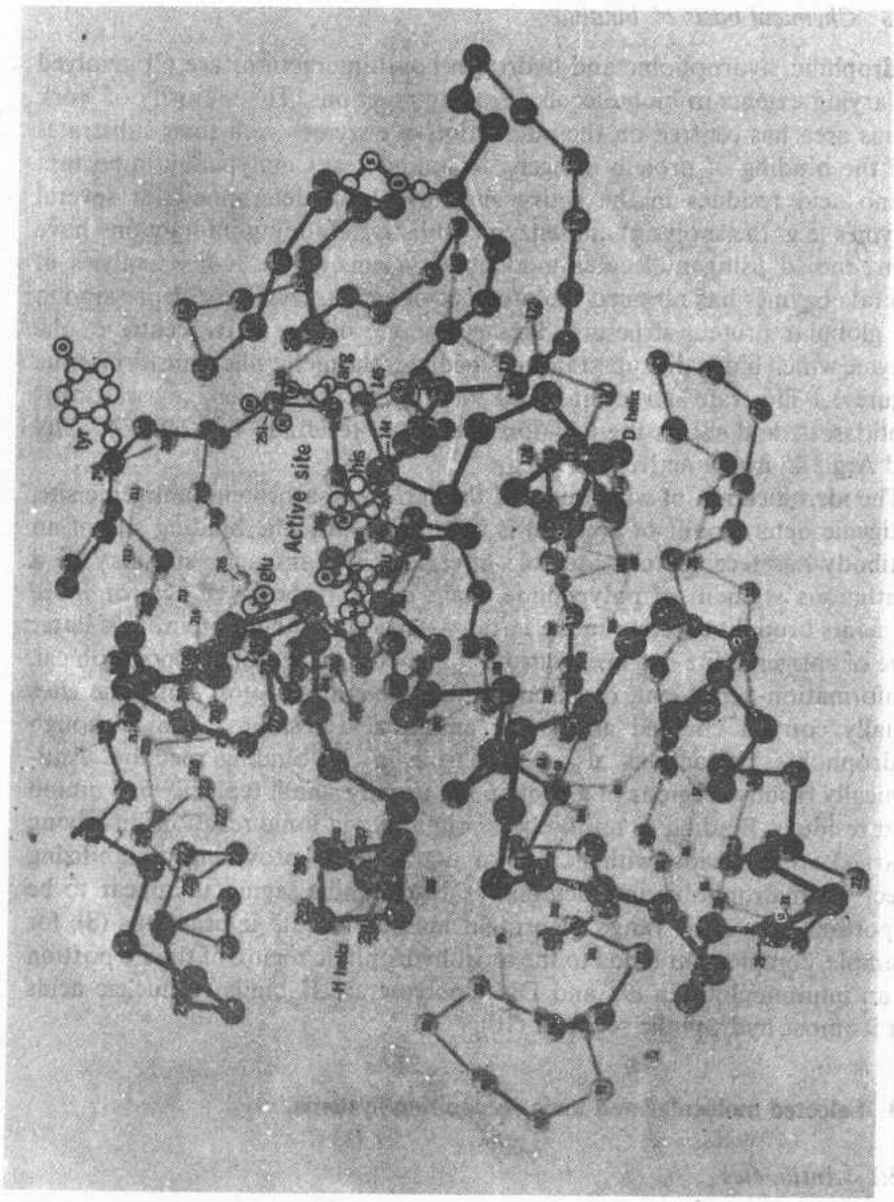

Figure 1.1 Structure of main chain of carboxypeptidase A showing location of the active site and the side chains of the active residues Tyr 248, Glu 270, and Arg 145. (Reproduced with permission from R.E. Dickerson and I. Geis (1970), *The Structure and Action of Proteins*, Harper and Row, New York.)