SOLUBILITY BEHAVIOR OF ORGANIC COMPOUNDS

DAVID J. W. GRANT
Professor of Pharmaceutics
University of Minnesota
Minneapolis, Minnesota

and

TAKERU HIGUCHI
Late Regents Distinguished Professor of Pharmacy
and of Chemistry
University of Kansas
Lawrence, Kansas
## CONTENTS

<table>
<thead>
<tr>
<th>List of Abbreviations</th>
<th>xix</th>
</tr>
</thead>
<tbody>
<tr>
<td>List of Symbols</td>
<td>xxi</td>
</tr>
</tbody>
</table>

### Chapter I

**Introduction and Survey**

1.1 General Considerations, 1

1.2 Outline of Subsequent Chapters, 2

1.2.1 Chapter 2, 2
1.2.2 Chapter 3, 3
1.2.3 Chapter 4, 3
1.2.4 Chapter 5, 4
1.2.5 Chapter 6, 5
1.2.6 Chapter 7, 5
1.2.7 Chapter 8, 7
1.2.8 Chapter 9, 8
1.2.9 Chapter 10, 8
1.2.10 Chapter 11, 9

1.3 Bounds to the Text, 9

### Chapter II

**Solubility, Intermolecular Forces, and Thermodynamics**

2.1 Solubility as an Equilibrium Process, 12

2.2 Solubility in Ideal Systems, 14

2.2.1 Definition of an Ideal Solution, 14
2.2.2 Solid Solutes, 15
2.2.3 Prediction of Solid Solubility in Ideal Systems, 17
2.2.4 Thermodynamics of Solid Solubility, 22
2.2.5 Influence of Hydrogen Bonding on Molecular Packing in the Solid State and Solubility, 27

2.2.6 Influence of Temperature on Enthalpy of Fusion, 29

2.3 Solubility of Polymorphs, 32

2.4 Thermodynamic Theory of Solubility of Solvates, 38

2.5 Solubility and Dissolution Rate of Solvates, 39

2.6 Quantitative Prediction Based on Solubility Parameters and Related Concepts, 46

2.7 Extensions of Regular Solution Theory, 54

2.8 The Molecular and Group-Surface-Area (MGSA) Approach, 57
## CONTENTS

2.9 Prediction of Solubility in Water from Partition Coefficients, 58
2.10 Athermal Solutions, 61
2.11 Intermolecular Interactions and Their Influence on Solubility, 62
    2.11.1 Introduction to Intermolecular Interactions, 62
    2.11.2 Coulombic Interactions, 63
    2.11.3 Dipole Moments, 65
    2.11.4 Induced Dipole Moments and Polarizability, 66
    2.11.5 Relative Importance of the Various Intermolecular Forces, 69
    2.11.6 Polarizability and Intermolecular Forces, 71
    2.11.7 Hydrogen Bonds, 76
    2.11.8 Interactions and Solubility, 80
2.12 Prediction of Solubility from Derived Molecular Parameters: The Solvatochromic Approach, 82

### Chapter III
Activities of Solutes, Selection of Standard State and Henry's Law Constants, 89

3.1 Introduction, 89
    3.1.1 Thermodynamic Activity, 89
    3.1.2 Standard States, 90
3.2 Recommended Standard State for Dissolved Solutes, 91
3.3 Standard States Based on Henry's Law, 93
3.4 Activity of the Pure Solute from the Henry's Law Constant, 97
3.5 Activity of the Pure Solute from Activity Coefficients or from the Solubility in Paraffinic Solvents, 103
    3.5.1 Introduction, 103
    3.5.2 Relationships Between Activity Coefficients, 103
    3.5.3 Activity of the Pure Solute from Henry's Law Constant or Solubility in a Paraffinic Solvent, 105
3.6 Solubility Prediction from the Activity of the Pure Solute and the Partition Coefficient, 113
3.7 Activity and Solubility of Bifunctional Compounds: Glycols, 116
3.8 Relevance of the Gas Phase and Gibbs Free Energies of Transfer, 118
3.9 Influence of Molecular Structure on the Activity of Pure Organic Compounds, 121
3.10 Thermodynamic Activity in Transdermal Drug Delivery, 128
3.11 Influence of Dipole--Induced-Dipole Interactions on Henry's Law Constants and Solubility, 128

### Chapter IV
Specific Interactions in Solubility Phenomena, 134

4.1 Introduction, 134
4.2 Limitations of Regular Solution Theory and the Athermal Treatment, 134
4.3 Importance of Specific Interactions with Solvents, 144
4.3.1 Theoretical Considerations, 144
4.3.2 Experimental Studies with Cosolvent, 145
4.3.3 Free Energies and Stability Constants, 155
4.4 Influence of Molecular Structure on Cosolvency and Complexation, 157
4.4.1 1:1 Complexation, 157
4.4.2 Bifunctional Compounds, 161
4.4.3 Indomethacin Solubility in Esters, 162
4.5 Conclusions, 163

Chapter V

Influence of Complexation, Especially Hydrogen Bonding, on Solubility in Organic Solvents: Prediction of Association Constants, 165

5.1 Introduction, 165
5.2 Stability Constants, 166
5.2.1 Theoretical Background, 166
5.2.2 First-Order (1:1) Complexes, 168
5.2.3 Second-Order (1:2) Complexes, 169
5.2.4 Third-Order (1:3) Complexes, 171
5.3 Experimental Methods for Determining Association Constants in Nonaqueous Solution, 173
5.3.1 Introduction, 173
5.3.2 Liquid–Liquid Partition Method, 173
5.3.3 Infrared Spectroscopic Method, 177
5.3.4 Spectropolarimetric (ORD) Method, 179
5.3.5 Ultraviolet Spectrophotometric Method, 180
5.3.6 Determination of the Stoichiometry of Complexes, 181
5.3.7 Iterative Methods for the Determination of Stability Constants of Complexes, 183
5.3.8 Calorimetric Studies of Hydrogen Bonding and Polyfunctionality, 188
5.4 Correlation and Prediction of Stability Constants for Complexation Between Polar Molecules in Solution, 191
5.5 Linear Free-Energy Relationships (LFERs), 191
5.5.1 Theory, 191
5.5.2 LFERs for Phenol and Alcohol Interactions, 193
5.5.3 LFERs for Carboxylic Acids and Their Anions, 199
5.5.4 LFERs for Ester Interactions, 201
5.5.5 LFERs for Ether Interactions, 204
5.5.6 LFERs for Amide Interactions, 205
5.5.7 Solubility and Type of Molecular Association, 206
5.6 Assigning Donor and Acceptor Contributions to the Stability Constants, 208
5.6.1 Separation of the Donor and Acceptor Contributions to $K_{DA}^*$, 208
5.6.2 Choice of Solvent and Temperature in Assigning Contributions to $K_{DA}$, 210
5.6.3 Choice of the Reference Hydrogen-Bond Donor for $h_D = 0$, 210
5.6.4 Choice of the Reference Hydrogen-Bond Acceptor for $h_A = 1$, 210
5.6.5 Comparisons of $h_D$ Values for Various Hydrogen-Bond Donors, 211

5.7 Solvent Effects in Molecular Complexation, 215
5.7.1 General Effects of Solute–Solvent Interaction, 215
5.7.2 Comparisons Between Carbon Tetrachloride and Paraffins as Solvents, 217
5.7.3 Comparison of $K_{DA}$ (and $K_{1:1}$) in Carbon Tetrachloride and Paraffins, 217
5.7.4 Choice of Concentration Scale for Expressing Complexation Constants, 220
5.7.5 Treatment of Solvent Effects as Competing Equilibria, 222
5.7.6 Treatment of Solvent Effects as Nonspecific Interactions, 224
5.7.7 Treatment of Solvent Effects by Regular Solution Theory, 225
5.7.8 Influence of Dielectric Constant and Dipole Moment of the Solvent, 225
5.7.9 Use of Homomorphs to Infer Nonspecific Contributions, 226
5.7.10 Study of Solvent Effects Using Solvation Cycles, 227

5.8 The Prediction of Stability Constants and of Solubilities of Polar Solutes in the Presence of Polar Solvents, 229
5.9 Examples of the Prediction of Complexation Constants for Hydrogen Bonding and the Resultant Solubility Behavior, 230

Chapter VI
Structure of Solvents and Effects of Self-Association on Solubility 234
6.1 Introduction, 234
6.2 Models for Self-Association, 236
   6.2.1 Monomer–Trimer Models, 236
   6.2.2 Monomer–Tetramer Models, 236
   6.2.3 Monomer–Dimer–Tetramer Model, 236
   6.2.4 Monomer–Pentamer Model, 236
6.3 Experimental Methods for Studying Self-Association, 236
   6.3.1 Calorimetry, 236
   6.3.2 Vapor-Pressure Method, 241
6.4 Relative Merits of Pentamer and Tetramer Models for $n$-Alkanol Self-Association, 249
6.5 Effects of Chain Length and Chain Branching, 251
6.5.1 Influence of Chain Length on Free Energies of Transfer, 251
6.5.2 Influence of Chain Length on Self-Association, 251
6.5.3 Influence of Chain Branching on Self-Association, 253
6.6 Studies with Alcohols as Cosolvents, 261
6.6.1 Influence of Alcohols on the Solubility of Polar Solutes in Nonpolar Solvents, 261
6.6.2 Model for the Effect of Alcohol Self-Association on Solubility, 265
6.6.3 Influence of Molecular Structure on Solubility and Complexation in Alcohol Solutions, 272
6.7 Influence of the Dimerization of Carboxylic Acids on Their Complexation Behavior, 274
6.8 Studies with Phenols as Solutes, 282
6.8.1 Phenol Self-Association: Solubility and Vapor-Pressure Studies, 282
6.8.2 Phenol Self-Association: An NMR Study, 288
6.8.3 Phenol Self-Association: A Calorimetric Study, 291
6.8.4 Phenol Self-Association: Discussion, 294
6.9 Implications of Self-Association Studies, 295
6.10 Influence of Self-Association on Free Diffusion, 296
6.10.1 Theoretical Considerations, 296
6.10.2 Influence of Self-Association on the Membrane Diffusion of Phenol, 298

Chapter VII
Group Contributions in Prediction, 307
7.1 Introduction, 307
7.2 Evaluation of Group Contributions, 318
7.2.1 Henry's Law Constants, 318
7.2.2 Partition Coefficients, 322
7.2.3 Chromatography, 327
7.2.4 Ion-Pair Partitioning, 331
7.3 Particular Group Contributions, 335
7.3.1 Methylene Group, 335
7.3.2 Methyl Group, 340
7.3.3 Cyclization, Double and Triple Bonds, 343
7.3.4 Polar Groups, 344
7.4 Rationale for Simple versus Elaborate Approaches to Group Contributions, 345
7.5 Predictions of Partition Coefficients and Solubility Using the UNIQUAC and UNIFAC Models, 346
7.5.1 The Principles of the UNIQUAC Model, 346
7.5.2 The Principles of the UNIFAC Model, 348
Chapter VIII

Solubility in and Partitioning into Water

8.1 Introduction, 355
8.2 The “Hydrophobic” Interaction, 355
  8.2.1 Survey, 355
  8.2.2 Theories of the Hydrophobic Interaction, 357
  8.2.3 “More Structured Water” Theory, 358
  8.2.4 “Restricted Solute Motion” Theory, 358
8.3 The Molecular and Group-Surface Area (MGSA) Approach to Solubility Prediction, 361
8.4 Influence of Chain Branching on the Aqueous Solubility and Partition Coefficient of Alkanes, 367
8.5 Prediction of Aqueous Solubility via the Supercooled Liquid and Solution in 1-Octanol, 368
8.6 Direct Correlation of Aqueous Solubility Using Simple Empirical Group-Contribution Approaches, 371
8.7 Four Alternative Routes for the Prediction of Solubility in Water, 373
  8.7.1 Introduction, 373
  8.7.2 Route: Pure Solute \rightarrow\text{Vapor} \rightarrow\text{Solution in Water}, 374
  8.7.3 Route: Pure Solute \rightarrow\text{Solution in a Paraffinic Hydrocarbon} \rightarrow\text{Solution in Water}, 375
  8.7.4 Route: Pure Solute \rightarrow\text{Solution in a Paraffinic Hydrocarbon} \rightarrow\text{Vapor} \rightarrow\text{Solution in Water}, 376
  8.7.5 Prediction of Solubility in Water via the Route: Pure Solute \rightarrow\text{Vapor} \rightarrow\text{Solution in Paraffinic Hydrocarbon} \rightarrow\text{Solution in Water}, 377
8.8 Use of Group Contributions to Estimate Aqueous Solubility, 378
8.9 Determination of Solubility, 384
  8.9.1 Analytical and Synthetic Methods for Moderately Soluble Substances, 384
  8.9.2 Special Problems with Very Sparingly Soluble Substances, 385
  8.9.3 Kinetics of Equilibration, 385
  8.9.4 Facilitated Dissolution Method, 388
  8.9.5 Synthetic Methods for Very Sparingly Soluble Solids, 390
8.10 Determination of Partition Coefficients, 391
8.11 Influence of Cosolvents and Salts on Aqueous Solubility, 393

Chapter IX

Ion Pairs and Solubility Behavior

9.1 Introduction, 399
9.2 Formation of Ion Pairs, 399
  9.2.1 Introduction, 399
  9.2.2 Influence of the Solvent, 400
9.3 Extraction of Ion Pairs, 402
  9.3.1 Simple Ion-Pair Extraction, 402
  9.3.1.1 Influences of the Organic Phase and of the Relative Ionic Sizes, 402
  9.3.1.2 Extraction of Dextromethorphan, 404
  9.3.1.3 Extraction of Chlorpheniramine, 410
  9.3.2 Selective Ion-Pair Extraction, 413
  9.3.3 Factors Influencing Ion-Pair Extraction, 413
  9.3.4 Mechanism and Kinetics of Ion-Pair Extraction, 417
9.4 Thermodynamics of Ion Pairing: Influence of Solution Structure, 419
9.5 Behavior of Hydrophobic (Case III) Ion Pairs in Water: Conductimetric Studies and Solubility of Complex Coacervates, 425
9.6 Applications of Ion-Pair Formation in the Chemical and Pharmaceutical Sciences, 433

Chapter X
  Phase-Solubility Analysis and Complexation in Aqueous Solution 440
  10.1 Introduction, 440
  10.2 General Approach and Interpretation of Phase-Solubility Analysis, 440
  10.3 Experimental Procedure for Purity Determination, 443
  10.4 Complexation Solubility Analysis, 446
  10.5 Determination of the Stoichiometry of Complexes, 453
  10.6 Estimation of Stability Constants of Complexes, 456
  10.7 Nature and Mechanism of Complexation, 459
  10.8 Hydrotropy, 467
  10.9 Analytical Applications of Solubility Complexation, 470
  10.10 Phase Titrations, 471

Chapter XI
  Dissolution Rates of Solids 474
  11.1 Introduction, 474
  11.2 Theories and Mechanisms for the Dissolution Process, 478
    11.2.1 Introduction to the Theories, 478
    11.2.2 Interfacial Barrier Theory, 479
    11.2.3 Diffusion-Layer Theory, 479
    11.2.4 Hydrodynamics of the Rotating Disc, 480
    11.2.5 Effects of Diffusivity and Agitation Rate, 484
  11.3 Influence of pH on Solubility, 486
  11.4 Influence of pH, Bases, and Buffers on the Aqueous Dissolution Rates of Acidic Solids, 489
    11.4.1 Development of a Theory Based on a Single Equilibrium, 489