THE HYDROPHOBIC FRAGMENTAL CONSTANT

Its Derivation and Application
A Means of Characterizing Membrane Systems

ROELOF F. REKKER

Gist-Brocades R & D, Haarlem, and Vrije Universiteit, Amsterdam

ELSEVIER SCIENTIFIC PUBLISHING COMPANY
Amsterdam — Oxford — New York 1977
PART I

THE HYDROPHOBIC FRAGMENTAL CONSTANT AND ITS APPLICATION IN THE CALCULATION OF PARTITION COEFFICIENTS OF ORGANIC STRUCTURES IN THE OCTANOL - WATER SYSTEM

Chapter I. THE PARTITION COEFFICIENT

| Introduction; the importance of partition coefficients in Structure - Activity Relationships | 1 |
| The NERNST law | 4 |
| Measurements of partition coefficients | 5 |
| Partitioning procedure | 5 |
| Temperature | 5 |
| Purity of solutes | 6 |
| Dissolution | 6 |
| Volatile solutes | 6 |
| Purity of solvents | 6 |
| Analysis | 8 |
| Spectrophotometric analysis | 8 |
| Gas-Liquid Chromatographic analysis | 9 |
| Other methods of analysis | 9 |
| Micellar properties of some compounds | 10 |
| Influence of dimerization and dissociation on the partition value | 10 |
| Special methods for measuring partition values | 17 |
| The AKUFVE system | 17 |
| Simultaneous determination of the partition coefficient and acidity constant of a substance | 18 |
| Determination of lipophilicities using Reversed-Phase Thin-Layer Chromatography | 19 |
| Determination of partition coefficients by High-Pressure Liquid Chromatography | 21 |
| References | 22 |

Chapter II. CALCULATION OF PARTITION COEFFICIENTS IN THE OCTANOL - WATER SYSTEM BY USING THE $\pi$-METHOD

| The HANSCH equation; the hydrophobic substituent constant, $\pi$ | 25 |
Chapter III. THE HYDROPHOBIC FRAGMENTAL CONSTANT, $f$

Introduction

Aliphatic structures

Primary set of $f$ values

Secondary set of $f$ values

Lipophilicity and folding

Aromatic structures

Substituted benzene derivatives with at least one saturated C link between ring and substituting functional group; Determination of unknown $f$ values

Monosubstituted benzene derivatives with the functional group directly connected to the ring; Di- and trisubstituted benzene derivatives

Secondary set of aromatic $f$ values

Differences between aliphatic and aromatic $f$ values

Differences between aromatic $\pi$ and $f$ values

Condensed ring systems and heterocyclic structures

Partially hydrogenated condensed ring systems

Condensed ring systems with benzene and pyridine units

Comparison of aliphatic and aromatic CH fragments

Extension of the $f$ system to other hetero-aromatic structures; Introduction of $[N]$, $[NH]$, $[S]$ and $[O]$

Cross-conjugated systems

Lipophilicity of H attached to an electron-withdrawing centre

Proximity effect

References

Chapter IV. A "MAGIC" CONSTANT CONNECTING ALL (?) PARTITION VALUES

A frequently occurring constant in the lipophilicity studies described so far

Proximity effect

H attached to a negative group
XI

Condensed aromatic units 108
Ar - Ar conjugation 108
Cross-conjugation 108
Aromatic - aliphatic differences 109
Incorrectly presumed folding 109
Abnormal proximity correction for phenoxyacetic acid and its derivatives 109
Closer inspection of the aromatic - aliphatic differences between functional groups; the "magic" constant; the "key number" 109
Partition values of aliphatic and aromatic structures on a general denominator 111
Equidistant alignment of partition values; the "nearest hole" theorem; Lipophilicity of inert gases 115
Application of \( f \) in the calculation of partition values of "small" molecules 123
Lipophilic behaviour of some complex functional groups 126
Calculation of partition coefficients with \( f \) values derived from "small" molecules 128
References 131

Chapter V. SOME SPECIAL APPLICATIONS OF THE HYDROPHOBIC FRAGMENTAL CONSTANT
Steric factors and lipophilicity 133
Correlations between \( E_s \) and lipophilicity 133
Steric effects in 2-alkyltriazinones 134
De-coupling of resonance and its effect on the partitional behaviour of a structure 136
Introduction 136
Lipophilic behaviour of some selected aromatic structures with de-coupled resonance interaction between aromatic ring and functional group 138
Aromatic structures with a CON\( ^< \) group 138
2,6-Dimethylbenzoic acid 141
N,N-dimethylbenzamide 142
Lidocaine 143
Lipophilic behaviour of a series of alkyl-substituted para-hydroxyacetanilides 145
Lactams and thiolactams 146
Lipophilicity of positively charged N-structures 150
Introduction 150
The anomalous $N^+$ centre (Concept A)  
Anomalous alkylchains (Concept B)  
"Magic" constant and $N^+$ lipophilicity  
Application of the $f$ system in a few SAR studies  
Denaturizing activity of aliphatic alcohols  
Lipophilic behaviour of carbamates  
Antihistamine activity in a series of diphenhydramine derivatives

References

PART II

MUTUAL DIFFERENCES BETWEEN PARTITIONING SOLVENT SYSTEMS AND THE CHARACTERIZATION OF MEMBRANE SYSTEMS

Chapter VI. SYSTEMS OTHER THAN OCTANOL - WATER

Introduction  
The COLLANDER equation  
Solvent regression equations of LEO et al.  
The application of solvent regression equations  
SEILER's increments to hydrogen bonding  
Accommodation of membrane lipids in the collection of solvent systems  
Discriminating properties of solvent systems

References

Chapter VII. DERIVATION OF APPROPRIATE SETS OF HYDROPHOBIC FRAGMENTAL CONSTANTS FOR SEVERAL SOLVENT SYSTEMS

Introduction  
Diethylether - water system  
Chloroform - water system  
Benzene - water system  
Oil - water system  
Oleyl alcohol - water system  
Toluene - water system  
Carbon tetrachloride - water system  
Xylene - water system  
Cyclohexane - water system  
$\eta$-Pentanol - water system  
$\eta$-Butanol - water system  
$\alpha$-Butanol - water system

References
Chapter VIII. A GENERAL FORMULATION FOR THE SOLVENT REGRESSION EQUATION

Differentiation in the solute structure; diethylether - water system 269
Other solvent systems 274
Proposal for a generally applicable solvent regression equation 268
Solvent - water to octanol - water conversion 288
Octanol - water to solvent - water conversion 290
Definition of hydro- and lipophilicity 291
Key numbers and STEIN's N values for describing hydrogen-bonding effects 293
References 296

Chapter IX. MEMBRANES AND THEIR CHARACTERIZATION

Introduction 297
Membrane function 298
Membrane structure 299
Buccal membrane systems

Buccal absorption of imipramine and its metabolites 303
The effect of alkyl substitution in acids on buccal absorption 306
Partitioning characteristics of the n-hexane and n-heptane systems 307
Buccal absorption of phenylacetic acids 311
Physical model approach by HO et al. for the analysis of buccal absorption 313
Buccal absorption of some analgesically active p-substituted acetonilides 315
Discriminative power of the buccal membrane 316
Human erythrocyte membrane lipid 317
Conclusion 320
References 322

Chapter X. A FEW APPLICATIONS OF f; PROPOSAL FOR FURTHER ELABORATION OF THE HANSCH APPROACH TO QSAR

Log P values of structures of the ureide type 325
Barbiturates 325
Urea derivatives 333
Uracil derivatives 336
Benzodiazepines and ketimines 337
The HANSCH approach 341
References 347
APPENDIX 350
AUTHOR INDEX 357
COMPOUND INDEX 365