

Handbook of Industrial Crystallization

Edited by
Allan S. Myerson,
Deniz Erdemir and
Alfred Y. Lee

THIRD EDITION

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Since publication of the first edition of this invaluable resource in 1993 and the second edition in 2001, interest in crystallization science and technology has increased dramatically, and with that interest has come major new developments in the field. This third edition builds on the increased interest in crystallization and incorporates new material in a number of areas, including new chapters on crystal nucleation, molecular modeling applications, and precipitation and crystallization of pigments and dyes as well as completely revised chapters on crystallization of proteins, crystallizer selection and design, control of crystallization processes and process analytical technologies, and an updating of all the other chapters. This book continues to be the perfect reference for industrial and academic scientists and engineers, with this new edition making it even timelier and more important in the field.

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Contents

List of Contributors viii

Preface to the First Edition ix

Preface to the Second Edition xi

Preface to the Third Edition xiii

-
- 1 **Solutions and Solution Properties** 1
Jennifer Moffitt Schall and Allan S. Myerson
- 1.1 Introduction and Motivation 1
 - 1.2 Units 1
 - 1.3 Solubility of Inorganics 1
 - 1.4 Solubility of Organics 9
 - 1.5 Supersaturation and Metastability 17
 - 1.6 Solution Properties 22
 - 1.7 Thermal Properties 25
 - References 31
- 2 **Crystals and Crystal Growth** 32
Alfred Y. Lee, Deniz Erdemir, and Allan S. Myerson
- 2.1 Introduction 32
 - 2.2 Basic Concepts of the Solid State 32
 - 2.3 Crystal Nucleation 41
 - 2.4 Crystal Growth 41
 - 2.5 Crystal Habit 51
 - 2.6 Crystal Polymorphism 59
 - 2.7 Multicomponent Crystals 64
 - 2.8 Crystal Size 68
 - 2.9 Concluding Remarks 70
 - References 71
- 3 **Crystal Nucleation** 76
Deniz Erdemir, Alfred Y. Lee, and Allan S. Myerson
- 3.1 Introduction 76
 - 3.2 Homogeneous Nucleation 77
 - 3.3 Heterogeneous Nucleation 95
 - 3.4 Secondary Nucleation 96
 - 3.5 Nucleation Kinetics 98
 - 3.6 Control of Nucleation 102
 - 3.7 Nucleation in Polymorphic Systems 104
 - 3.8 Methods to Induce Nucleation 108
 - References 110
- 4 **The Influence of Impurities and Additives on Crystallization** 115
Lucrèce H. Nicoud and Allan S. Myerson
- 4.1 Introduction 115
 - 4.2 Retention of Foreign Species in Crystals 115
 - 4.3 Impact of Foreign Species on Growth Rate 122
 - 4.4 Impact of Foreign Species on Crystal Properties 128
 - 4.5 Conclusion 132
 - References 133
- 5 **Molecular Modeling Applications in Crystallization** 136
Keith Chadwick, Jie Chen, Erik E. Santiso, and Bernhardt L. Trout
- 5.1 Introduction 136
 - 5.2 Crystal Structure Visualization and Analysis Software 136
 - 5.3 Morphology Prediction 138
 - 5.4 Crystal Structure Determination from X-Ray Powder Diffraction Data 145
 - 5.5 Modeling Nucleation and Phase Transitions 147
 - 5.6 Polymorph Searching and Prediction 154
 - 5.7 Solubility Prediction 164
 - 5.8 Chapter Summary and Outlook 168
 - References 169
- 6 **Crystallization Process Analysis by Population Balance Modeling** 172
Åke C. Rasmuson
- 6.1 Introduction 172
 - 6.2 Particle Size and Size Distribution 173
 - 6.3 Crystallization Kinetics 177
 - 6.4 Population Balance Modeling 178
 - 6.5 The Idealized MSMR Concept 181
 - 6.6 Continuous Crystallization and Deviations from the MSMR Model 184
 - 6.7 Batch Crystallization 186
 - 6.8 Population Balance Modeling of Non-Well-Mixed Processes 188
 - 6.9 Determination of Crystallization Kinetics for Process Modeling 189
 - 6.10 Conclusions 193
 - References 194

- 7 **Selection and Design of Industrial Crystallizers** 197
Herman J. M. Kramer and Richard Lakerveld
- 7.1 Introduction 197
 - 7.2 Performance Criteria 198
 - 7.3 Crystallization Methods 198
 - 7.4 Equipment Design 201
 - 7.5 Instrumentation and Actuation 211
 - 7.6 Case Study: Optimization of a Base-Case Design 212
 - References 215
- 8 **Precipitation Processes** 216
Piotr H. Karpiński and Jerzy Bałdyga
- 8.1 Introduction 216
 - 8.2 Physical and Thermodynamic Properties 217
 - 8.3 Nucleation Kinetics 225
 - 8.4 Crystal Growth Kinetics in Precipitation 228
 - 8.5 Other Processes and Models in Precipitation 231
 - 8.6 Experimental Techniques 245
 - 8.7 Modeling and Control of Crystal Size and Crystal Size Distribution 248
 - 8.8 Scale-Up Rules for Precipitation 253
 - 8.9 Precipitation in Practice 256
 - 8.10 Summary 262
 - References 263
- 9 **Melt Crystallization** 266
Joachim Ulrich and Torsten Stelzer
- 9.1 Definitions 266
 - 9.2 Benefits of Melt Crystallization 266
 - 9.3 Phase Diagrams 268
 - 9.4 Crystallization Kinetics 270
 - 9.5 Processes of Melt Crystallization 273
 - 9.6 Post-Crystallization Treatments 275
 - 9.7 Concepts of Commercial Plants 280
 - 9.8 Eutectic Freeze Crystallization 285
 - 9.9 Summary and View to the Future 287
 - References 287
- 10 **Crystallizer Mixing** 290
Understanding and Modeling Crystallizer Mixing and Suspension Flow
Daniel A. Green
- 10.1 Introduction 290
 - 10.2 Crystallizer Flows 290
 - 10.3 Crystallizers 294
 - 10.4 Scale-Up 300
 - 10.5 Modeling 302
 - 10.6 Summary 310
 - References 311
- 11 **Monitoring and Advanced Control of Crystallization Processes** 313
Zoltan K. Nagy, Mitsuko Fujiwara, and Richard D. Braatz
- 11.1 Introduction 313
 - 11.2 Crystallization Process Monitoring 316
 - 11.3 Model-Based Optimization and Control of Crystallization Processes 323
 - 11.4 Model-Free (Direct Design) Approaches 337
 - 11.5 Summary 342
 - References 342
- 12 **Batch Crystallization** 346
Piotr H. Karpiński and Jerzy Bałdyga
- 12.1 Introduction 346
 - 12.2 Batch Crystallizers 346
 - 12.3 Batch Crystallization Analysis 349
 - 12.4 Factors Affecting Batch Crystallization 356
 - 12.5 Batch Crystallization Operations 368
 - 12.6 Scale-Up of Batch Crystallization 375
 - 12.7 Summary 376
 - References 377
- 13 **Crystallization in the Pharmaceutical Industry** 380
Simon N. Black
- 13.1 Introduction 380
 - 13.2 Simple Systems 381
 - 13.3 Increasing Complexity 385
 - 13.4 Crystallization Kinetics 391
 - 13.5 Particle Engineering 400
 - 13.6 After the Crystallizer 405
 - 13.7 Intermediates 407
 - 13.8 Other Crystallizations 408
 - 13.9 Summary 411
 - References 411
- 14 **Crystallization of Proteins** 414
Peter G. Vekilov
- 14.1 Introduction 414
 - 14.2 Protein and Protein Crystals 414
 - 14.3 The Thermodynamics of Protein Crystallization 417
 - 14.4 Methods of Protein Crystallization 421
 - 14.5 The Role of Nonprotein Solution Components and the Intermolecular Interactions in Solution 424
 - 14.6 Crystal Nucleation 430
 - 14.7 Mechanisms of Crystal Growth 441
 - 14.8 Impurities 448
 - 14.9 Crystal Perfection 449
 - 14.10 Concluding Remarks 454
 - References 454

- 15 **Crystallization in Foods** 460
Richard W. Hartel
- 15.1 **Characteristics of Crystallization in Foods** 460
 - 15.2 **Controlling Crystallization in Foods** 463
 - 15.3 **Factors Affecting Control of Crystallization in Foods** 474
 - 15.4 **Summary** 477
 - References** 477
- 16 **Precipitation and Crystallization of Pigments** 479
Lars Vicum, Marco Mazzotti, and Martin Igglund
- 16.1 **Introduction** 479
 - 16.2 **Types of Pigments, Pigment Chemistry, and Pigment Properties** 479
 - 16.3 **On the Design of Pigment Synthesis Processes** 489
 - 16.4 **Practical Applications and Special Aspects** 502
 - References** 511

Index 513

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Preface to the First Edition

Crystallization is a separation and purification process used in the production of a wide range of materials, from bulk commodity chemicals to specialty chemicals and pharmaceuticals. While the industrial practice of crystallization is quite old, many practitioners still treat it as an art. Many aspects of industrial crystallization have a well-developed scientific basis, and much progress has been made in recent years. Unfortunately, the number of researchers in the field is small, and this information is widely dispersed in the scientific and technical literature. This book will address this gap in the literature by providing a means for scientists or engineers to develop a basic understanding of industrial crystallization and provide the information necessary to begin work in the field, be it in design, research, or plant troubleshooting.

Of the eleven chapters in this book, the first two deal with fundamentals such as solubility, supersaturation, and basic concepts in crystallography, nucleation, and crystal growth and are aimed at those with limited exposure in these areas.

The second two chapters provide background *in* the important area of impurity crystal interactions and an introduction to crystal size distribution measurements and the population balance method for modeling crystallization processes. These four chapters provide the background information that is needed to access and understand the technical literature and are aimed at those individuals who have not been previously exposed to this material or who need a review.

The remaining seven chapters deal with individual topics important to industrial practice, such as design, mixing, precipitation, crystallizer control, and batch crystallization. In addition, topics that have become important in recent years, such as melt crystallization and the crystallization of biomolecules, are also included. Each chapter is self-contained but assumes that the reader has knowledge of the fundamentals discussed in the first part of the book.

Allan S. Myerson

Preface to the Second Edition

Crystallization from solution and the melt continues to be an important separation and purification process in a wide variety of industries. Since the publication of this volume's first edition in 1993, interest in crystallization technology, particularly in the pharmaceutical and biotech industries, has increased dramatically. The first edition served as an introduction to the field and provided the information necessary to begin work in crystallization. This new edition incorporates and builds on increased interest in crystallization and incorporates new material in a number of areas. This edition of the book includes a new chapter on crystallization of proteins (Chapter 12), a revised chapter on crystallization of pharmaceuticals (Chapter 11), and a new chapter in an area gaining great importance: crystallization in the food industry (Chapter 13).

Other topics that have become important in crystallization research and technology include molecular modeling applications, which are discussed in Chapters 2 and 3; computational fluid dynamics, which is discussed in Chapter 8; and precipitation, which is discussed in a totally revised Chapter 6.

As in the first edition, the first four chapters provide an introduction to newcomers to the field, giving fundamental information and background needed to access and understand the field's technical literature. The remaining nine chapters deal with individual topics important to industrial crystallization and assume a working knowledge of the fundamentals presented in Chapters 1 to 4.

Allan S. Myerson

Preface to the Third Edition

Crystallization science and technology have expanded dramatically since the first edition of this *Handbook* appeared in 1993. Advances in instrumentation and computation have improved our fundamental understanding of crystallization and have also advanced and improved the practice of crystallization in the chemical, food, and pharmaceutical industries. Interest in crystallization and the development of new crystalline materials has resulted in several new research journals such as *Crystal Growth and Design* (American Chemical Society) and *Crystal Engineering Communications* (Royal Society of Chemistry), both established around the same time as the second edition of this *Handbook* appeared in 2001. This new edition attempts to address the many developments in the field by the addition of a number of new chapters as well as revisions and updates to all the other chapters. This edition includes new chapters on crystal nucleation (Chapter 3), molecular modeling applications in crystallization (Chapter 5),

precipitation and crystallization of pigments and dyes (Chapter 16) and completely revised chapters on crystallizer selection and design (Chapter 7), crystallization process monitoring and control by process analytical technology (Chapter 11), crystallization in the pharmaceutical and bioprocess industries (Chapter 13), and crystallization of proteins (Chapter 14).

As in the previous editions, the first five chapters provide an introduction to newcomers to the field, giving fundamental information and background needed to access and understand the field's technical literature. The remaining eleven chapters focus on individual topics relevant to industrial crystallization and assume a working knowledge of the crystallization fundamentals presented in Chapters 1 to 5.

Allan S. Myerson, Deniz Erdemir, and Alfred Y. Lee

Solutions and Solution Properties

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Allan S. Myerson Massachusetts Institute of Technology

1.1 Introduction and Motivation

Crystallization is a separation and purification technique employed to produce a wide variety of materials. *Crystallization* may be defined as a phase change in which a crystalline product is obtained from a solution. A solution is a mixture of two or more species that form a homogeneous single phase. Solutions are normally thought of in terms of liquids, but solutions may include solids and even gases. Typically, the term *solution* has come to mean a liquid solution consisting of a solvent, which is a liquid, and a solute, which is a solid, at the conditions of interest. The term *melt* is used to describe a material that is solid at normal conditions and is heated until it becomes a molten liquid. Melts may be pure materials, such as molten silicon used for wafers in semiconductors, or they may be mixtures of materials. In that sense, a homogeneous melt with more than one component is also a solution, but it is normally referred to as a melt. A solution can also be gaseous; an example of this is a solution of a solid in a supercritical fluid.

Virtually all industrial crystallization processes involve solutions. The development, design, and control of any of these processes involve knowledge of a number of the properties of the solution. This chapter presents and explains solutions and solution properties and relates these properties to industrial crystallization operations.

1.2 Units

Solutions are made up of two or more components, of which one is the solvent and the other is the solute(s). There are a variety of ways to express the composition of a solution. If we consider the simple system of a solvent and a solute, its composition may be expressed in terms of mass fraction, mole fraction, or a variety of concentration units, as shown in Table 1.1. The types of units that are commonly used can be divided into those that are ratios of the mass (or moles) of solute to the mass (or moles) of the solvent, those that are ratios of the mass (or moles) of the solute to the mass (or moles) of the solution, and those that are ratios of the mass (or moles) of the solute to the volume of the solution.

While all three units are commonly used, it is important to note that use of units of type 3 requires knowledge of the solution density to convert these units into those of the other types. In addition, type 3 units must be defined at a particular temperature because the volume of a solution is a function of temperature. The best units to use for solution preparation are mass of solute per mass of solvent. These units have no temperature dependence, and solutions can be prepared simply by weighing each species.

Table 1.1 Concentration Units

Type 1: Mass (or moles) solute/mass (or moles) solvent

grams solute/100 grams solvent
 moles solute/100 grams solvent
Molal: moles solute/1000 grams solvent
 lb_m solute/ lb_m solvent
 moles solute/moles solvent

Type 2: Mass (or moles) solute/mass (or moles) solution

Mass fraction: grams solute/grams total
Mole fraction: moles solute/moles total

Type 3: Mass (or moles) solute/volume solution

Molar: moles solute/liter of solution
 grams solute/liter of solution
 lb_m solute/gallon solution

Conversion among mass (or mole) -based units is also simple. Example 1.1 demonstrates conversion of units of all three types.

1.3 Solubility of Inorganics

1.3.1 Basic Concepts

A solution is formed by the addition of a solid solute to a solvent. The solid dissolves, forming the homogeneous solution. At a given temperature, there is a maximum amount of solute that can dissolve in a given amount of solvent. When this maximum is reached, the solution is said to be *saturated*. The amount of solute required to make a saturated solution at a given condition is called the *solubility*.

Solubilities of common materials vary widely, even when the materials appear to be similar. Table 1.2 lists the solubility of a number of inorganic species (Mullen 1972; Myerson et al. 1990). The first five species all have calcium as the cation, but their solubilities vary over several orders of magnitude. At 20°C, the solubility of calcium hydroxide is 0.17 g/100 g water, while that of calcium iodide is 204 g/100 g water. The same variation can be seen in the six sulfates listed in Table 1.2. Calcium sulfate has a solubility of 0.2 g/100 g water at 20°C, while ammonium sulfate has a solubility of 75.4 g/100 g water.

The solubility of materials depends on temperature. In the majority of cases, the solubility increases with

Example 1.1 Conversion of Concentration Units**Given:** 1 molar solution of NaCl at 25°CDensity of solution = 1.042 g/cm³

Molecular weight (MW) NaCl = 58.44 g/mol

Solution:

$$1 \text{ molar} = \frac{1 \text{ mol NaCl}}{\text{liter of solution}} \frac{1 \text{ liter}}{1000 \text{ cm}^3} \frac{58.44 \text{ g NaCl}}{\text{mol NaCl}} \frac{1 \text{ cm}^3}{1.042 \text{ g}}$$

$$= \frac{0.056 \text{ g NaCl}}{\text{g solution}}$$

$$= 0.056 \text{ wt fraction NaCl} = 5.6 \text{ wt\% NaCl}$$

$$\frac{0.056 \text{ g NaCl}}{\text{g solution}} = \frac{0.056 \text{ g NaCl}}{0.944 \text{ g water} + 0.056 \text{ g NaCl}}$$

$$= 0.059 \text{ g NaCl/g water}$$

$$0.056 \text{ wt fraction NaCl} = \frac{0.056 \text{ g NaCl}}{0.944 \text{ g water} + 0.056 \text{ g NaCl}}$$

$$= \frac{\frac{0.056 \text{ g NaCl}}{58.44 \text{ g/mol NaCl}}}{\frac{0.056 \text{ g NaCl}}{58.44 \text{ g/mol NaCl}} + \frac{0.944 \text{ g water}}{18 \text{ g/mol water}}}$$

$$= 0.018 \text{ mol fraction NaCl}$$

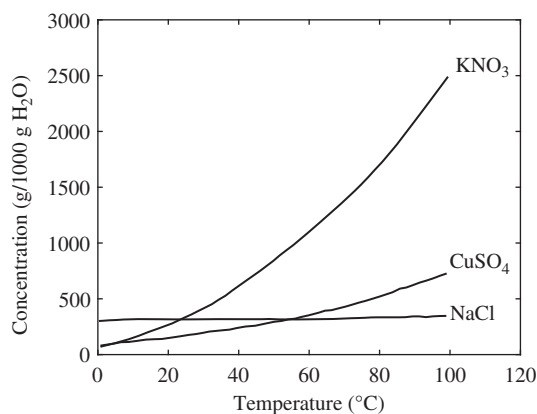


Figure 1.1 Solubility of KNO₃, CuSO₄, and NaCl in aqueous solution
Source: Data from Mullen 1972.

increasing temperature, although the rate of the increase varies widely from compound to compound. The solubilities of several inorganics as a function of temperature are shown in Figure 1.1. Sodium chloride is seen to have a relatively weak temperature dependence, with the solubility changing from 35.7 to 39.8 g/100 g water over a 100°C range. Potassium nitrate, by contrast, changes from 13.4 to 247 g/100 g water over the same temperature range. This kind of information is very important in crystallization processes because it will determine the amount of cooling required to yield a given amount of product and whether cooling will provide a reasonable product yield.

Table 1.2 Solubilities of Inorganics at 20°C

Compound	Chemical formula	Solubility (g anhydrous/100 g H ₂ O)
Calcium chloride	CaCl ₂	74.5
Calcium iodide	CaI ₂	204
Calcium nitrate	Ca(NO ₃) ₂	129
Calcium hydroxide	Ca(OH) ₂	0.17
Calcium sulfate	CaSO ₄	0.20
Ammonium sulfate	(NH ₄) ₂ SO ₄	75.4
Copper sulfate	CuSO ₄	20.7
Lithium sulfate	Li ₂ SO ₄	34
Magnesium sulfate	MgSO ₄	35.5
Silver sulfate	Ag ₂ SO ₄	0.7

Source: Based on data from Mullen 1972 and Myerson et al. 1990.

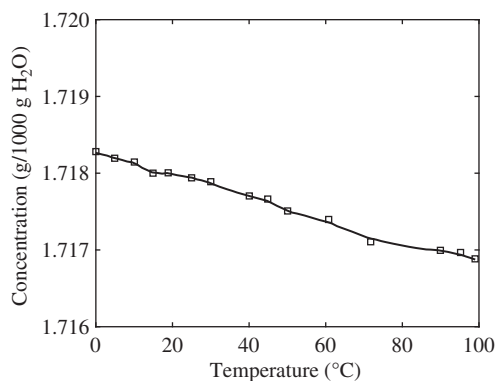


Figure 1.2 Solubility of calcium hydroxide in aqueous solution
Source: Data from Myerson et al. 1990.

In sparingly soluble materials, solubility can also decrease with increasing temperature. A good example of this is the calcium hydroxide–water system shown in Figure 1.2.

The solubility of a compound in a particular solvent is part of the system phase behavior and can be described graphically by a phase diagram. In phase diagrams of solid-liquid equilibria, the mass fraction of the solid is usually plotted versus temperature. An example is Figure 1.3, which shows the phase diagram for the magnesium sulfate–water system. This system demonstrates another common property of inorganic solids, the formation of hydrates. A *hydrate* is a solid formed on crystallization from water that contains water molecules as part of its crystal structure. The chemical formula of a hydrate indicates the number of moles of water present per mole of the solute species by listing a stoichiometric number and water after the dot in the chemical formula. Many compounds that form hydrates form several hydrates with varying amounts of

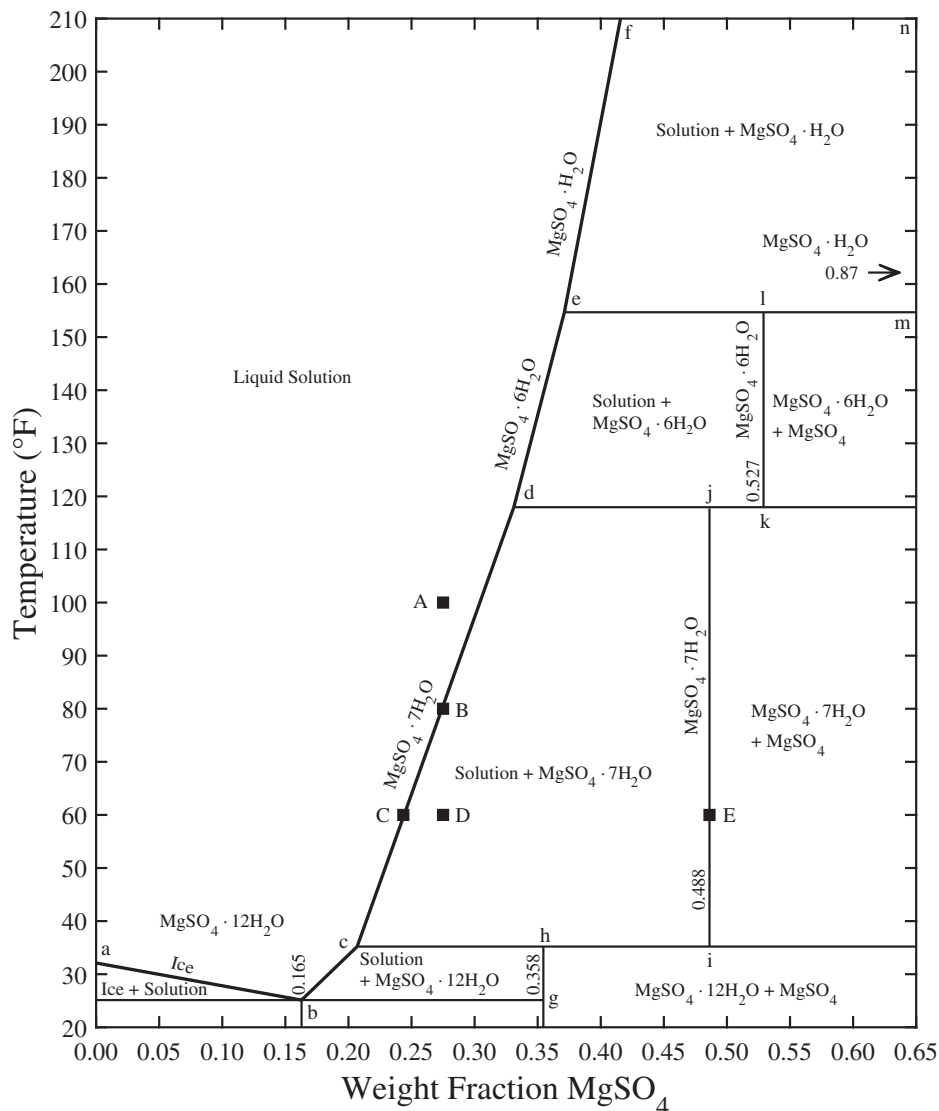


Figure 1.3 Phase diagram for MgSO₄·H₂O

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water. From the phase diagram (Figure 1.3) we can see that MgSO₄ forms four stable hydrates ranging from 12 mol of water/mol MgSO₄ to 1 mol of water/mol of MgSO₄. As is usual with hydrates, as the temperature rises, the number of moles of water in the stable hydrate declines, and at some temperature, the anhydrous material is the stable form.

The phase diagram contains much useful information. Referring to Figure 1.3, the line *abcdef* is the solubility or saturation line that defines a saturated solution at a given temperature. Line *ab* is the solubility line for the solvent (water) because when a solution in this region is cooled, ice crystallizes out and is in equilibrium with the solution. Point *b* marks what is known as the *eutectic composition*. If the solution is cooled at this composition (0.165 wt fraction MgSO₄), both ice and MgSO₄ will separate as solids. The rest of the curve from *b* to *f* represents the solubility of MgSO₄ as a function of temperature. If we were to start with a solution at 100°F and 27.5 wt% MgSO₄ (point A in Figure

1.3) and cool that solution, the solution would be saturated at the point where a vertical line from A crosses the saturation curve, which is at 80°F. If the solution were cooled to 60°F as shown at point D, the solution will have separated at equilibrium into solid MgSO₄·7H₂O and a saturated solution of the composition corresponding to point C.

The phase diagram also illustrates a general practice concerning hydrate solubility. The solubilities of compounds that form hydrates are usually given in terms of the anhydrous species. This saves much confusion when multiple stable hydrates can exist but requires that care be taken when performing mass balances or preparing solutions. Example 1.2 illustrates these types of calculations.

Phase diagrams can be significantly more complex than the example presented in Figure 1.3 and may involve additional stable phases and/or species. A number of references discuss these issues in detail (Gordon 1968; Rosenberger 1981).

Example 1.2 Calculations Involving Hydrates

Given solid $\text{MgSO}_4 \cdot 7\text{H}_2\text{O}$, prepare a saturated solution of MgSO_4 at 100°F .

(a) Looking at the phase diagram (Figure 1.3), the solubility of MgSO_4 at 100°F is 0.31 wt. fraction MgSO_4 (anhydrous), and the stable phase is $\text{MgSO}_4 \cdot 7\text{H}_2\text{O}$. First, calculate the amount of MgSO_4 (anhydrous) necessary to make a saturated solution at 100°F .

$$0.31 = x_f = \frac{\text{weight MgSO}_4(\text{g})}{\text{weight MgSO}_4(\text{g}) + \text{weight H}_2\text{O}(\text{g})}$$

Using a basis:

For 1000 g H_2O , the weight of MgSO_4 (g) needed to make a saturated solution is 449 g MgSO_4 (anhydrous).

(b) Because the stable form of the MgSO_4 available is $\text{MgSO}_4 \cdot 7\text{H}_2\text{O}$, to do this, we need to know the molecular masses of MgSO_4 , H_2O , and $\text{MgSO}_4 \cdot 7\text{H}_2\text{O}$. These are 120.37 g/gmol and 246.48 g/gmol, respectively.

$$x_{\text{MgSO}_4} = \frac{\text{wt of MgSO}_4 \text{ in the hydrate}}{\text{wt of MgSO}_4 \cdot 7\text{H}_2\text{O}} = \frac{120.37}{246.48} = 0.488$$

$$x_{\text{H}_2\text{O}} = \frac{\text{wt of H}_2\text{O in the hydrate}}{\text{wt of MgSO}_4 \cdot 7\text{H}_2\text{O}} = \frac{126.11}{246.48} = 0.512$$

Mass balances:

$$\begin{aligned} \text{Total weight} &= \text{wt H}_2\text{O} + \text{wt of MgSO}_4 \text{ in the hydrate} \\ 0.31(\text{total weight}) &= \text{wt of MgSO}_4 \text{ in the hydrate} \\ 0.69(\text{total weight}) &= \text{wt of H}_2\text{O in the hydrate} + \text{wt of H}_2\text{O solvent} \end{aligned}$$

First, we will examine the total mass balance. Because we are using a basis of 1000 g of H_2O , and the weight of MgSO_4 in the hydrate is equal to the weight of MgSO_4 (anhydrous) calculated in (a), the total weight of our system is 1449 g.

By substituting the mole fraction expressions into the species material balances, we can solve for the amount of $\text{MgSO}_4 \cdot 7\text{H}_2\text{O}$ needed to make a saturated solution at 100°F .

$$\begin{aligned} 0.31(1449 \text{ g}) &= 0.488(\text{wt of MgSO}_4 \cdot 7\text{H}_2\text{O}) \\ \text{wt of MgSO}_4 \cdot 7\text{H}_2\text{O g} &= 920 \text{ g} \end{aligned}$$

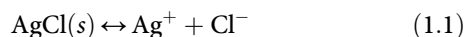
$$\begin{aligned} 0.69(1449 \text{ g}) &= \text{wt H}_2\text{O solvent} + 0.512(\text{wt of MgSO}_4 \cdot 7\text{H}_2\text{O}) \\ 0.69(1449 \text{ g}) &= \text{wt H}_2\text{O solvent} + 0.512(920 \text{ g}) \\ \text{wt H}_2\text{O solvent} &= 529 \text{ g} \end{aligned}$$

Therefore, to make a saturated solution of MgSO_4 at 100°F starting with $\text{MgSO}_4 \cdot 7\text{H}_2\text{O}$, we need to add 920 g of the hydrate to 529 g of H_2O .

1.3.2 Sparingly Soluble Species: Dilute Solutions

As we saw in Section 1.3.1, the solubility of materials varies according to their chemical composition and with temperature. Solubility is also affected by the presence of additional species in the solution, by the pH, and by the use of different solvents (or solvent mixtures). When discussing inorganic species, the solvent is usually water, whereas with organics, the solvent can be water or a number of organic solvents or solvent mixtures.

If we start with a sparingly soluble inorganic species such as silver chloride and add silver chloride to water in excess of the saturation concentration, we will eventually have equilibrium between solid AgCl and the saturated solution. The AgCl is, like most of the common inorganics, an electrolyte and dissociates into its ionic constituents in solution. The dissociation reaction can be written as



The equilibrium constant for this reaction can be written as

$$K = \frac{a_{\text{Ag}^+} a_{\text{Cl}^-}}{a_{\text{AgCl}}} \quad (1.2)$$

where a denotes the activities of the species. If the solid AgCl is in its stable crystal form and at atmospheric pressure, it is at a standard state and will have an activity of 1. The equation can then be written as

$$K_{sp} = a_{\text{Ag}^+} a_{\text{Cl}^-} = (\gamma_{\text{Ag}^+} m_{\text{Ag}^+})(\gamma_{\text{Cl}^-} m_{\text{Cl}^-}) \quad (1.3)$$

where γ is the activity coefficient of the species and m represents the concentration in solution of the ions in molal units. For sparingly soluble species such as AgCl , the activity coefficient can be assumed to be unity (using the asymmetric convention for activity coefficients), so that Equation (1.3) reduces to

$$K_{sp} = (m_{\text{Ag}^+})(m_{\text{Cl}^-}) \quad (1.4)$$

This equation represents the solubility product of silver chloride. Solubility products are generally used to describe the solubility and equilibria of sparingly soluble salts in aqueous solutions. Solubility products of a number of substances are given in Table 1.3. It is important to remember that use of solubility product relations based on concentrations assumes that the solution is saturated, in equilibrium, and ideal (the activity coefficient is equal to 1). It is therefore an approximation, except with very dilute solutions of one solute.

Equation (1.4) can be used for electrolytes in which there is a 1:1 molar ratio of the anion and cation. For an electrolyte that consists of univalent and bivalent ions, such as silver sulfate, which dissociates into 2 mol of silver ions for each mole of sulfate ions, the solubility product equation would be written as

$$K_{sp} = (m_{\text{Ag}^+})^2(m_{\text{SO}_4^{2-}}) \quad (1.5)$$

In the dissociation equation, the concentration of the ions of each species is raised to the power of the species' stoichiometric number.

The solubility product principle enables simple calculations to be made of the effect of other species on the solubility of a given substance and may be used to determine the species that

Table 1.3 Solubility Products

Substance	Solubility Product at 25°C
Aluminum hydroxide	3.70×10^{-15}
Barium carbonate	2.58×10^{-9}
Barium chromate	1.17×10^{-10}
Barium fluoride	1.84×10^{-7}
Barium iodate monohydrate	1.67×10^{-9}
Barium sulfate	1.08×10^{-10}
Calcium carbonate (calcite)	3.36×10^{-9}
Calcium fluoride	3.45×10^{-11}
Calcium iodate hexahydrate	7.10×10^{-7}
Calcium oxalate monohydrate	2.32×10^{-9}
Calcium sulfate	4.93×10^{-5}
Cupric iodate monohydrate	6.94×10^{-8}
Cupric oxalate	4.43×10^{-10}
Cuprous bromide	6.27×10^{-9}
Cuprous chloride	1.72×10^{-7}
Cuprous iodide	1.27×10^{-12}
Ferric hydroxide	2.79×10^{-39}
Ferrous hydroxide	4.87×10^{-17}
Lead carbonate	7.40×10^{-14}
Lead sulfate	2.53×10^{-8}
Lithium carbonate	8.15×10^{-4}
Magnesium carbonate	6.82×10^{-6}
Magnesium fluoride	5.16×10^{-11}
Magnesium hydroxide	5.61×10^{-12}
Magnesium oxalate dehydrate	4.83×10^{-6}
Manganese carbonate	2.24×10^{-11}
Silver bromate	5.38×10^{-5}
Silver iodide	8.52×10^{-17}
Zinc hydroxide	3.00×10^{-17}

Source: Data from Weast 1975.

will precipitate in an electrolyte mixture. One simple result of applying the solubility product principle is the common ion effect. This is the effect caused by the addition of an ionic species that has an ion in common with the species of interest. Because the solubility of a species is given by the product of the concentration of its ions, when the concentration of one type of ion increases, the concentration of the other must decline, or the overall concentration of that compound must decline. We can illustrate this simply by using our previous example of silver

chloride. The solubility product of silver chloride at 25°C is 1.56×10^{-10} . This means that at saturation we can dissolve 1.25×10^{-5} mol of AgCl/1000 g of water. If, however, we were to start with a solution that has a concentration of 1×10^{-5} molal NaCl (hence 1×10^{-5} molal Cl^-), the solubility product equation would be written in the form

$$K_{sp} = (m_{\text{Ag}^+})(m_{\text{Cl}^-}) = (x_{\text{Ag}^+})(x_{\text{Cl}^-} + 1 \times 10^{-5}) \quad (1.6)$$

$$K_{sp} = x^2 + 10^{-5}x \quad (1.7)$$

where x is the amount of AgCl that can dissolve in the solution. Solving Equation (1.7) results in $x = 0.725 \times 10^{-5}$ molal. The common ion effect has worked to decrease the solubility of the compound of interest. It is important to remember that this is true only for very dilute solutions. In more concentrated solutions, the activity coefficients are not unity, and more complex electrical effects and complexation may occur. This is discussed in detail in Section 1.3.3.

Another use of solubility products is the determination, in a mixture of slightly soluble materials, as to what material is likely to precipitate. This is done by looking at all the ion concentrations and calculating their products in all possible combinations. These are then compared with the solubility products that must already be known. This is useful in situations where scale formation is of interest or in determining the behavior of slightly soluble mixtures.

1.3.3 Concentrated Solutions

Unfortunately, like all easy-to-use principles, the solubility product principle is not generally applicable. At higher concentrations, electrical interactions, complex formation, and solution nonideality make the prediction of the effect of ionic species on the solubility of other ionic species much more complicated.

In Section 1.3.2 we used the solubility product principle to calculate the effect of a common ion on the solubility of a sparingly soluble species. The common ion effect, however, is completely dominated by a more powerful effect when a large concentration of another electrolyte is present. In fact, the solubility of sparingly soluble materials increases with increasing ion concentration in solution. This is called the *salt effect* and is illustrated in Figures 1.4 through 1.6, where we see the increase in solubility of AgCl as a function of increasing concentrations of added electrolytes. We see this effect in both added salts with a common ion and without. This effect can also be induced by changing the pH of the solution because this changes the ion content of the solution.

The solubility of many inorganics in aqueous solution is available in the book by Linke and Seidell (1965). This reference also contains the solubilities of electrolytes in the presence of other species. For example, Figure 1.7 shows the solubility of NaCl as a function of NaOH concentration. As a general rule, the solubility of most inorganics in water is available as a function of temperature. What is more difficult to find is the effect of other species on the solubility. If several other species are present, the data will usually not be available. Given this situation, there are two alternatives. The first is to measure the solubility at the conditions and composition of interest. Experimental

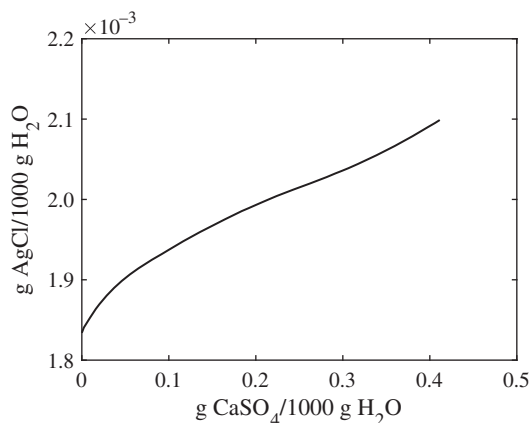


Figure 1.4 Solubility of AgCl in aqueous CaSO_4 solution at 25°C
Source: Data from Linke and Seidell 1965.

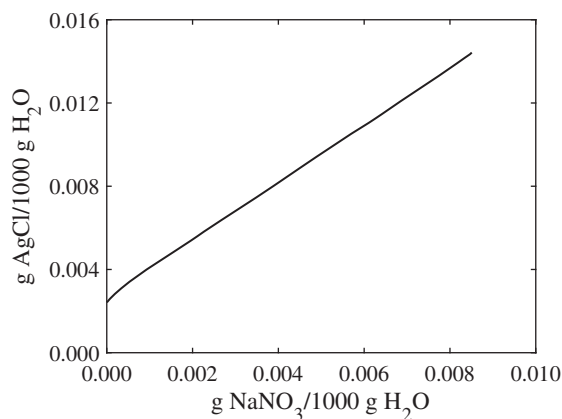


Figure 1.5 Solubility of AgCl in aqueous NaNO_3 solution at 30°C
Source: Data from Linke and Seidell 1965.

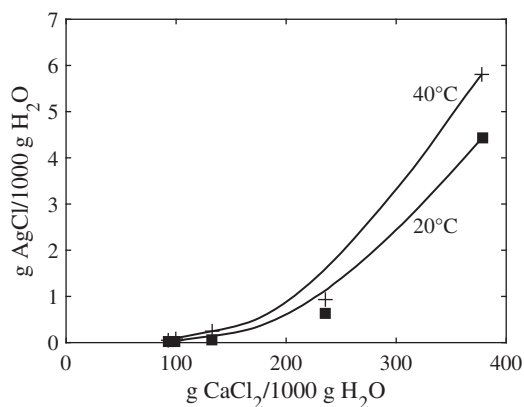


Figure 1.6 Solubility of AgCl in aqueous CaCl_2 solution
Source: Data from Linke and Seidell 1965.

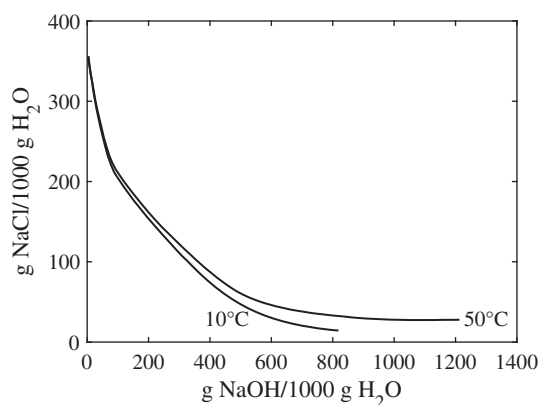


Figure 1.7 Solubility of NaCl in aqueous NaOH solution
Source: Data from Linke and Seidell 1965.

methods for solubility measurement will be discussed in Section 1.4.6. The second alternative is to calculate the solubility. This is a viable alternative when thermodynamic data are available for the pure components (in solution) making up the multicomponent mixture. An excellent reference for calculation techniques in this area is the *Handbook of Aqueous Electrolyte Thermodynamics* by Zemaitis et al. (1986). A simplified description of calculation techniques is presented later in Section 1.3.3.

Solution Thermodynamics. As we have seen previously, for a solution to be saturated, it must be at equilibrium with the solid solute. Thermodynamically, this means that the chemical potential of the solute in the solution is the same as the chemical potential of the species in the solid phase.

$$\mu_{i,\text{solid}} = \mu_{i,\text{solution}} \quad (1.8)$$

If the solute is an electrolyte that completely dissociates in solution (strong electrolyte), Equation (1.8) can be rewritten as

$$\mu_{i,\text{solid}} = \nu_c \mu_c + \nu_a \mu_a \quad (1.9)$$

where ν_c and ν_a are the stoichiometric numbers, and μ_c and μ_a are the chemical potentials of the cation and anion,

respectively. The chemical potential of a species is related to the species activity by

$$\mu_i(T) = \mu_{(aq)}^0(T) + RT \ln(a_i) \quad (1.10)$$

where a_i is the activity of species i , $\mu_{(aq)}^0$ is an arbitrary reference state chemical potential, R is the gas constant, and T is temperature. The activity coefficient is defined as

$$\gamma_i = \frac{a_i}{m_i} \quad (1.11)$$

where m_i is the concentration in molal units. In electrolyte solutions, because of the condition of electroneutrality, the charges of the anion and cation will always balance. When a salt dissolves, it will dissociate into its component ions. This has led to the definition of a mean ionic activity coefficient and mean ionic molality defined as

$$\gamma_{\pm} = (\gamma_c^{\nu_c} \gamma_a^{\nu_a})^{1/\nu} \quad (1.12)$$

$$m_{\pm} = (m_c^{\nu_c} m_a^{\nu_a})^{1/\nu} \quad (1.13)$$

where ν_c and ν_a are the stoichiometric number of ions of each type present in a given salt. The chemical potential for a salt can be written as

$$\mu_{\text{salt}(aq)} = \mu_{(aq)}^0 + \nu RT \ln(\gamma_{\pm} m_{\pm})^{\nu} \quad (1.14)$$

where $\mu_{(aq)}^0$ is the sum of the two ionic standard-state chemical potentials, and ν is the stoichiometric number of moles of ions in 1 mole of solid. In practice, experimental data are usually reported in terms of mean ionic activity coefficients. As we discussed earlier, various concentration units can be used. We have defined the activity coefficient on a molal scale. On a molar scale, it is

$$y_i = \frac{a_i(c)}{c_i} \quad (1.15)$$

where y_i is the molar activity coefficient, and c_i is the molar concentration. We can also define the activity coefficient on a mole fraction scale as

$$f_i = \frac{a_i(x)}{x_i} \quad (1.16)$$

where f_i is the activity coefficient, and x_i the mole fraction. Converting activity coefficients from one type of unit to another is neither simple nor obvious. Equations that can be used for this conversion have been developed and include (Zemaitis et al. 1986)

$$f_{\pm} = (1.0 + 0.01M_s \nu m) \gamma_{\pm} \quad (1.17)$$

$$f_{\pm} = \frac{\rho + 0.001c(\nu M_s - M)}{\rho_0} \gamma_{\pm} \quad (1.18)$$

$$\gamma_{\pm} = \frac{\rho - 0.001cM}{\rho_0} \gamma_{\pm} = \left(\frac{c}{m\rho_0} \right) \gamma_{\pm} \quad (1.19)$$

$$\gamma_{\pm} = (1 + 0.001mM) \left(\frac{\rho}{\rho_0} \right) \gamma_{\pm} = \left(\frac{m\rho_0}{c} \right) \gamma_{\pm} \quad (1.20)$$

where ν = stoichiometric number = $\nu_+ + \nu_-$

ρ = solution density

ρ_0 = solvent density

M = molecular weight of the solute

M_s = molecular weight of the solvent

Solubility of a Pure-Component Strong Electrolyte.

Calculation of the solubility of a pure-component solid in solution requires that the mean ionic activity coefficient be known along with a thermodynamic solubility product (a solubility product based on activity). Thermodynamic solubility products can be calculated from standard-state Gibbs free energy of formation data. If, for example, we wish to calculate the solubility of KCl in water at 25°C,



the equilibrium constant is given by

$$K_{sp} = \frac{a_{\text{K}^+} a_{\text{Cl}^-}}{a_{\text{KCl}}} = (\gamma_{\text{K}^+} m_{\text{K}^+})(\gamma_{\text{Cl}^-} m_{\text{Cl}^-}) = \gamma_{\pm}^2 m_{\pm}^2 \quad (1.22)$$

The equilibrium constant is related to the Gibbs free energy of formation by the relation

$$K_{sp} = \exp\left(\frac{-\Delta G_{f^0}}{RT}\right) \quad (1.23)$$

The free energy of formation of KCl can be written as

$$\Delta G_{f^0} = \Delta G_{f^0\text{K}^+} + \Delta G_{f^0\text{Cl}^-} - \Delta G_{f^0\text{KCl}} \quad (1.24)$$

Using data from the literature, one finds (Zemaitis et al. 1986)

$$\Delta G_{f^0} = -1282 \text{ cal/gmol} \quad (1.25)$$

so that

$$K_{sp} = 8.704 \quad (1.26)$$

Employing this equilibrium constant and assuming an activity coefficient of 1 yields a solubility concentration of 2.95 molal. This compares with an experimental value of 4.803 molal (Linke and Seidell 1965). Obviously, assuming an activity coefficient of unity is a very poor approximation in this case and results in a large error.

The calculation of mean ionic activity coefficients can be complex, and a number of methods are available. Several references describe these various methods (Robinson and Stokes 1970; Guggenheim 1986; Zemaitis et al. 1986). The method of Bromley (1972, 1973, 1974) can be used up to a concentration of 6 molal and can be written as

$$\log \gamma_{\pm} = \frac{A|z^+z^-|\sqrt{I}}{1 + \sqrt{I}} + \frac{(0.06 + 0.6B)|z^+z^-|I}{\left(1 + \frac{1.5}{|z^+z^-|}I\right)^2} + BI \quad (1.27)$$

where γ_{\pm} = activity coefficient

A = Debye-Hückel constant

z = number of charges on the cation or anion

I = ionic strength, which is $\frac{1}{2} \sum_i m_i z_i^2$

B = constant for ion interaction

Values for the constant B are tabulated for a number of systems (Zemaitis et al. 1986). For KCl, $B = 0.0240$. Employing Equation (1.27), γ_{\pm} can be calculated as a function of m . This must be done until the product $\gamma_{\pm}^2 m^2 = K_{sp}$. For the KCl-water system at 25°C, γ_{\pm} is given as a function of concentration in Table 1.4 along with $\gamma_{\pm}^2 m^2$. You can see that the resulting calculated solubility is approximately 5 molal, which compares reasonably well with the experimental value of 4.8 molal.

Electrolyte Mixtures. Calculation of the solubility of mixtures of strong electrolytes requires knowledge of the thermodynamic solubility product for all species that can precipitate and requires using an activity coefficient calculation method that takes into account ionic interactions. These techniques are well described by Zemaitis et al. (1986), but we will discuss a simple case in this section.

The simplest case would be a calculation involving a single possible precipitating species. A good example is the effect of HCl on the solubility of KCl. The thermodynamic solubility product K_{sp} for KCl is defined as

$$K_{sp} = (\gamma_{\text{K}^+} m_{\text{K}^+})(\gamma_{\text{Cl}^-} m_{\text{Cl}^-}) = \gamma_{\pm}^2 m^2 \quad (1.28)$$

Table 1.4 Calculated Activity Coefficients for KCl in Water at 25°C

m (molality)	γ_{\pm}	$\gamma_{\pm}m$
0.01	0.901	8.11×10^{-6}
0.1	0.768	5.8×10^{-3}
1.0	0.603	0.364
1.5	0.582	0.762
2.0	0.573	1.31
2.5	0.569	2.02
3.0	0.569	2.91
3.5	0.572	4.01
4.0	0.577	5.32
4.5	0.584	6.91
5.0	0.592	8.76

Note: $K_{sp} = 8.704$ from Gibbs free energy of formation.
Source: Data from Zemaitis et al. 1986.

In the preceding example, we obtained K_{sp} from the Gibbs free energy data and used this to calculate the solubility of KCl. Normally for a common salt, solubility data are available. K_{sp} is therefore obtained from the experimental solubility data and activity coefficients. Using the experimental KCl solubility at 25°C (4.8 molal) and the Bromley activity coefficients yields $K_{sp} = 8.01$. If we wish to calculate the KCl solubility in a 1 molal HCl solution, we can write the following equations:

$$\frac{(\gamma_{K^+}m_{K^+})(\gamma_{Cl^-}m_{Cl^-})}{K_{sp}} = 1 \quad (1.29)$$

$$z_{K^+}m_{K^+} + z_{H^+}m_{H^+} = z_{Cl^-}m_{Cl^-} + z_{Cl^-}m_{Cl^-} \quad (1.30)$$

(from KCl) (from HCl) (from KCl) (from HCl)

Equations (1.29) and (1.30) must be satisfied simultaneously for a fixed value of 1 molal HCl.

Using Bromley's method for multicomponent electrolytes,

$$\log \gamma_i = \frac{-Az_i^2\sqrt{I}}{I + \sqrt{I}} + F_i \quad (1.31)$$

where A = Hückel constant

I = ionic strength

i = any ion present

z_i = number of charges on ion i

F_i = an interaction parameter term

$$F_i = \sum B_{ij}z_{ij}^2m_j \quad (1.32)$$

where j indicates all ions of opposite charge to i

$$z_{ij} = \frac{z_i + z_j}{2} \quad (1.33)$$

where m_j = molality of ion j

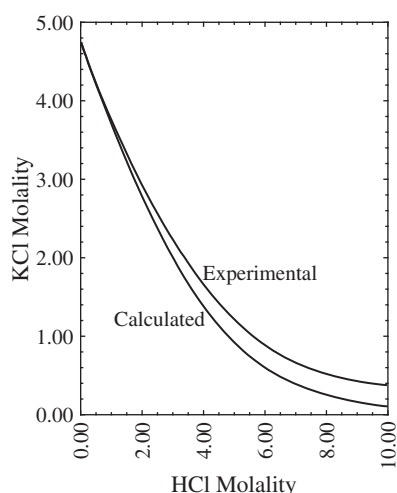


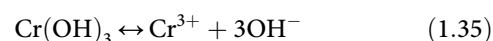
Figure 1.8 Calculated versus experimental KCl solubility in aqueous HCl solution at 25°C

Source: Reproduced from J. F. Zemaitis, Jr., D. M. Clark, M. Rafal, and N. C. Scrivner (1986), *Handbook of Aqueous Electrolyte Thermodynamics*, p. 284. Used by permission of the American Institute of Chemical Engineers © 1986 AIChE.

$$B_{ij} = \frac{(0.06 + 0.6B)|z_i z_j|}{[1 + (1.5/|z_i z_j|)I]^2} + B \quad (1.34)$$

Employing these equations, the activity coefficient for K^+ and Cl^- are calculated as a function of KCl concentration at a fixed HCl concentration of 1 molar. These values, along with the molalities of the ions, are then substituted into Equation (1.29) until it is an equality (within a desired error). The solubility of KCl in a 1 molal solution of HCl is found to be 3.73 molal, which compares with an experimental value of 3.92 molal. This calculation can then be repeated for other fixed HCl concentrations. Figure 1.8 compares the calculated and experimental values of KCl solubility over a range of HCl concentrations. Unfortunately, many systems of interest include species that form complexes, intermediates, and undissociated aqueous species. This greatly increases the complexity of solubility calculations because of the large number of possible species. In addition, mixtures with many species often include a number of species that may precipitate. These calculations are extremely tedious and time consuming to do by hand or to write a specific computer program for each application. Commercial software is available for calculations in complex electrolyte mixtures. ProChem, part of the OLI Toolkit developed by OLI Systems, Inc. (Cedar Knolls, NJ), is an excellent example. The purpose of the package is to simultaneously consider the effects of the detailed reactions as well as the underlying species interactions that determine the actual activity coefficient values. Only by such a calculation can the solubility be determined.

A good example of the complexity of these calculations can be seen when looking at the solubility of $Cr(OH)_3$. Simply assuming the dissociation reaction



and calculating a solubility using the K_{sp} obtained from Gibbs free energy of formation lead to serious error. This is because a

Table 1.5 Calculated Results for $\text{Cr}(\text{OH})_3$ Solubility at 25°C

Equilibrium constant	K (mol/kg)	
H_2O	9.94×10^{-15}	
CrOH^{+2}	1.30×10^{-10}	
$\text{Cr}(\text{OH})_2^+$	2.72×10^{-9}	
$\text{Cr}(\text{OH})_3(\text{aq})$	2.03×10^{-6}	
$\text{Cr}(\text{OH})_3(\text{crystal})$	6.44×10^{-31}	
$\text{Cr}(\text{OH})_4^-$	1.67×10^{-5}	
$\text{Cr}_2(\text{OH})_2^{+4}$	2.35×10^{-5}	
$\text{Cr}_3(\text{OH})_4^{+5}$	2.52×10^{-7}	
Liquid-phase pH = 10	Ionic strength = 1.01×10^{-2}	
Species	Moles	Activity coefficient
H_2O	55.5	1.0
H^+	1.22×10^{-10}	0.904
OH^-	1.00×10^{-4}	0.902
Cr^{+3}	2.21×10^{-18}	0.397
CrOH^{+2}	9.32×10^{-13}	0.655
$\text{Cr}(\text{OH})_2^+$	1.65×10^{-8}	0.899
$\text{Cr}(\text{OH})_3(\text{aq})$	6.56×10^{-7}	1.0
$\text{Cr}(\text{OH})_4^-$	3.95×10^{-6}	0.899
$\text{Cr}_2(\text{OH})_2^{+4}$	2.98×10^{-21}	0.185
$\text{Cr}_3(\text{OH})_4^{+5}$	4.48×10^{-22}	0.0725
Cl^-	1.00×10^{-2}	0.898
Na^-	1.01×10^{-2}	0.898

Source: Data from Zemaitis et al. 1986.

number of other dissociation reactions and species are possible. These include $\text{Cr}(\text{OH})_3$ (undissociated molecule in solution), $\text{Cr}(\text{OH})_4^-$, $\text{Cr}(\text{OH})_2^+$, $\text{Cr}(\text{OH})^{2+}$, $\text{Cr}_2(\text{OH})_2^{4+}$, and $\text{Cr}_3(\text{OH})_4^{5+}$.

Calculation of the solubility of $\text{Cr}(\text{OH})_3$ as a function of pH using HCl and NaOH to adjust the pH requires taking into account all species, equilibrium relationships, mass balances, and electroneutrality, as well as calculation of the ionic activity coefficients. The results of such a calculation (employing Prochem) is shown in Table 1.5 and Figures 1.9 and 1.10. Table 1.5 shows the results obtained at a pH of 10. Figure 1.9 gives the solubility results obtained from a series of calculations and also shows the concentration of the various species, whereas Figure 1.10 compares the solubility obtained with that calculated from a solubility product. The solubility results obtained by the simple solubility product calculation are orders of magnitude less than those obtained by the complex calculation, demonstrating the importance of considering all possible species in the calculation.

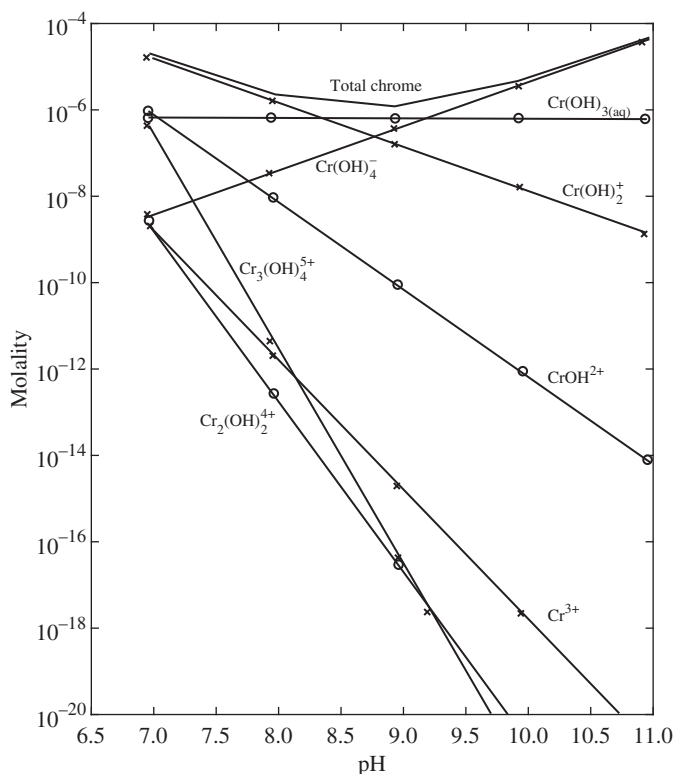


Figure 1.9 Chrome hydroxide solubility and speciation versus pH at 25°C
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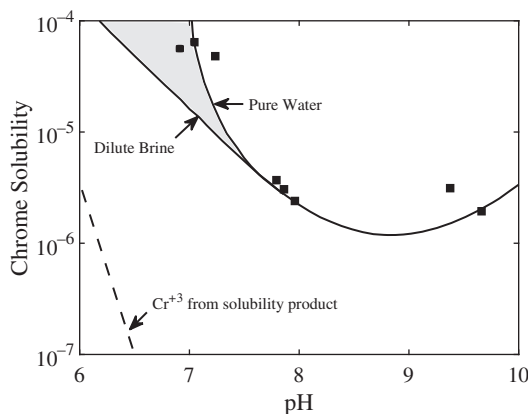


Figure 1.10 Chrome solubility versus pH
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1.4 Solubility of Organics

In crystallization operations involving inorganic materials, we virtually always employ water as the solvent, thus requiring solubility data on inorganic water systems. Because most inorganic materials are ionic, this means that dissociation reactions, ionic interactions, and pH play a major role in determining the solubility of a particular inorganic species in aqueous solution. When dealing with organic species (or inorganics in nonaqueous solvents), a wide variety of solvents and solvent mixtures usually can be employed. The interaction between the solute and

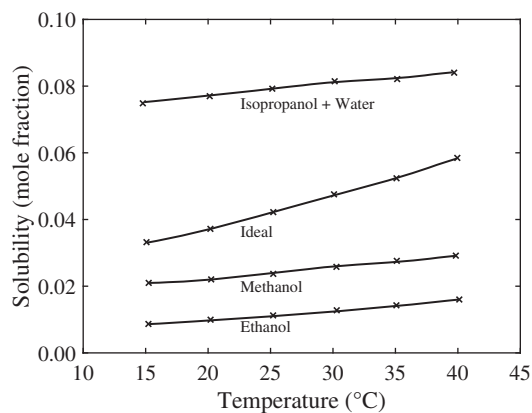


Figure 1.11 Solubility of hexamethylenetetramine in different solvents
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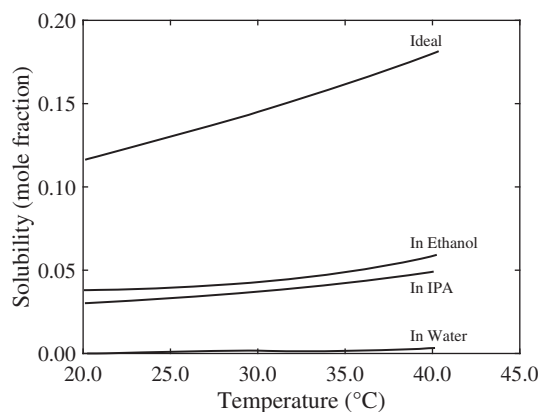


Figure 1.12 Solubility of adipic acid in different solvents
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the solvent determines the differences in solubility commonly observed for a given organic species in a number of different solvents. This is illustrated in Figures 1.11 and 1.12 for hexamethylene tetramine and adipic acid in several different solvents. In the development of crystallization processes, this can be a powerful tool. In many cases the solvent chosen for a particular process is an arbitrary choice made in the laboratory with no thought of the downstream processing consequences. Frequently, from a chemical synthesis or reaction point of view, a number of different solvents could be used with no significant change in product yield or quality. This means that the solubility and physical properties of the solvent (solubility as a function of temperature, absolute solubility, and vapor pressure) should be evaluated so that the solvent that provides the best characteristics for the crystallization step is chosen. This requires that the process-development engineers be in contact with the synthetic organic chemists early in process development. In this section we will describe the basic principles required to estimate and

calculate the solubility of an organic solute in different solvents and explain how to assess mixed solvents.

1.4.1 Thermodynamic Concepts and Ideal Solubility

As we have shown previously, the condition for equilibrium between a solid solute and a solvent is given by the relation

$$\mu_{i,\text{solid}} = \mu_{i,\text{solution}} \quad (1.36)$$

A thermodynamic function known as the *fugacity* can be defined as

$$\mu_i - \mu_i^0 = RT \ln \left(\frac{f_i}{f_i^0} \right) \quad (1.37)$$

Comparing Equation (1.10) with Equation (1.37) shows us that the activity $a_i = f_i/f_i^0$. Through a series of manipulations, it can be shown that for phases in equilibrium (Prausnitz et al. 1986),

$$f_{i,\text{solid}} = f_{i,\text{solution}} \quad (1.38)$$

Equation (1.38) will be more convenient for us to use in describing the solubility of organic solids in various solvents. The fugacity is often thought of as a “corrected pressure” and reduces to pressure when the solution is ideal. Equation (1.38) can be rewritten as

$$f_{2,\text{solid}} = \gamma_2 x_2 f_2^0 \quad (1.39)$$

where f_2 = fugacity of the solid

x_2 = mole fraction of the solute in the solution

f_2^0 = standard state fugacity

γ_2 = activity coefficient of the solute

or

$$x_2 = \frac{f_{2,\text{solid}}}{\gamma_2 f_2^0} \quad (1.40)$$

Equation (1.40) is a general equation for the solubility of any solute in any solvent. We can see from this equation that the solubility depends on the activity coefficient and on the fugacity ratio f_2/f_2^0 . The standard state fugacity normally used for solid-liquid equilibrium is the fugacity of the pure solute in a subcooled liquid state below its melting point. We can simplify Equation (1.40) further by assuming that our solid and subcooled liquid have small vapor pressures. We can then substitute vapor pressure for fugacity. If we further assume that the solute and solvent are chemically similar so that $\gamma_2 = 1$, then we can write

$$x_2 = \frac{P_{2,\text{solid}}^s}{P_{2,\text{subcooled liquid}}^s} \quad (1.41)$$

Equation (1.41) gives the ideal solubility. Figure 1.13, an example phase diagram for a pure component, illustrates several points. First, we are interested in temperatures below the triple point because we are interested in conditions where the solute is a solid. Second, the subcooled liquid pressure is obtained by extrapolating the liquid-vapor line to the correct temperature.

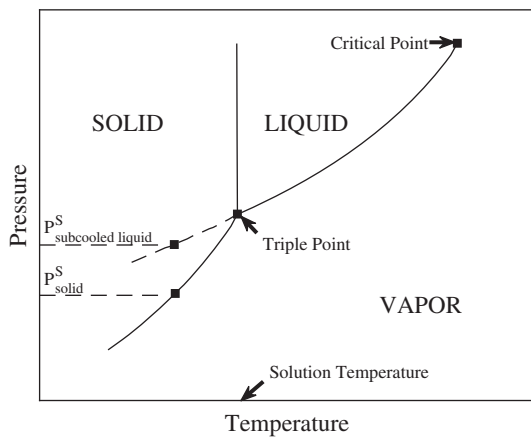


Figure 1.13 Schematic of a pure-component phase diagram
 Source: Reprinted by permission of Prentice-Hall from J. M. Prausnitz, R. N. Lichenthaler, and E. Gomes de Azvedo (1986), *Molecular Thermodynamics of Fluid-Phase Equilibria*, 2nd ed. Copyright © 1986, Prentice-Hall Publishers.

Equation (1.41) gives us two important pieces of information. The first is that the ideal solubility of the solute does not depend on the solvent chosen; the ideal solubility depends only on the solute properties. Second, it shows that differences in the pure-component phase diagrams that result from structural differences in materials will alter the triple point and hence the ideal solubility.

A general equation for the fugacity ratio is

$$\ln\left(\frac{f_2}{f_{2,\text{subcooled liquid solute}}}\right) = \frac{\Delta H_{tp}}{R} \left(\frac{1}{T_{tp}} - \frac{1}{T}\right) - \frac{\Delta C_p}{R} \left(\ln \frac{T_{tp}}{T} - \frac{T_{tp}}{T} + 1\right) - \frac{\Delta V}{RT}(P - P_{tp}) \quad (1.42)$$

where ΔH_{tp} = enthalpy change for the liquid solute transformation at the triple point

T_{tp} = triple point temperature

ΔC_p = difference between the C_p of the liquid and the solid

ΔV = volume change for liquid–solid transformation

R = universal gas constant

If substituted into Equation (1.40), this yields the solubility equation

$$x_2 = \frac{1}{\gamma_2} \exp \left[\frac{\Delta H_{tp}}{R} \left(\frac{1}{T_{tp}} - \frac{1}{T}\right) - \frac{\Delta C_p}{R} \left(\ln \frac{T_{tp}}{T} - \frac{T_{tp}}{T} + 1\right) - \frac{\Delta V}{RT}(P - P_{tp}) \right] \quad (1.43)$$

Equation (1.43) is the most general form of the solubility equation. In most situations (though not all), the effect of pressure on solubility is negligible, so the last term on the right-hand side of the equation can be dropped. In addition, the heat-capacity term also usually can be dropped from the equation. This yields

$$x_2 = \frac{1}{\gamma_2} \exp \left[\frac{\Delta H_{tp}}{R} \left(\frac{1}{T_{tp}} - \frac{1}{T}\right) \right] \quad (1.44)$$

or because

$$\Delta S_{tp} = \Delta H_{tp}/T_{tp} \quad (1.45)$$

$$x_2 = \frac{1}{\gamma_2} \exp \left[\frac{\Delta S_{tp}}{R} \left(1 - \frac{T_{tp}}{T}\right) \right] \quad (1.46)$$

In many instances, the triple-point temperature of a substance is not known. In those cases, the enthalpy of melting (fusion) and the melting-point temperature are used because they are usually close to the triple-point temperature:

$$x_2 = \frac{1}{\gamma_2} \exp \left[\frac{\Delta H_m}{R} \left(\frac{1}{T_m} - \frac{1}{T}\right) \right] \quad (1.47)$$

For an ideal solution, when the activity coefficient equation equals 1, this reduces to

$$x_2 = \exp \left[\frac{\Delta H_m}{R} \left(\frac{1}{T_m} - \frac{1}{T}\right) \right] \quad (1.48)$$

Equation (1.48) allows the simple calculation of ideal solubilities and can be used profitably to see the differences in solubility of chemically similar species with different structures. This is illustrated in Table 1.6, where calculated ideal solubilities are shown together with ΔH_m and T_m . Isomers of the same species can have widely different ideal solubilities based on changes in their physical properties, which relate back to their chemical structures. Equation (1.48) also tells us that for an ideal solution, solubility increases with increasing temperature. The rate of increase is approximately proportional to the magnitude of the heat of fusion (melting). For materials with similar melting temperatures, the lower the heat of fusion, the higher is the solubility. For materials with similar heats of fusion, the material with the lower melting temperature has the higher solubility. A good example of this is shown in Table 1.6 when looking at *ortho*-, *meta*-, and *para*-chloronitrobenzene. The lower-melting *ortho* has an ideal solubility of 79 mol% compared with 25 mol% for the higher-melting *para*. While Equation (1.48) is useful for comparing relative solubilities of various solutes, it takes no account of the solvent used or solute–solvent interactions. To account for the role of the solvent, activity coefficients must be calculated.

1.4.2 Regular Solution Theory

In electrolytic solutions, we were concerned with electrostatic interactions between ions in the solution and with the solvent (water). In solutions of nonelectrolytes, we will be concerned with molecule–solvent interactions due to electrostatic forces, dispersion forces, and chemical forces. Even though a solution contains no ions, electrostatic interactions can still be significant. This is because of a property called *polarity*. An electrically neutral molecule can have a dipole moment that is due to an asymmetric distribution of its electrical charge. This means that one end of the molecule is positive and the other end is negative. The dipole moment is defined by

Table 1.6 Melting Temperature, Enthalpy of Melting, and Ideal Solubility of Organic Solutes at 25°C

Substance	T_m (K)	ΔH_m (cal/mol)	Ideal solubility (mol%)
<i>ortho</i> -Chloronitrobenzene	307.5	4546	79
<i>meta</i> -Chloronitrobenzene	317.5	4629	62
<i>para</i> -Chloronitrobenzene	356.7	4965	25
Naphthalene	353.4	4494	31
Urea	406.0	3472	21
Phenol	314.1	2695	79
Anthracene	489.7	6898	1
Phenanthrene	369.5	4456	23
Biphenyl	342.2	4235	39

Source: Based on data from Walas 1985.

$$\mu = el \quad (1.49)$$

where e is the magnitude of the electric charge and l is the distance between the two charges. The dipole moment is a measure of how polar a molecule is. As the dipole moment increases, the molecule is less symmetric in terms of its electrical charge. A list of molecules and their dipole moments is given in Table 1.7. As you can see from the table, water is quite polar. There are also molecules with more complex charge distributions called *quadrupoles*, which also display this asymmetric charge behavior. This shows that even without ions, electrostatic interactions between polar solvent molecules and polar solute molecules will be of importance in activity coefficient calculations and will therefore affect the solubility.

Organic solutes and solvents are usually classified as polar or nonpolar, although, of course, there is a range of polarity. Nonpolar solutes and solvents also interact through forms of attraction and repulsion known as *dispersion forces*. Dispersion forces result from oscillations of electrons around the nucleus and have a rather complex explanation; however, it is sufficient to say that nonidealities can result from molecule–solvent interactions that result in values of the activity coefficient not equal to 1. An excellent reference in this area is the book by Prausnitz et al. (1986).

Generally, the activity coefficients are less than 1 when polar interactions are important, with a resulting increase in solubility of compounds compared with the ideal solubility. The opposite is often true in mixed polar–nonpolar systems, with the activity coefficients being greater than 1. Nonpolar solutions typically have activity coefficients around 1 because they do not tend to exhibit the high degree of interactions that exist in polar and hydrogen-bonding systems. A number of methods are used to calculate activity coefficients of solid solutes in solution. A

Table 1.7 Permanent Dipole Moments

Molecule	μ (Debyes)	Molecule	μ (Debyes)
CO	0.10	CH ₃ I	1.64
C ₃ H ₆	0.35	CH ₃ COOCH ₃	1.67
C ₆ H ₅ CH ₃	0.37	C ₂ H ₅ OH	1.70
PH ₃	0.55	H ₂ O	1.84
HBr	0.80	HF	1.91
CHCl ₃	1.05	C ₂ H ₅ F	1.92
(C ₂ H ₅) ₂ O	1.18	(CH ₃) ₂ CO	2.87
NH ₃	1.47	C ₆ H ₅ COCH ₃	3.00
C ₆ H ₅ NH ₂	1.48	C ₂ H ₅ NO ₂	3.70
C ₆ H ₅ Cl	1.55	CH ₃ CN	3.94
C ₂ H ₅ SH	1.56	CO(NH ₂) ₂	4.60
SO ₂	1.61	KBr	9.07

Source: Data from Prausnitz et al. 1986.

frequently used method is that of Scatchard–Hildebrand, which is also known as *regular solution theory* (Prausnitz et al. 1986):

$$\ln \gamma_2 = \frac{V_2^L (\delta_1 - \delta_2)^2 \phi_1^2}{RT} \quad (1.50)$$

where V_2^L = molar volume of the subcooled liquid solute

δ_2 = solubility parameter of the subcooled liquid

δ_1 = solubility parameter of the solvent

ϕ_1 = volume fraction of the solvent, defined by

$$\phi_1 = \frac{x_1 V_1^L}{x_1 V_1^L + x_2 V_2^L} \quad (1.51)$$

The solubility parameters are defined by the relations

$$\delta_1 = \left(\frac{\Delta u_1^v}{v_1} \right)^{1/2} \quad \delta_2 = \left(\frac{\Delta u_2^v}{v_2} \right)^{1/2} \quad (1.52)$$

where Δu is the enthalpy of vaporization and v is the molar liquid volume. Solubility parameters for a number of solvents and solutes are given in Table 1.8. This method works moderately well at predicting solubilities in nonpolar materials. Calculated solubility results employing this theory are shown in Table 1.9 along with experimentally determined values.

It is apparent that in many cases this theory predicts results very far from the experiment. Regular solution theory has limitations in predicting activity coefficients because it was developed to quantitatively describe solutions with no excess entropy, no change in volume on mixing, and a nonzero enthalpy of mixing. This theory always predicts that all deviations from ideality will be positive, with $\gamma > 1$. Because strong polar–polar interactions generally exhibit behavior with $\gamma < 1$, regular solution theory should not be used for polar systems without extreme caution.

Table 1.8 Solubility Parameters at 25°C

Substance	δ (cal/cm ³) ^{1/2}
Anthracene	9.9
Naphthalene	9.38
Phenanthrene	10.52
Acetic acid	10.05
Acetone	9.51
Aniline	11.46
1-Butanol	11.44
Carbon disulfide	9.86
Carbon tetrachloride	9.34
Chloroform	9.24
Cyclohexane	8.19
Cyclohexanol	11.4
Diethyl ether	7.54
Ethanol	12.92
<i>n</i> -Hexane	7.27
Methanol	14.51
Phenol	12.11
1-Propanol	12.05
2-Propanol	11.57
Perfluoro- <i>n</i> -heptane	6.0
Neopentane	6.2
Isopentane	6.8
<i>n</i> -Pentane	7.1
1-Hexene	7.3
<i>n</i> -Octane	7.5
<i>n</i> -Hexadecane	8.0
Ethyl benzene	8.8
Toluene	8.9
Benzene	9.2
Styrene	9.3
Tetrachloroethylene	9.3
Bromine	9.5

Sources: Based on data from Prausnitz et al. 1986 and Walas 1985.

Similarly, regular solution theory cannot generally describe solutions with strong hydrogen bonding or acid–base interactions. A number of modifications of the Scatchard–Hildebrand theory as well as other methods are available for activity

coefficient calculations and are described in various other texts (Walas 1985; Prausnitz et al. 1986; Reid et al. 1987).

Empirical methods have been developed to mitigate some of the limitations of regular solution theory. For example, Hansen solubility parameters (HSPs) account for hydrogen bonding, dispersion, and polar bonding forces, expanding on the Hildebrand solubility parameters, which divided interactive forces into dispersive and polar interactions (Hansen 2007). Using HSPs, qualitative comparisons of solubility can be made for compounds in various solvents using the relation

$$R_a = [4(D_{\text{solvent}} - D_{\text{solute}})^2 + (P_{\text{solvent}} - P_{\text{solute}})^2 + (H_{\text{solvent}} - H_{\text{solute}})^2]^{0.5} \quad (1.53)$$

where R_a is the distance between the solute and the solvent in Hansen phase space, D is the dispersive solubility parameter, P is the polar solubility parameter, and H is the solubility parameter for hydrogen bonding. Tabulated HSPs may be found in *Hansen Solubility Parameters: A User's Handbook* (Hansen 2007). Solute–solvent systems with smaller R_a values tend to have higher solubilities. Still, no theoretical method is accurate for activity coefficient calculation of solid solutes in liquids for all types of systems.

1.4.3 Group Contribution Methods

As we discussed in Section 1.3 for inorganic materials, industrial crystallization rarely takes place in systems that contain only the solute and solvent. In many situations, additional components are present in the solution that affect the solubility of the species of interest. With an organic solute, data for solubility in a particular solvent are often not available, whereas data for the effect of other species on the solubility are virtually nonexistent. This means that the only option available for determining solubility in a complex mixture of solute, solvent, and other components (impurities or by-products) is through calculation or experimental measurement. While experimental measurement is often necessary, estimation through calculation can be worthwhile.

The main methods available for the calculation of activity coefficients in multicomponent mixtures are called *group contribution methods*. This is because they are based on the idea of treating a molecule as a combination of functional groups and summing the contribution of the groups. This allows the calculation of properties for a large number of components from a limited number of groups. Unlike calculations completed using regular solutions, activity coefficient predictions from group contribution methods can predict both negative and positive deviations from ideality.

Two similar methods are used for these types of calculations: analytical solution of groups (ASOG) and universal quasi-chemical (UNQUAC) functional group activity coefficient (UNIFAC). In the ASOG method, activity coefficients are assumed to be temperature-dependent functions of size, as estimated using the Flory–Huggins equation, and interactions between structural groups. Similarly, the UNIFAC method can be used to estimate activity coefficients in nonelectrolyte mixtures by assuming that activity coefficients are functions of molecular size and shape, as well as intermolecular forces. While UNIFAC makes the limiting

Table 1.9 Solubility of Naphthalene in Various Solvents by UNIFAC and Scatchard–Hildebrand Theory

Solvent	Solubility (mol%)		
	Experimental	UNIFAC	Scatchard–Hildebrand
Methanol	4.4	4.8	0.64
Ethanol	7.3	5.4	4.9
1-Propanol	9.4	9.3	11.3
2-Propanol	7.6	9.3	16.3
1-Butanol	11.6	11.1	18.8
<i>n</i> -Hexane	22.2	25.9	11.5
Cyclohexanol	22.5	20.5	20.0
Acetic acid	11.7	12.5	40.1
Acetone	37.8	35.8	42.2
Chloroform	47.3	47.0	37.8
Ideal solubility = 4.1 mol%			

Source: Data from Walas 1985.

assumption that each functional group is independent of other functional groups, it can still be used to predict eutectic compositions and solubilities in binary and higher solvent mixtures with reasonable accuracy in many cases. For very large or complex molecules, though, UNIFAC parameters may not exist to describe all functional groups. Modifications to the original UNIFAC method include defining new functional groups and expanding parameters to be temperature dependent. Further explanations of these and other group contribution methods are detailed in a number of references (Fredenslund et al. 1977; Kojima and Tochigi 1979; Walas 1985; Reid et al. 1987), and a survey of group contribution methods and advancements is provided by Gmehling (2009) and Gmehling et al. (2015).

Both ASOG and UNIFAC rely on the use of experimental activity coefficient data to obtain parameters that represent interactions between pairs of structural groups. These parameters are then combined to predict activity coefficients for complex species and mixtures of species made up from a number of these functional groups. An example of this would be calculation of the behavior of a ternary system by employing data on the three possible binary pairs. Lists of parameters and detailed explanations of these calculations can be found in the references mentioned previously.

Group contribution methods can also be used to calculate solubility in binary (solute–solvent) systems. A comparison of solubilities calculated employing the UNIFAC method with experimental values and values obtained from the Scatchard–Hildebrand theory is given in Table 1.9.

1.4.4 Quantum Mechanical Predictions

In previous sections we discussed ways to estimate solubility using empirical methods or methods that only work for certain classes of molecules. Those methods have limitations and cannot predict

solubility for all classes of compounds. Quantum mechanics (QM) and statistical thermodynamic calculations overcome some of these barriers by enabling us to estimate molecular chemical potentials without relying on a database of parametrized functional group contributions. Instead, only universal parameters are used in predictions. Calculated chemical potentials can then be used to estimate thermodynamic equilibrium properties such as solubility, activity coefficients, and partition coefficients.

To describe how QM and statistical thermodynamic calculations are completed, we will focus on a commonly used software package: COSMO-RS (Conductor-like Screening Model for Real Solvents; Software for Chemistry & Materials BV, Amsterdam, The Netherlands). First, the molecular electronic structure is optimized using density functional theory (DFT) calculations. Then the charge distribution of the surface of the molecule is calculated using QM, assuming a reference state where the molecule is embedded in a perfect conductor. With this reference state for each molecule of interest, COSMO-RS can use statistical thermodynamics to analyze surface interactions between solvent and solute molecules. From the surface interactions, a charge-density profile can be constructed and used to estimate chemical potential and, subsequently, solubility at infinite dissolution. Calculations can be updated for various temperatures of interest, allowing solubility curves to be constructed. Using this general procedure, solubility can be screened qualitatively in hundreds of solvents rapidly, enabling selection of a solvent list for further experimental evaluation.

When using COSMO-RS, it is important to be aware of three major assumptions embedded in the software calculation blocks:

1. The liquid phase is incompressible.
2. The dielectric permittivity of the solvent is infinite.

3. Only pairwise molecular interactions are allowed at the molecular surface, but all parts of the molecular surfaces can contact other molecular surfaces.

These assumptions allow chemical potentials to be calculated, but they also expose some limitations of using COSMO-RS. From assumption 1, we see that COSMO-RS cannot be used to estimate pressure-dependent equilibrium properties, and assumption 2 indicates that we are defining the solvent as a conductor. From assumption 3, we see that COSMO-RS cannot be used to calculate ternary and higher-order interactions. This assumption can be expanded by using associated molecules as the model molecular complex. For example, acetic acid molecules may be modeled as dimers instead of monomers to enable three-body interactions to be estimated and account for internal hydrogen bonding between molecules.

Although COSMO-RS can be used to qualitatively compare solubilities of compounds in various solvent systems, COSMO-RS is limited in its ability to predict experimental data. For example, bond lengths and angles, as well as intermolecular interactions, may be different in bulk fluid than in the small numbers of molecules that can be simulated in COSMO-RS. Therefore, it is useful to use physical property data, such as heat of fusion derived from differential scanning calorimetry (DSC) experiments, to train COSMO-RS and improve the program's quantitative prediction capabilities.

Beyond polarizable continuum models (PCMs) like COSMO-RS, explicit solvation models also may be used to estimate solubility without the use of empirical equations or experimental data. These methods include using Monte Carlo (MC) and molecular dynamics (MD) simulations. Further information on these and other methods is presented in the review article by Skyner et al. (2015).

1.4.5 Solubility in Mixed Solvents

In looking for an appropriate solvent system for a particular solute to allow for the development of a crystallization process, often the desired properties cannot be obtained with the pure solvents that can be used. For a number of economic, safety, or product stability reasons, you may be forced to consider a small group of solvents. The solute might not have the desired solubility in any of these solvents, or if soluble, the solubility may not vary with temperature sufficiently to allow cooling crystallization. In these cases, a possible solution is to use a solvent mixture to obtain the desired solution properties. The solubility of a species in a solvent mixture can significantly exceed the solubility of that species in either pure-component solvent. This is illustrated in Figure 1.14 for the solute phenanthrene in the solvents cyclohexane and methyl iodide. Instead of a linear relation between the solvent composition and the solubility, the solubility has a maximum at a solvent composition of 38 mol% cyclohexane (solute-free basis). The large change in solubility with solvent composition can be very useful in crystallization processes. It provides a method other than temperature change to alter the solubility of the system. The solubility can be easily altered up or down by adding the appropriate solvent to the system. The method of changing solvent composition to induce crystallization will be discussed in more detail in Section 1.5.4.

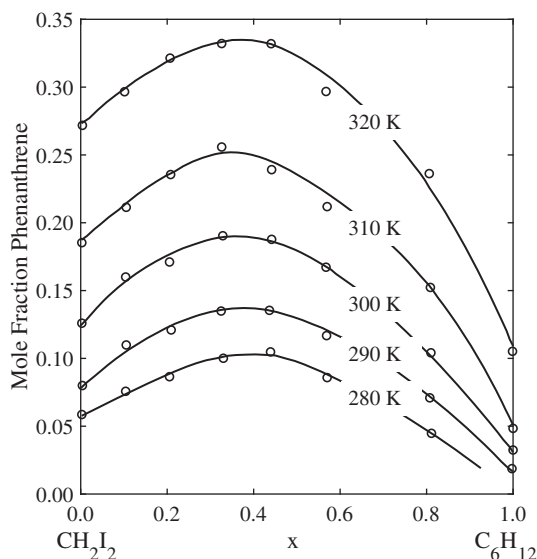


Figure 1.14 Solubility of phenanthrene in cyclohexane–methylene iodide mixtures

Source: Reprinted with permission from L. J. Gordon and R. L. Scott, Enhanced methylene iodide solubility in solvent mixtures: I. The system phenanthrene–cyclohexane–methylene iodide,” *J. Am. Chem. Soc.* 1952; 74:4138. Copyright © 1952, American Chemical Society.

Finding an appropriate mixed solvent system should not be done on a strictly trial and error basis. It should be examined systematically based on the binary solubility behavior of the solute in solvents of interest. It is important to remember that the mixed solvent system with the solute present must be miscible at the conditions of interest. Initial estimates may be completed without collecting experimental solubility data. For systems that exhibit positive deviations from ideality, are not highly polar, and are not strongly hydrogen bonding, the observed maximum in the solubility of solutes in mixtures can be predicted by Scatchard–Hildebrand theory. Looking at Equation (1.50), we see that when the solubility parameter of the solvent is the same as that of the subcooled liquid solute, the activity coefficient will be 1. This is the minimum value of the activity coefficient possible employing this relation. When the activity coefficient is equal to 1, the solubility of the solute is at a maximum. This then tells us that by picking two solvents with solubility parameters that are greater than and less than the solubility parameter of the solute, we can prepare a solvent mixture in which the solubility will be a maximum. For example, let us look at the solute anthracene. Its solubility parameter is $9.9 \text{ (cal/cm}^3)^{1/2}$. Looking at Table 1.8, which lists solubility parameters for a number of common solvents, we see that ethanol and toluene have solubility parameters that bracket the value of anthracene. If we define a mean solubility parameter by the relation

$$\delta = \frac{\sum x_i V_i \delta_i}{\sum x_i V_i} \quad (1.54)$$

we can then calculate the solvent composition that will have the maximum solubility. This is a useful way to estimate the optimal solvent composition prior to experimental