

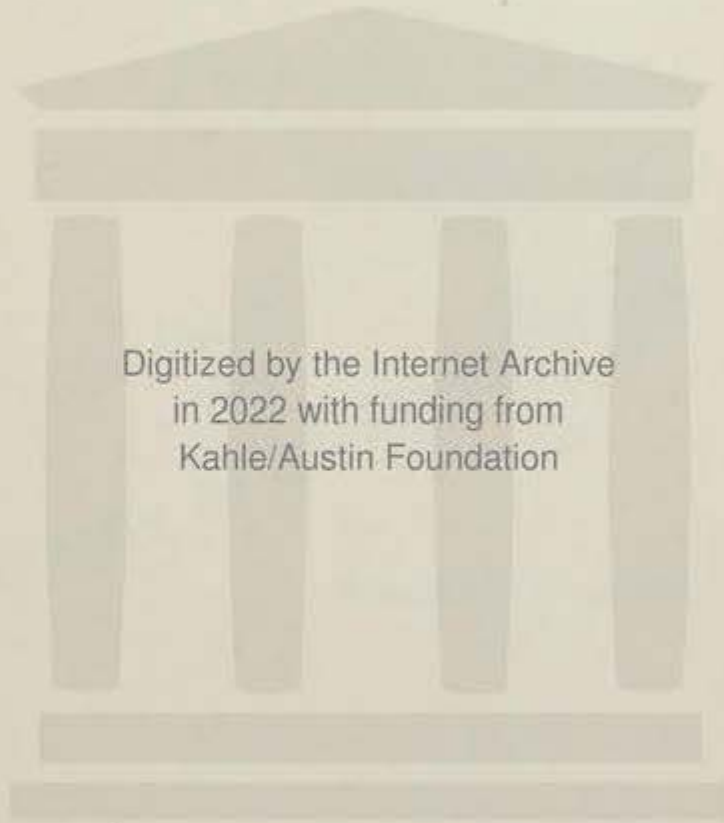
AMERICAN PHARMACEUTICAL ASSOCIATION / ACADEMY OF PHARMACEUTICAL SCIENCES

Design of
Biopharmaceutical
Properties through
Prodrugs and
Analogs

Edward B. Roche, *Editor*

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** Design of*
Biopharmaceutical
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Published by
AMERICAN PHARMACEUTICAL ASSOCIATION
ACADEMY OF PHARMACEUTICAL SCIENCES
2215 Constitution Avenue, N.W.
Washington, DC 20037

A Symposium

Sponsored by
Medicinal Chemistry Section

APhA ACADEMY OF PHARMACEUTICAL SCIENCES

November 1976 National Meeting

Orlando, Florida

International Standard Book Number: 0-917330-16-1
Library of Congress Catalog Card Number: 77-81663

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AMERICAN PHARMACEUTICAL ASSOCIATION

2215 Constitution Avenue, N.W.
Washington, DC 20037

Printed in the United States of America

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PREFACE

This volume contains the papers presented during the symposium on the Design of Biopharmaceutical Properties Through Prodrugs and Analogs held in Orlando, Florida, November 16 and 17, 1976. This symposium was sponsored by the Medicinal Chemistry Section of the APhA Academy of Pharmaceutical Sciences, and was held as part of the 21st National Meeting of the APhA/APS. The program was intended to provide a rather broad coverage of the subject. As the title indicates, authors were allowed the latitude to describe the development of both prodrugs and analogs having specific effects on absorption, distribution, metabolism, and excretion.

The first chapter provides a suitable overview of the general symposium topic. This is followed by a chapter considering drug-receptor interactions. This current state-of-the-art approach provides the necessary awareness of the fact that during the design of biopharmaceutical properties, those structural features required for eliciting the response in the target tissue must be maintained.

The third chapter provides a review and a functional classification of groups or substituents which provide varying degrees of selective distribution to target tissues. The intention was to provide a background in physicochemical and biochemical properties important to selectivity. The next two chapters describe quantitative approaches to analyzing the effects of substituents on the distribution properties and actions of drugs.

The sixth chapter discusses the effects of structure on pharmacokinetics. The emphasis is on prodrugs and problems associated with measuring active and inactive forms of a drug. The next two chapters describe approaches to the control of drug transport across membranes. The first of these describes a novel approach to the development of polar character in amine drugs, while the latter discusses the improvement of intestinal absorption using a physical model.

The topics of *in vitro* and *in vivo* stability are presented in the next four chapters. Chapter 9 discusses the use of substituent constants as a means of predicting chemical stability of drug systems. Chapter 10 describes the application of structural specificities for various enzyme systems to the design of prodrugs. The design of structural features affecting drug metabolism is approached through the ideas presented in Chapter 11. Examples of the use of physical organic principles in the design of prodrugs are discussed in Chapter 12.

Aspects of drug solubility, topical absorption, and the design of taste properties round out the symposium, and comprise the last three chapters.

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Chapter 1
PERSPECTIVE ON PRODRUGS AND ANALOGS IN DRUG DESIGN
Anthony A. Sinkula

This volume presents the basic principles of organic, physical, and biochemistry which are important to the design of biopharmaceutical properties, and illustrates these principles with many examples. The authors have presented the reader with sufficient information to understand the concepts, and to initiate research in this important area of drug design.

I would like to take this opportunity to thank Dr. Walt Morozowich for his extremely valuable discussions and assistance in organizing this symposium. My thanks also goes to the participants for their efforts during the symposium and their diligence in submitting manuscripts for this publication. A special note of thanks is given to Mrs. Sue McQuade for her secretarial assistance in preparing this volume. I would also like to acknowledge and thank Mr. Walid Al-Turk and my wife, Vickie, for their assistance in preparing the index.

University of Nebraska
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May 13, 1977

Edward B. Roche

The alteration of bio-pharmaceutical properties by the use of prodrugs and analogs for improvement of drug delivery is of extreme interest to a growing number of pharmaceutical scientists. Eloquent testimony for this premise is evident by the number and diversity of subjects that will be discussed during the course of this symposium. The term bio-pharmaceutical property is somewhat general in meaning and can perhaps be separated into pharmaceutical (physicochemical) and biological components. The pharmaceutical aspects of the definition include considerations such as solubility, stability and related physicochemical phenomena responsible for pharmaceutical elegance (taste, odor, patient acceptance). Alteration in biological properties by the use of prodrugs and analogs result in significant clinical improvement of the drug.

The Analog

In the case of the analog, biological alteration can be manifested by enhancement of potency, spectrum of activity and increase of the therapeutic ratio. In certain situations, however, analogs have been utilized to enhance bio-pharmaceutical properties other than those mentioned above. A comparison of selected antidiabetic sulfonylurea analogs, for example, exhibited significantly different duration of effect characteristics. The duration of activity of several of these sulfonylureas is variable and most probably is dependent on a variety of factors such as degree and rate of absorption, volume of distribution, extent of metabolism and excretion rate. Perhaps the most important parameter affecting duration is metabolism. Tolbutamide is rapidly oxidized to the inactive p-carboxy metabolite (1) with a metabolic half-life of approximately five hours (2). A single dose of tolbutamide which produces an effective hypoglycemic response lasts about seven hours in man. The half-life of chlorpropamide, on the other hand, is about 35 hours and that of carbutamide 40 hours. There is little correlation of serum half-life with volume of distribution (3). Excretion of chlorpropamide is relatively slow (96 hours for 80-90% of a single dose to be excreted in urine) with total elimination taking 3-7 days. Its peak hypoglycemic effect is retarded (3-6 hours) and persists for ~24 hours.

The duration of effect of carbutamide is dependent on its rate of acetylation and excretion. In diabetics a satisfactory reduction in blood-sugar levels lasts for up to 24 hours (4). Acetohexamide has a half-life of about one hour and duration of effect of 12-24 hours (5). The metabolically reduced form of acetohexamide, p- α -hydroxyethylhexamide however, has a half-life of 4-6 hours and possesses equal or greater hypoglycemic activity than acetohexamide and may be responsible for its longer duration of activity (6). Similarly, the longer duration of effect seen with the 15-methyl prostaglandins vs. the nor methyl prostaglandins is probably also due to inhibition of metabolism (7). Another bio-pharmaceutical property that has been modified via the analog approach is absorption. Clindamycin [7(S)-chloro-7-deoxylincomycin] hydrochloride is a semisynthetic antibiotic derived from lincomycin. Its activity against gram-positive aerobes and gram-positive and gram-negative anaerobic pathogens is greater than that of lincomycin. Clindamycin is well absorbed from the GI tract and produces

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Chapter 4

STRUCTURAL EFFECTS OF PARTITIONING BEHAVIOR OF DRUGS

William J. Dunn, III

Researchers in pharmaceutical sciences, whether they be in medicinal chemistry, pharmaceuticals or pharmacokinetics, have always been aware of the role that physical properties play in determining a desired biological response. Such effects as protein binding, distribution and excretion, all of which play a major role in determining the therapeutic efficacy of a drug, are dependent upon the physical properties associated with the molecular structure of the drug.

Various relationships between response and physical properties have been proposed to account for changes in biological activity when physical properties of drugs are systematically altered (1,2,3,4). In all these approaches lipophilicity occupies a dominant role in determining drug action. A striking example of this has recently been reported by Fowler and co-workers (5) who used C-11 labeled aliphatic amines to determine their uptake in lungs of mice. Their results are shown graphically below.

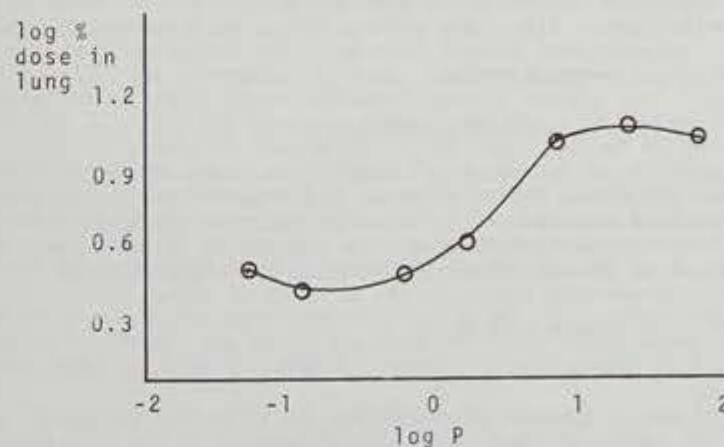
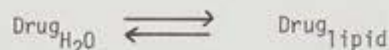


Fig. 1 Accumulation of amines in rat lung

Lipophilicity can be considered as the relative affinity of a substance for the lipoidal phases of a biosystem with which the drug interacts. It is quantitatively defined in terms of the equilibrium below in which the drug equilibrates between the aqueous and lipid phases. From



this the equilibrium constant, P, or partition coefficient is defined as

$$P = \frac{[\text{Drug}]_{\text{lipid}}}{[\text{Drug}]_{\text{H}_2\text{O}}}$$

where P is a ratio of concentrations. Since P in actuality cannot be determined between lipid and water, a model for the lipid phase is required. Model systems which have been proposed are benzene, chloroform, cyclohexane, 1-octanol, etc. Also consistency with the concentration units is necessary since P may be reported in molar or mole fraction units. Comparing partition coefficients on different concentration scales can lead to errors (6). In this review the model solvent for lipoidal phases will be 1-octanol and P will be expressed in molar concentration terms. There are disadvantages to this convention and these have been pointed out (6).

A convenient property of the partition coefficient, since it is related to the molar free energy of the substance, is that it is an additive-constitutive function of molecular structure. This has been expressed by Hansch and the π constant approach (7), by Higuchi and his co-workers in their F group contribution approach (8), by Nys and Rekker (9,10) and their fragment constant approach and by Hopfinger and Battershell (11) and their solvent dependent conformational analysis approach, (SCAP). In comparing these, the π , group contribution and fragment constant approaches are, for the most part semiempirical, while the SCAP approach to lipophilicity is more theoretically based. All of the methods listed can be used, with some limitations, to estimate drug lipophilicities. This review will, however, focus on the fragment constant method.

Fragment Constants

In an examination of the additive constitutive nature of the partition coefficient, Nys and Rekker (9,10) observed that some of the non-additive effects that had been proposed earlier were the result of inappropriate application of equation which defines π . Nys and Rekker (9,10) adopted an empirical approach to the estimation of partition coefficients based on EQ. 2 below

$$\log P = \sum_{n=1}^n a_n f_n$$

(EQ. 2)

where f_n are defined as fragment constants for the molecular fragments, n ; a_n represents the number of times this fragment appears in the structure. By assuming this model and analyzing 198 partition values for 154 structures which were mono-, diortho, dimeta and dipara benzenes, a set of fragment

constants was derived. This set of fragment constants was then used to derive a more comprehensive set.

This method of derivation is significant in that the constants derived are statistically based and each constant is the resultant of several partition values. The resulting set is not subject to error that may be present in one defined on the basis of a single observation. It is also important that 33 diortho substituted benzenes were included with none of them exhibiting non-additive behavior. No benzoic acids were included, however.

The low error associated with each value makes possible the detection of deviations from additivity that may result from intramolecular interactions. Such interactions as hydrogen bonding, steric shielding or an electronic effect may cause irregular solvation and may lead to non-additivity. In such cases corrections must be applied. Such irregularities in partitioning behavior were observed and appropriate correction factors are given in Table II.

A similar treatment of aliphatic and heterocyclic structures yielded other fragment constants which can be used to estimate partitioning behavior of a large number of structures (10).

One result of this study by Nys and Rekker was the prediction that the hydrogen atom in a structure contributed significantly toward partitioning behavior and the fragment constant for this contribution was 0.19. Leo, Jow, Silipo and Hansch (12) confirmed this by determining the partition coefficient for H_2 to be 0.45 (± 0.01). Also determined for a number of other molecules were partition coefficients which had proven to be experimentally difficult. These were low molecular weight hydrocarbons and alcohols such as methane, ethane, propane, butane, methanol and propanol.

Based on the partition coefficients of hydrogen, methane and ethane, a set of constants for the H, CH_3 and CH_2 fragments were determined.

The constants determined by these two groups are given in Table I. A comparison of the aliphatic carbon fragments reveals that those proposed by Leo, et al., (12) are somewhat higher than those of Nys and Rekker (9, 10). This difference is the result of the basis sets of molecules from which the fragments were calculated. The origin of this difference can be illustrated by considering Fig. 2 which is a plot of $\Delta \log P/C$ as a function of the number carbon atoms for a series of alkyl amines and 1-alkanols. It can be seen that for the molecules containing one and two carbon atoms there is not a constant contribution to partitioning behavior for each carbon atom. After the third carbon is added to the substance each resulting methylene group makes a constant contribution. Leo et al. (12) define fragment constants in the former region of the curve with the result being that a correction factor must be included for each aliphatic carbon after the first two.

Table I
Compilation of f values

Fragment	f ^a (Nys & Rekker)		f(Leo, et al.)	
	Aliphat.	Aromat.	Aliphat.	Aromat.
H		0.19		0.23
CH ₃		0.70		0.89
CH ₂		0.52		0.66
CH		0.24		0.43
C		0.14		0.20
CH ₂ =CH		0.93		
CH=C		0.51		
F	-0.51	0.42	-0.38	0.37
Cl	0.06	0.93	0.06	0.94
Br	0.24	1.17	0.20	1.09
I	0.59	1.46	0.60	1.35
OH	-1.44	-0.37	-1.64	-0.40
O	-1.54	-0.46	-1.81	-0.57
COOH	-1.00	0.00	-1.09	-0.03
COO	-1.28	-0.40	-1.49	-0.56
NH ₂	-1.38	-0.91	-1.54	-1.00
NH	-1.86	-0.93	-2.11	-1.03
N	-2.13	-1.07		
OCH ₂ COOH		1.21		
NO ₂	-1.06	-0.09	-1.26	-0.02
CONH ₂	-1.99	-1.26	-2.18	-1.26
C=O	-1.69	-0.99	-1.90	-0.32
CF ₃		1.28		
CN	-1.13	-0.20	-1.28	-0.34
SH	0.00	0.62		
S	-0.51	0.14	-0.79	0.03
OCH ₃	-0.83	0.24		
C ₆ H ₅		1.90		1.90
C ₆ H ₄		1.73		
C ₆ H ₃		1.48		
C ₁₀ H ₇ (naphthalenyl)		3.17		
C ₅ H ₄ N (pyridinyl)		0.54		
C ₄ H ₃ O (furanyl)		1.22		
C ₄ H ₃ S (thienyl)		1.62		
C ₄ H ₄ N (pyrrolyl)		0.59		

Table I cont'd
Compilation of f values

Fragment	f ^a (Nys & Rekker)		f(Leo, et al.)	
	Aliphat.	Aromat.	Aliphat.	Aromat.
C ₉ H ₇ N (quinolinyl)		1.85		
{NH}		-0.60		
{S}		0.44		
{O}		0.10		
{N}		-0.98		
CH _{Ar}		0.34		
C _{Ar}		0.30		
C _{Ar}		0.15		

a) Rounded off to two significant figures.

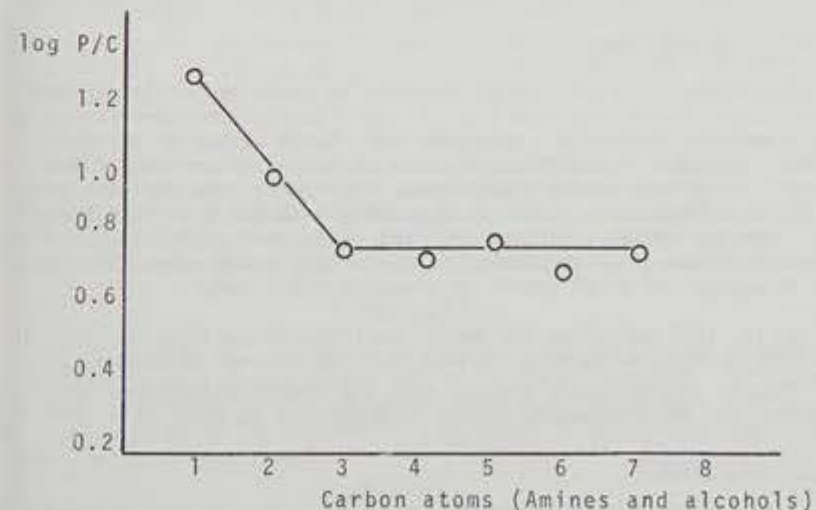


Fig. 2 Change in log P as a function of number of carbon atoms in alkyl amines and alcohols.

Table II
Proximity Effects

Interacting Groups		Number of Separating C's	Proximity Effects
HO	COOH	1	0.78
HO	COOH	1	0.85
HO	COOH	1	0.70
O	O	1	0.88
HOOC	COOH	2	0.33
HO	NH	2	0.39
HO	NH ₂	2	0.48
O	O	2	0.49
HO	NH	2	0.47

Methyl and Methylene Fragments

The contribution to partitioning behavior by these two fragments are the most studied. In earlier work their lipophilic contributions were considered equivalent. Davis (13), on examining a large number of partition coefficients concluded that the contribution of the methyl and methylene groups were similar in aromatic substituents, but found that the terminal methyl group contribution in aliphatic systems was larger than that for a methylene. Nys and Rekker concluded that the methyl and methylene contributions were different with the methyl larger. Each group makes the same contribution whether in an aliphatic or aromatic substituent.

Leo, et al. (12) calculate the methyl contribution as $f_{CH_3} = \frac{1}{2} \log P_{CH_3CH_3} = 0.91$ or $f_{CH_3} = \log P_{CH_4} - f_H = 0.86$. The average of 0.89 is adopted. This is significantly greater than the contribution found by Nys and Rekker and the difference arises as discussed earlier.

Aromatic Carbon Fragments

Nys and Rekker have proposed that carbon atoms in aromatic systems can contribute to lipophilicity differently depending upon their degree of substitution. This led to the different fragments for $C_6H(n=3,4)$ in

Table I. For fused ring hydrocarbon groups the CH_{Ar} , C_{Ar} (C-X group) and C_{Ar} (ring juncture carbons) fragments were proposed. Also fragments for the naphthalenyl ($C_{10}H_7$) group were derived.

Halogen and Polar Fragments

The halogens contribute differently to lipophilicity depending on their environment. The contribution in aromatic systems is generally greater than in aliphatic ones. There also is a relationship between volume of the halogen and lipophilicity. Davis also has pointed out that a specific solvent effect is associated with the fluoro group (13). Such conclusions are based on enthalpy and entropy calculations and, as Davis points out, such determinations would be helpful in establishing mechanistic explanations for partitioning behavior.

Hydrogen bonding and polar groups such as the hydroxyl, carboxamide, carbonyl, cyano or amino can be used to lower lipophilicity as all have negative contributions to this property.

Of the groups capable of significant ionization, only the carboxyl and carboxylate groups have been assigned fragment constants. The quaternary nitrogen contribution has not been determined due to the lack of reliable partition values for molecules containing this group.

Nonadditive Effects

With a minimum of experience in estimating structural effects on lipophilicity, it becomes obvious that the additivity assumptions breakdown. Such effects can result from: 1) intramolecular hydrogen bonding, 2) steric interactions and 3) electronic interactions such as induction or resonance. In order to obtain reliable estimates of partitioning behavior in molecules where such interactions are possible it is necessary that correction factors be applied in order to compensate for the non-additivity.

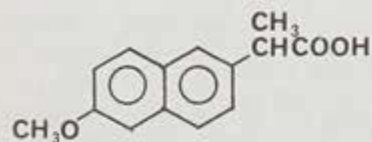
Those nonadditive effects that have been reliably determined are given in Table II and result from intramolecular hydrogen bonding and electronic effects. Intramolecular hydrogen bonding generally leads to an increase in lipophilicity, the effect tending to decrease as a function of the number of carbon atoms between the donor and acceptor atoms increases. Steric effects are poorly understood and difficult to assess quantitatively.

Applications

To illustrate the use of the fragment constant approach to estimating the log of the partition coefficient, drugs whose partition coefficients have been determined in our laboratory have been chosen as examples. In some cases the drugs are capable of ionization in which case log P for the neutral form is calculated.

Naproxen (I)

Naproxen is an experimental nonsteroidal antiinflammatory agent contain-



I

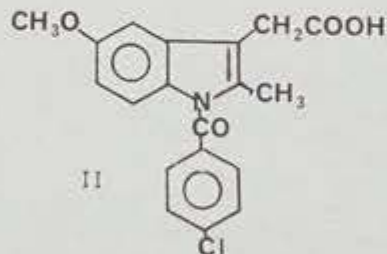
ing an aromatic naphthyl fragment. Using it and the fragment for the neutral carboxyl fragment its log P is estimated by the equation below.

$$\begin{aligned}\text{Log } P &= f_{C_{10}H_7} - f_H + 2f_{CH_3} + \\ &\quad f_{-O-} + f_{CH} + f_{COOH} \\ &= 3.17 - 0.19 + 1.40 - \\ &\quad 0.46 + 0.24 - 1.00 \\ &= 3.16\end{aligned}\quad (\text{EQ. 3})$$

To obtain the contributions of the $C_{10}H_6$ (naphthyl) group the contribution for H is subtracted. The value of log P = 3.16 compares well with the experimental value of 3.18.

Indomethacin (II)

This substance presents a problem in that no fragment constant is available for the indolyl fragment and it must be calculated from aromatic carbon fragments and a heterocyclic nitrogen (NH) contribution. The result is given in EQ. 4.



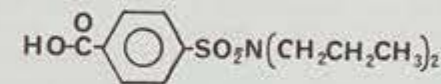
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$$\begin{aligned}\text{Log } P &= 3f_{CH_{Ar}} + 3f_{C_{Ar}} + 2f_{C_{Ar}} + 2f_{CH_3} + f_{-O-} + f_{CH_2} + f_{COOH} + f_{(NH)} - \\ &\quad f_H + f_{CO} + f_{C_6H_4} + f_{Cl} \\ &= 1.02 + 0.48 + 0.60 + 1.40 - 0.60 + 0.53 - 1.00 - 0.60 - 0.19 \\ &\quad - 0.99 + 1.73 + 0.93 \\ &= 2.91\end{aligned}\quad (\text{EQ. 4})$$

Although slightly lower than the experimental value of 3.08, the estimated value of 2.91 is acceptable.

Probenecid (III)

In order to estimate the log P for this substance, f_{-SONH} was required. From partition values of benzene-sulfonamides a value of $f_{-SONH_2} = -1.56$ was calculated. By subtracting the contribution of two H's the result was used in EQ. 5.



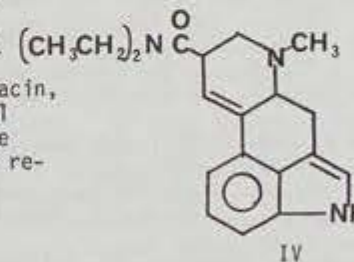
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$$\begin{aligned}\text{Log } P &= f_{COOH} + f_{C_6H_4} + f_{SO_2NH_2} - 2f_H + 4f_{CH_2} + 2f_{CH_3} \\ &= 0.00 + 1.73 - 1.56 - 0.38 + 2.12 + 1.40 \\ &= 3.31\end{aligned}\quad (\text{EQ. 5})$$

The experimental value is 3.21.

Lysergic Acid Diethylamide (IV)

As in the case of indomethacin, the contribution for the indolyl fragment was calculated from the aromatic carbon fragments. The result is given in EQ. 6.



IV

$$\begin{aligned}\text{Log } P &= 4f_{CH_{Ar}} + 2f_{C_{Ar}} + 2f_{C_{Ar}} + f_{(NH)} + f_{CH=CH_2} - 2f_H + 4f_{CH_2} + \\ &\quad 2f_{CH} + f_N + 3f_{CH_3} + f_{CONH_2} - 2f_H \\ &= 1.36 + 0.60 + 0.32 - 0.60 + 0.93 - 0.38 + 2.12 + 0.48 - \\ &\quad 1.99 - 0.38 + 2.10 - 2.13 \\ &= 2.43\end{aligned}\quad (\text{EQ. 6})$$

The experimental value is 2.96 which is higher than expected. The deviation of +0.53 is similar to what may result from an intramolecular interaction which would result in shielding of one of the polar groups in the molecule. Examination of a CPK model of the active form of IV indicates that such an interaction between the amino-nitrogen and carbonyl group is possible and probable.

This example illustrates the difficulties that can be encountered when attempting to assess structural effects on partitioning behavior. The fragment constant approach is a straightforward method which can be used to determine partition coefficients for a large number of molecules. There are limitations to applying it generally since the factors which can lead to nonadditivity are not well understood. More work needs to be done on the theoretical aspects of the partitioning process to answer such questions as how, mechanistically, such interactions as those possible in LSD can lead to greater than expected partition coefficients.

The future direction of work in the partitioning process will undoubtedly extend into the area of developing methods of estimation of partition coefficients by automation. The fragment constant approach is well suited for such calculations.

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Chapter 5

CORRELATION ANALYSIS IN THE DESIGN OF PHARMACODYNAMIC PROPERTIES OF DRUGS

Corwin Hansch

Introduction

In a recent lecture, Michael Tute noted that his first boss said, "SAR* was only fit for discussion between consenting adults in private". Mores in medicinal chemistry have been changing rapidly in recent years. With the use of more powerful methods of analysis, SAR is evolving into QSAR (quantitative SAR). We can now make much more objective comparison of various SAR models with the hope of allowing discussion of SAR in the most circumspect circles of society.

Many ways are under study to uncover new types of drugs. An approach which seems attractive to me is that of the regulation of enzymes by selective inhibitors. There are fine examples of success in this approach and, no doubt, many unrecorded instances of failure. The successes up to the present have been achieved without the benefit of x-ray structures of enzymes and isozymes. The science of x-ray crystallography is now moving so rapidly with so many laboratories working out structures of enzymes and other macromolecules that it seems inevitable this new information must have importance for the drug designer. We have therefore been devoting attention to the formulation of enzymic QSAR (1,2) from data obtained from purified enzymes. The molecular probes used with the enzymes or similar ones can then be used in living systems to compare enzyme function in the purified and natural states. Almost nothing is known at present as to whether or not enzymes *in situ* have the same conformation and activity as their purified forms in buffer solution. Hopefully, information gleaned from such a mapping program will contribute to our general understanding of the interaction of drugs with their macromolecular receptors.

Nonspecific Interactions between Mini- and Macromolecules

In the past 15 years it has become abundantly clear that the binding of small organic compounds with proteins and enzymes can often be correlated with the hydrophobic parameters $\log P$ and π from the octanol/water

*Structure-activity relationship.