IUCr MONOGRAPHS ON CRYSTALLOGRAPHY • 30

Polymorphism in Molecular Crystals

SECOND EDITION

JOEL BERNSTEIN

OXFORD SCIENCE PUBLICATIONS

INTERNATIONAL UNION OF CRYSTALLOGRAPHY
BOOK SERIES

IUCr Monographs on Crystallography

1 *Accurate molecular structures*
A. Domenicano, I. Hargittai, editors
2 *P. P. Ewald and his dynamical theory of X-ray diffraction*
D. W. J. Cruickshank, H. J. Juretschke, N. Kato, editors
3 *Electron diffraction techniques, Vol. 1*
J. M. Cowley, editor
4 *Electron diffraction techniques, Vol. 2*
J. M. Cowley, editor
5 *The Rietveld method*
R. A. Young, editor
6 *Introduction to crystallographic statistics*
U. Shmueli, G. H. Weiss
7 *Crystallographic instrumentation*
L. A. Aslanov, G. V. Fetisov, J. A. K. Howard
8 *Direct phasing in crystallography*
C. Giacovazzo
9 *The weak hydrogen bond*
G. R. Desiraju, T. Steiner
10 *Defect and microstructure analysis by diffraction*
R. L. Snyder, J. Fiala, H. J. Bunge
11 *Dynamical theory of X-ray diffraction*
A. Authier
12 *The chemical bond in inorganic chemistry*
I. D. Brown
13 *Structure determination from powder diffraction data*
W. I. F. David, K. Shankland, L. B. McCusker, Ch. Baerlocher, editors
14 *Polymorphism in molecular crystals*
J. Bernstein
15 *Crystallography of modular materials*
G. Ferraris, E. Makovicky, S. Merlino
16 *Diffuse X-ray scattering and models of disorder*
T. R. Welberry
17 *Crystallography of the polymethylene chain: an inquiry into the structure of waxes*
D. L. Dorset
18 *Crystalline molecular complexes and compounds: structure and principles*
F. H. Herbstein
19 *Molecular aggregation: structure analysis and molecular simulation of crystals and liquids*
A. Gavezzotti
20 *Aperiodic crystals: from modulated phases to quasicrystals*
T. Janssen, G. Chapuis, M. de Boissieu
21 *Incommensurate crystallography*
S. van Smaalen
22 *Structural crystallography of inorganic oxysalts*
S. V. Krivovichev
23 *The nature of the hydrogen bond: outline of a comprehensive hydrogen bond theory*
G. Gilli, P. Gilli
24 *Macromolecular crystallization and crystal perfection*
N. E. Chayen, J. R. Helliwell, E. H. Snell
25 *Neutron protein crystallography: hydrogen, protons, and hydration in bio-macromolecules*
N. Niimura, A. Podjarny
26 *Intermetallics: structures, properties, and statistics*
W. Steurer, J. Dshemuchadse
27 *The chemical bond in inorganic chemistry: The bond valence model, second edition*
I. D. Brown
28 *Aperiodic crystals: From modulated phases to quasicrystals: Structure and properties, second edition*
T. Janssen, G. Chapuis, M. de Boissieu

29 *Biological small angle scattering: Theory and practice*
E. E. Lattman, T. D. Grant, E. H. Snell
30 *Polymorphism in molecular crystals, second edition*
J. Bernstein

IUCr Texts on Crystallography

1 *The solid state*
A. Guinier, R. Julien
4 *X-ray charge densities and chemical bonding*
P. Coppens
8 *Crystal structure refinement: a crystallographer's guide to SHELXL*
P. Müller, editor
9 *Theories and techniques of crystal structure determination*
U. Shmueli
10 *Advanced structural inorganic chemistry*
W.-K. Li, G.-D. Zhou, T. Mak
11 *Diffuse scattering and defect structure simulations: a cook book using the program DISCUS*
R. B. Neder, T. Proffen
13 *Crystal structure analysis: principles and practice, second edition*
W. Clegg, editor
14 *Crystal structure analysis: a primer, third edition*
J. P. Glusker, K. N. Trueblood
15 *Fundamentals of crystallography, third edition*
C. Giacovazzo, editor
16 *Electron crystallography: electron microscopy and electron diffraction*
X. Zou, S. Hovmöller, P. Oleynikov
17 *Symmetry in crystallography: understanding the International Tables*
P. G. Radaelli
18 *Symmetry relationships between crystal structures: applications of crystallographic group theory in crystal chemistry*
U. Müller
19 *Small angle X-ray and neutron scattering from solutions of biological macromolecules*
D. I. Svergun, M. H. J. Koch, P. A. Timmins, R. P. May
20 *Phasing in crystallography: a modern perspective*
C. Giacovazzo
21 *The basics of crystallography and diffraction, fourth edition*
C. Hammond

Polymorphism in Molecular Crystals

Second Edition

Joel Bernstein

Department of Chemistry
Ben-Gurion University of the Negev
New York University Abu Dhabi and Shanghai

OXFORD
UNIVERSITY PRESS

OXFORD
UNIVERSITY PRESS

Great Clarendon Street, Oxford, OX2 6DP,
United Kingdom

Oxford University Press is a department of the University of Oxford.
It furthers the University's objective of excellence in research, scholarship,
and education by publishing worldwide. Oxford is a registered trade mark of
Oxford University Press in the UK and in certain other countries

First Edition published in 2002
First published in paperback 2008
Second Edition published in 2020

Impression: 1

Published in the United States of America by Oxford University Press
198 Madison Avenue, New York, NY 10016, United States of America

British Library Cataloguing in Publication Data
Data available

Library of Congress Control Number: 2018968361

ISBN 978–0–19–965544–1

DOI: 10.1093/oso/ 9780199655441.001.0001

Printed and bound by
CPI Group (UK) Ltd, Croydon, CR0 4YY

To Tzipi

AT FIRST SIGHT

Once made, this stolid mauve
powder would seem forever;

but people intent on repro-
duction fire up pots next door

or across the sea, and out
of the odd one crystallizes

another, the same, but for
a tell-tale (to X-rays) part

that twists a tad; in a tango
of attractions and absences

molecules nestle in a variant
pattern. Neat, but from here on,

the first will not be made. So
it seems; the ur-makers once

patient hands grow limp—
has desire fled? In all flasks

the second precipitates. Who,
oh who, is to blame? Yes, lay it

to the other coming—as if
seed crystals flew the world.

But the first is the accident,
a small well in a chanced

landscape, a nicked knife edge,
the one parcel of phase space

never to be sampled again,
the vanishing polymorph…you.

Roald Hoffmann

Foreword

In January 2019 we were deeply saddened to suddenly lose Professor Joel Bernstein, a colleague, collaborator, parent, husband, grandfather, and a highly accomplished individual. Joel obtained his BA degree in chemistry from Cornell University in 1962 and an MSc in physical chemistry from Yale University in 1964. He obtained his PhD in 1967 from Yale, working with Basil G. Anex on spectroscopy of organic compounds. Following two postdoctoral positions, researching in X-ray crystallography with Kenneth Trueblood at UCLA and in organic solid-state chemistry with Gerhardt Schmidt at the Weizmann Institute of Science, he joined the Department of Chemistry of the newly established Ben-Gurion University of the Negev in Israel, where he later became the Barry and Carol Kaye Professor of Applied Science. Joel was instrumental in setting up the chemistry department at Ben-Gurion University. Later on, as a Distinguished Global Professor, he contributed to building the chemistry program and taught general chemistry at New York University's Global Network, particularly in their portal campuses in Abu Dhabi and Shanghai.

Joel was an incredible speaker, a dedicated mentor, a supportive colleague, a seasoned wine connoisseur, and a true friend to many of us in the solid-state research community. Those of us who had the privilege to be part of his life professionally will always cherish his immense contributions to the solid-state research, and will remember him the way he really was—a great, yet subtly humble person, a true gentle giant. Joel came with a combination of generosity and kindness that is uncommon with professionals of his caliber. He was able to talk to an undergraduate student or to a junior colleague with the same level of patience, appreciation and respect as he would with some of the most distinguished scientists or Nobel laureates. Joel taught his fellow faculty to approach problems with patience, and with a warm smile he was always ready to provide an endless support and encouragement to his colleagues and collaborators. He had an incredible and rare ability of narration with an extraordinary charisma that would make even a layperson want to hear and learn more about science. He had the ability to comfort others when they needed. He gained a respect from others by true interest, appreciation, sincerity and kindness. He had the ability to convey science with a great, sincere passion, and in addition to the polymorphism, a topic to which he dedicated most of his career, he will be remembered for his interest in popular science, particularly his research on the shroud of Turin, the fuzzy logic, and one his favorite subjects, the disappearing polymorphs. Joel's colleagues from his student days will always remember him for his generosity and readiness to help, his students will remember his inspirational and moving lectures, and those of us who

had the privilege to collaborate with him will remember him for the rigor and depth of his scientific work. He believed in the power of knowledge as a universal human value that should be accessible to anyone, regardless of their religion, ethnicity, creed or color. He selflessly shared his knowledge with a great passion, and truly inspired so many of us.

Joel was inspired by the occurrence of *polymorphism*—the ability of solids to crystallize with different crystal structures and hence have different properties—and recognized its potential and the immense impact it could have for both science and practice very early on in his career, during one of his post-doctoral terms. Being inspired by the early works of Paul Heinrich von Groth, and particularly by the later works of Walter McCrone, he decided to pursue this subject as his life-long career. Over the years, he gave a number of lectures on the conceptual, terminological and scientific aspects or specific cases related to the topic, in what he used to refer to as his "adventures in polymorphland". Being the most comprehensive review on this immensely broad chemistry field to date, since the publishing of the first edition in 2002, Joel's book "*Polymoprhism in Molecular Crystals*" has quickly become the prime text on this important topic that has been appreciated as a precious source and comprehensive yet concise read equally by researchers and students. His book is very frequently cited as a reliable and relevant source of information on polymorphism in both academic and patent literature.

As with any active field of research, being a fundamental solid-state phenomenon, our understanding of polymorphism has continued to evolve and many new examples have been added to the related literature over the past ten years. This second edition of Bernstein's "*Polymorphism in Molecular Crystals*", on which he started working tirelessly and passionately several years after the publication of the first edition to the day of his sudden passing, builds on the first edition by subliming the past 15 years of the author's research of the related literature. In this edition, as well as in the previous one, he shares his experience as one of the most eminent scholars in the solid-state chemistry, but also his expertise as an expert witness in multiple patent litigation cases in the court. The examples presented were carefully selected to illustrate a multitude of aspects of the polymorphism in molecular crystals, in communication with his colleagues, collaborators and professional contacts, his and others' experience with legal cases related to the topic, and from his own original research over the last decade. In selecting the examples, he carefully maintained the balance between examples from the older literature, and those from the most recent literature, particularly with respect to the computational techniques that have been developed in the meantime to explain or to predict the occurrence of polymorphism.

In over 600 pages of text and citing over 2060 references, the author delves in the basic aspects of polymorphism, such as the related thermodynamics, the nucleation processes, difference in structure between polymorphs, and the analytical methods that are commonly used to distinguish between polymorphs. With great passion and in considerable depth, he describes specific topics of this multifaceted subject, spanning a thorough historical overview of the subject, the different

definitions and thermodynamics principles, and applications in pharmaceutical industry, dye and pigment technology, and electronics. In the book he is particularly elaborate on the topic of disappearing polymorphs, definitional issues related to polymorphism, and the conclusiveness of the presence of polymorphism by using various analytical techniques. This second edition of the book brings a much more elaborate reading on the computational aspects of predicting and detecting polymorphism, on crystallization as determining step in the evolution of polymorphism, and also provides an updated analytical techniques section. As some of the most important applications of polymorphs, the author has also included timely and thorough overview of the emerging directions and practical aspects in polymorph research—the polymorphism in dyes and pigments, high-energy materials that are becoming increasingly researched due to the potential global safety threats, and provides a set of selected examples of the relevance of polymorphism to the patent literature, particularly such that are related to the pharmaceutical industry. The narrative is comprehensive, with reference to the relevant research contributions from some of the leading research groups in the field, as well as to particular illustrative examples that are not commonly accessible to the wider readership. The writing style is accessible, while also being meticulous, thorough, and rigorous. Joel firmly believed in the value of a long-lasting, good, timeless science, such that has already passed or will most certainly pass the test of time, and which is based on facts, not on fiction—as he would often discuss in his lectures or articles on the topic—and he deeply appreciated quality over quantity, and rigor over hype in scientific research. The structure and contents of this second edition of the book reflects that approach. Together with Joel's own original publications and detailed reviews on polymorphism, the book will remain a testament of his valuable contribution to the chemistry research and his legacy to the solid-state chemistry community.

I would like to take this opportunity to thank all parties who kindly provided materials and information that was needed to complete the proofreading of this book posthumously.

Pančе Naumov
Abu Dhabi, March 13, 2020

Preface to the second edition

Allow me to discourse on polymorphism
A subject oft greeted with cynicism
It's about multiple crystal forms
Whose behavior not always conforms
To every sacred scientific or linguistic formalism.

Nearly 20 years have elapsed since the publication of the first edition of this work. The exponential increase in the activity and interest in the subject far exceeded our expectations and our imaginations when the first edition was sent to the printer in July of 2001. The varieties of reasons we attribute to these developments are documented throughout the current volume.

We noted in the Preface to the first edition that the book was intended to provide a starting point for individuals encountering the phenomenon of polymorphism in molecular crystals for the first time. Therefore, considerable attention was paid to fundamentals. That intention has not changed, nor have most of the fundamentals (e.g., thermodynamics, structural principles, basic analytical techniques, some still classic systems, etc.) so those sections have very much been left intact. The change in the title of Chapter 3 from "Controlling the polymorphic form obtained" to "Exploring the crystal form landscape" reflects a change in the investigative nature of the search for solid forms and the increasing emphasis on discovering new forms.

In pursuit of that search there has been considerable progress in our understanding of the phenomenon of polymorphism, the experimental procedures for the exploration of the solid form landscape, the analytical techniques for identifying and characterizing polymorphs, the utilization of polymorphism to tune and improve the properties of materials, the application of polymorphism to the study of structure–property relations, and the impact of polymorphism in a wide variety of industrial/commercial applications, in particular those involving the development and protection of intellectual property. We attempt here to provide examples, indeed representative examples, of many of these very impressive developments, but the literature contains much more than can be contained in a single volume, and in preparing this work we were faced with a quandary of the rich. The choice of those examples to include is a difficult one, but the choice of what not to include is even more difficult. The first edition of this title contained approximately 1500 references, and this one contains at least 1000 more. Given the growing size of the community of practitioners in this field it is inevitable that some, indeed many, works that warrant inclusion or citation have not been included or cited due to lack of space. This is a subjective judgment; any slights to the increasing numbers of members of our very talented and very productive scientific community are unintended.

A number of the topics in the first edition have been the subjects of excellent review papers. As was our intent in the first edition to provide as useful a literature resource in one volume as possible to bring the reader up to date, we have tried to cite as many of those. In many cases, especially those for which the time lag between the publication date of the review and this edition was short, we briefly summarize the contents of the review and invite the reader to seek out the full review. As in the previous edition these reviews are meant to serve as literary milestones for future citations.

Any work of this sort cannot be completed with out the aid and support of many, and I wish to acknowledge them with deep-felt thanks. As before, the accomplished experts in specific areas of polymorphism responded with enthusiasm to my requests for information and key publications. But clearly first among them is Jan-Olav Henck from Bayer who contributed his vast experience and deep insight in reviewing and critiquing every chapter. Martin Schmidt from the University of Frankfurt lent his encyclopedic knowledge of pigments and dyes; Colin Pulham from the University of Edinburgh provided the latest developments in high pressure studies; Thomas Klapötke at the Ludwig Maximillian University of Munich contributed updated information on high energy materials.

Dario Braga, Fabrizia Grepioni, and Lucia Maini were consummate hosts during a three-month sojourn at the Institute for Advanced Study at the University of Bologna for much of the final writing, and the living quarters at the Collegio di Espagna in Bologna provided an ideal environment for contemplation and writing. The extraordinary library facilities of New York University were accessible from virtually anywhere in the world thanks to the efforts of Mike Ward in New York and his colleagues at other NYU locations; this in addition to Mike's constant sage scientific advice and support.

Others were crucial in our own work during the interim that is included in this volume. Among them special thanks and gratitude must go to Aurora Cruz-Cabeza from the University of Manchester and Ulrich Griesser from the University of Innsbruck. For education, guidance, and review on the preparation of Chapter 10 on the connection between polymorphs and patents I am deeply indebted to Howard Levine and Jill MacAlpine of Finnegan Henderson who combine scientific expertise with extensive experience in chemical and pharmaceutical patent issues.

There are always some specific visual inclusions that can be obtained only from unique sources. Two of those included here, and supplied with enthusiasm, are the Table on the solid forms of aripiprazole prepared by Anna Kowal, presently at Glaxo, and the excerpt on screening solvents from Walter McCrone's microscopy course manual provided by Gary Laughlin of the McCrone Research Institute.

Finally, my wife Tzipi has enthusiastically encouraged and devotedly supported this enterprise virtually from the day we met seventeen years ago; without that encouragement, support and wise counsel, which often left her in isolation, it could not have been completed. Dedicating this edition to her is only one symbolic way of expressing my deepest appreciation and gratitude.

Preface to the first edition

Sometime in the middle 1960s during an evening stint in the laboratory a fellow graduate student and I were struggling to determine the orientation of a known crystal on a quarter circle manual X-ray diffractometer. When things didn't turn out as expected he raised the possibility that it might be a polymorph (it wasn't). However, I recall being fascinated by the whole idea of a single molecule crystallizing in different structures, and the consequences of such a phenomenon. That fascination has not waned over the intervening years.

In the same period polymorphism has become a much more widely recognized and observed phenomenon, with both fundamental and commercial ramifications. The literature has grown enormously, albeit scattered in a variety of primary sources. In view of the growing interest in the subject there appeared to be the need for a monograph on the subject. Work in polymorphism and on polymorphs is quite interdisciplinary in nature, and as a result there is no single book that provides an introduction and overview of the subject.

The purpose of this book is to summarize and to bring up to date the current knowledge and understanding of polymorphism in molecular crystals, and to concentrate it in one source. It is meant to serve as a starting point and source book both for those encountering the phenomenon of polymorphism for the first time, and for more seasoned practitioners in any of the disciplines concerned with the organic solid state. It is intended to serve a readership from advanced undergraduate students through to experienced professionals. Much of the information in the book does appear in the open literature; however, because of the increasing commercial importance of the phenomenon, a significant portion of the information (for instance, on industrial applications, patents, or previously restricted distribution) is less accessible, and we have attempted to include both the information from those sources as well as full details of their citations. The intention is that even with the passage of time developments in many of the areas covered in the book can be followed by searching for the citations of the relevant papers cited here.

A work of this type cannot be completed without the help of many other people. This project was initiated during a sabbatical leave (in 1997–98) at the Cambridge Crystallographic Data Centre. My hosts there and in the contiguous Department of Chemistry at Cambridge University put all their resources at my disposal and simply let me go about my business of reading and writing. I am particularly grateful to Olga Kennard for encouraging me to spend that time there and to Frank Allen and his colleagues for making it so collegial and so congenial.

I have been particularly fortunate to have benefited from the assistance of a small army of bright, enthusiastic students who put up with my changing whims and wishes and managed the logistical aspects of organizing the reprints collection,

obtaining reprint permissions, checking and completing the details of references, scanning, modifying, and preparing figures, etc.: Megan Fisher, Michal Stark, Avital Furlanger, Margalit Lerner, Noa Zamstein, Shai Allon, and Janice Rubin.

Over the years I have been in touch with countless colleagues—many of whom I have never met—who have willingly, indeed enthusiastically, provided me with preprints, obscure reprints, private documents, observations, and insights on a variety of polymorphic behavior and systems. To all of them I am grateful, and in the course of this work, a number of them provided exceptional assistance which made my task considerably easier and more enjoyable. They deserve special mention here. Peter Erk at BASF spent many hours helping put the connection between polymorphism and colorants into focus. His colleague Martin Schmidt at Clariant provided almost instantaneous responses and faxes to what must have seemed like an endless stream of questions and requests. The chapter on high energy materials probably could not have been written without the help of Charlotte Lowe-Ma of the Ford Motor Company. Following a brief conversation with her at a scientific meeting a courier showed up in my office with a box of historically important documents and personal notes and summaries on polymorphism of high energy materials that were invaluable. Richard Gilardi from the U.S. Naval Research Laboratories provided similar advice and assistance on many of the newer compounds and systems. Stephen Tarling from Birkbeck College availed himself of his time and experiences in a number of patent litigations involving crystal modifications to lead me to the appropriate cases. Michelle O'Brien of the firm of Finnegan, Henderson, Farabow, Garrett and Dunner, Washington, DC managed to get hold of every legal document I requested.

When it came to finding examples, systems, and references among the pharmaceuticals Jan-Olav Henck of Bayer and Ulrich Griesser of the University of Innsbruck were always ready and willing with immediate detailed answers, and faxed reprints if necessary.

Many graduate students and associates in my laboratory carried out the examples taken from our own work described here. I am grateful for their dedication and their contribution to the contents: Ilana Bar, Ehud Goldstein (Chosen), Leah Shahal, Liat Shimoni, Sharona Zamir, Arkady Ellern, Oshrit Navon, and the same Jan-Olav Henck mentioned above.

The exchanges with Roald Hoffmann of Cornell University on disappearing polymorphs in song and story were particularly memorable, and I am grateful for his permission to reprint his poem on the subject as the frontispiece of this tome. As he has been for a couple of generations of chemical crystallographers, Jack Dunitz was a constant inspiration and standard of excellence.

As a postdoctoral fellow myself I was very fortunate to have worked with two inspiring scientists whose scientific integrity and talent for precision in writing and expression have served as models throughout my career: K. N. Trueblood at UCLA and Gerhard Schmidt at the Weizmann Institute. Countless times in the course of preparing this work I found myself asking if they would have passed a sentence, a phrase or a scientific judgment or opinion that had just been written.

I hope they would, but as they also taught me, I alone am responsible for what follows.

My late wife Judy was a source of constant encouragement and support for nearly 35 wonderful years together, especially those during which this book developed and took shape. Dedicating it to her is but a minor recognition of her contribution and the life we shared.

Contents

Abbreviations

Abbreviations for specific high energy compounds are given in Chapter 9.

ADF	Atomic density functions
AFM	Atomic force microscopy
AIE	Aggregation-induced emission
ANDA	Abbreviated new drug application
API	Active pharmaceutical ingredient
BEDTT-TTF	See **ET**
BFDH	Bravais, Friedel, Donnay, Harker crystal morphology, a routine in the CSD Mercury software for determining theoretical crystal habits
CA	chloranil
CCDC	Cambridge Crystallographic Data Centre
COMPACK	A computer program for identifying crystal structure similarity using interatomic distances
Cp^*	pentamethylcyclopentadienyl
CP/MAS	Cross polarization/magic angle spinning
CPU	Central processing unit
CSD	Cambridge Structural Database
CSP	Crystal structure prediction
CuPc	copper phthalocyanine
DFT	Density functional theory
DFT-D, DFT-D2, etc.	Density functional theory with various dispersion corrections
DOFlex	Degree of flexibility
DSC	Differential scanning calorimetry
EP	European Pharmacopoeia
esd	Estimated standard deviation
ESR	Electron spin resonance
ET	bisethylenedithio-tetrathiafulvalene
FDA	Food and Drug Administration
GBP	gabapentin
GSK	GlaxoSmithKline
HCB	hexabenzocoronene
HPMC	hydroxypropyl methylcellulose
ICDD	International Centre for Diffraction Data, the depository for powder diffraction data and a provider of software in support of that extensive data base
ILs	Ionic liquids
MfPc	Metal-free phthalocyanine
N-I	Neutral-ionic
NMR	Nuclear magnetic resonance

NQR	Nuclear quadrupole resonance
PC	Personal computer
Pc	phthalocyanine
PDF	Powder Diffraction File of the ICDD
POSA	Person of skill in the art
R-bonds	Rotatable bonds
RHCl	ranitidine hydrochloride
rmsd	Root mean square deviation
ROY	Iconic red–orange–yellow polymorphic system
SC	Supramolecular construct
SCDS	Semi-classical density sums
SIP	Substrate-induced phase
SMATCH	Simultaneous mass and temperature change
SSCI	Solid State Chemical Information, a service and consulting company in West Lafayette, Indiana
STM	Scanning tunneling microscopy
T_c	Critical temperature, below which a material becomes electrically superconducting
TCNQ	tetracyanoquinodimethane
TMAFM	Tapping mode atomic force microscopy
TORMAT	A computer program for the automated structural alignment of molecular conformations
TTF	tetrathiafulvalene
XRPD	X-ray powder diffraction
Z'	number of crystallographically independent molecules in the asymmetric unit
ZnPc	zinc phthalocyanine

1

Introduction and historical background

With the accumulation of data, there is developing a gradual realization of the generality of polymorphic behavior, but to many chemists polymorphism is still a strange and unusual phenomenon.

Buerger and Bloom (1937)

In spite of the fact that different polymorphs of a given compound are, in general, as different in structure and properties as the crystals of two different compounds, most chemists are almost completely unaware of the nature of polymorphism and the potential usefulness of knowledge of this phenomenon in research.

McCrone (1965)

1.1 Introduction

Notwithstanding chemists' occupation and fascination with structure and the connection between structure and properties, in McCrone's view in the nearly three decades following the observation of Buerger and Bloom there had not been any serious change in their awareness of polymorphism, its importance to chemistry, and its potential usefulness. In 2002 I wrote, "More than thirty-five additional years have passed, and that awareness is now increasing." As Figure 1.1 demonstrates, the number of publications, patents, and citations relating to polymorphism has increased exponentially. As analytical methods have become more sophisticated, more precise, and more rapidly carried out, the proliferation of data has revealed differences in structure and behavior that can be attributed to polymorphism. As I demonstrate in a number of instances in subsequent chapters, the increasingly rapid accumulation and archiving of structural data has allowed for the systematic search and retrieval of those data for the purpose of correlating both structural trends and structure with properties. In short, polymorphism in chemistry has moved from a "strange and unusual phenomenon" to one that is a legitimate and important area of research in and of itself that can also be utilized by chemists in unique and efficient ways for the study, understanding, development,

Polymorphism in Molecular Crystals. Second Edition. Joel Bernstein. © Joel Bernstein 2020. Published in 2020 by Oxford University Press. DOI: 10.1093/oso/ 9780199655441.001.0001

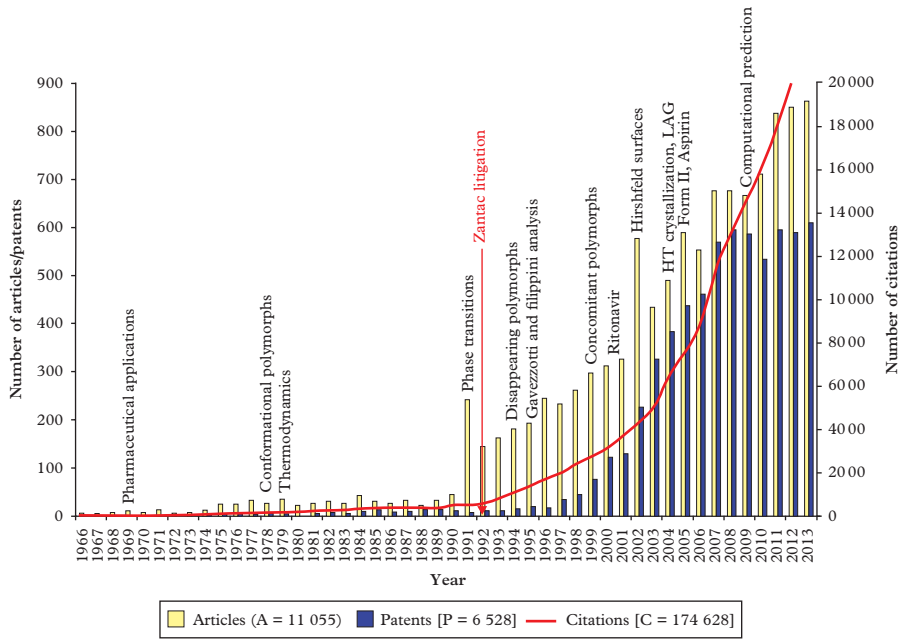


Figure 1.1 *Statistics for number of publications, citations to those, and patents related to polymorphism. Landmarks in the development of polymorphism are indicated and commented on further throughout the text. (Reproduced from Cruz-Cabeza, A., Reutzel-Edens, S., and Bernstein, J. (2015). Facts and fictions about polymorphism.* Chem. Soc. Rev.*, 44, 8619–35, 10.1039/c5cs00227c with permission from The Royal Society of Chemistry.)*

and utilization of specific properties of solids and structure–property relations in those solids.

The vertical marker in Figure 1.1 at ca. 1991–1992 with the notation "Zantac litigation" demarks what I believe to be a seminal event in the increasing interest and activity in polymorphism. As detailed in Chapter 10, this patent litigation, which began in 1991, involved the world's largest selling drug (generically ranitidine hydrochloride) and significant portions of the scientific aspects of that litigation involved many of the aspects of polymorphism with which this volume deals. As I will also show, additional citation statistics testify to the importance of that litigation in the development of the field.

Structural diversity surfaces in almost every facet of nature. Chemistry in general is no exception, nor in particular is structural chemistry, and crystal polymorphism is one manifestation of that diversity. The emphasis in this treatise is on molecular crystals for a number of reasons. Inorganic compounds and minerals traditionally have been the purview of geologists and inorganic chemists and their innate interest in structure–property relationships led naturally to more organization and more awareness of polymorphism than in other pursuits. Monographs such as Wells'

(1984) *Structural Inorganic Chemistry* and Verma and Krishna's (1966) *Polytypism and Polymorphism in Crystals* are typical examples. On the other hand, organic solid-state chemistry is a relatively new discipline (or multidiscipline), founded (or re-founded) in the 1960s by the schools of G. M. J. Schmidt (1971) in Israel and I. C. Paul and D.Y. Curtin (1973, 1975) in Urbana, Illinois, so that information and knowledge of polymorphism in this area is scattered through a wider variety of literature. My aim is to provide within the framework of a single volume an introduction to the fundamental physical principles upon which this polymorphism is based, together with a variety of examples from the literature that demonstrate the importance of understanding polymorphism and, in McCrone's words (1965), the "potential usefulness of knowledge of this phenomenon in research." This work can then be used as a reference and source book for those encountering polymorphism for the first time, those embarking on polymorphism-related research, or those already involved in such endeavors who wish to find additional examples and an entrance to the related literature. The diversity of the field as well as its exponential development in the past few years makes a comprehensive survey prohibitive in terms of space and almost immediately out of date. As a necessary compromise I have attempted to choose examples which are meant to be representative of the phenomena they exhibit, as well as to provide leading references that can be updated with subsequent citations.

1.2 Definitions and nomenclature

1.2.1 Polymorphism

Polymorphism (Greek: *poly* = many, *morph* = form), specifying the diversity of nature, is a term used in many disciplines.[1] According to the Oxford English Dictionary the term first appears in 1656 in relation to the diversity of fashion. In the context of crystallography, the first use is generally credited to Mitscherlich (1823), who recognized different crystal structures of the same compound in a number of arsenate and phosphate salts. The historical development of polymorphism is discussed in Section 1.4.

As with many terms in chemistry, an all-encompassing definition of polymorphism is elusive. The problem has been discussed by McCrone (1965), whose working definition and accompanying caveats are as relevant today as when they were first enunciated. McCrone defines a polymorph as "a solid crystalline phase of a given

[1] In an internet search Threlfall (2000) found 1.5 million references to the term, of which 90% refer to video games in which creatures change shape. Ninety percent of the remainder refer to *genetic* polymorphism, which involves minor change of protein or DNA sequences that may lead, for instance, to particular sensitivity to drugs. Of references that refer to crystallographic polymorphism, approximately 90% are devoted to inorganic structures, which are not covered here. The remainder deal with molecular crystals.

compound resulting from the possibility of at least two different arrangements of the molecules of that compound in the solid state."

At first glance this definition seems straightforward. What are some of the complications? For flexible molecules McCrone would include *conformational polymorphs*, wherein the molecule can adopt different conformations in the different crystal structures (Corradini 1973; Panagiotopoulos et al. 1974; Bernstein and Hagler 1978; Bernstein 1987; Cruz-Cabeza and Bernstein 2014). But this is a matter of degree: dynamic isomerism or tautomerism would be excluded, because they involve the formation of different molecules. The "safe" criterion for classification of a system as polymorphic would be if the crystal structures are different but lead to identical liquid and vapor states. For dynamically converting isomers, this criterion invokes a time factor (Dunitz 1995). As with polymorphs, dynamic isomers will melt at different temperatures. However, the composition of the melt will differ. That composition can change with time until equilibrium is reached, however, and the equilibrium composition will be temperature dependent. Using these criteria, a system in which the isomers (or the limit conformers) were rapidly interconverting would be considered a polymorphic one, while a slowly interconverting system would not be characteristic of polymorphic solids. As Dunitz (1995) has pointed out, such a definition would lead to the situation in which a racemate and a conglomerate would be determined to be polymorphic when the rate of interconversion of enantiomers in the melt or in solution is fast, but would be classified as three different compounds when that rate of interconversion is slow. Since no time frame is defined for slow or fast, the borderline is indeed fuzzy. Dunitz has also noted that the distinction has important ramifications when considering the phase rule (see Section 2.2.1), since application of the phase rule requires definition of the number of components. In general, components are "chemically distinct constituents" whose concentrations may be varied independently at the temperature concerned. McCrone (1965) has attempted to clarify the distinction between polymorphism and dynamic isomerism. The latter involves chemically different molecules "more or less readily convertible in the melt state. The basic difference between two polymorphs can occur in the solid state, and the difference between any two polymorphs disappears in the melt state." A number of examples of these phenomena are described in Section 3.6.2. Chemists may certainly differ on precisely what comprises "chemically distinct molecules" and "more or less readily convertible" that can lead to the lack of precision in the definition of polymorphism.

Some additional aspects of the definition deserve mention here. Since polymorphism involves different states of matter with potentially different properties, debates about definitions of the phenomenon have centered alternatively on differences in thermodynamic, structural, or other physical properties. For instance, Buerger and Bloom (1937) cited Goldschmidt's use of "building blocks," "polarization properties," and "thermodynamic environment" to describe the state of the art and understanding of polymorphism at that time:

> …if a member of an isomorphous series is constructed of building blocks whose size and polarization properties lie near the limit which the structure of this series can

> accommodate, changes in the thermodynamic environment may cause this limit to be exceeded and a new structure to be developed. This is polymorphism.

On the other hand McCrone's definition appears to have been simplified by Rosenstein and Lamy (1969) as "when a substance can exist in more than one crystalline state it is said to exhibit polymorphism." This simplified definition was apparently adopted by Burger (1983), "If these [solids composed of only one component] can exist in different crystal lattices, then we speak of polymorphism," which unfortunately confuses the concepts of *crystal lattice* and *crystal structure*. Some of these misconceptions have been carried through to more recent publications (Wood 1997).

There has also been an ongoing debate about the use and misuse of the terms allotropy and polymorphism (Jensen 1998). The former was originally introduced by Berzelius (1844) to describe the existence of different crystal structures of elements, as opposed to different structures of compounds. Findlay (1951) opposed the use of two terms for essentially the same phenomenon, and even proposed that polymorphism be abandoned in favor of allotropism as a description for the general phenomenon. The distinction between the two terms was debated by Sharma (1987) and Reinke et al. (1993). Sharma suggested that polymorphs be denoted as "different crystal forms, belonging to the same or different crystal systems, in which the identical units of the same element or the identical units of the same compound or the identical formulas or identical repeating units are packed differently." Reinke et al. invoked the modern language of supramolecular chemistry, by proposing "an extended and modified definition" for polymorphism as "the phenomenon where supermolecular structures with different, well defined physical properties can be formed by chemically uniform species both in the liquid and solid state." This line of thought has apparently come full circle, with Dunitz's (1991, 1996) description of the crystal as the "supermolecule par excellence" and on that basis, "If a crystal is a supermolecule, then polymorphic modifications are superisomers and polymorphism is a kind of superisomerism…"

As with many other concepts in chemistry, in a room full of chemists there is general agreement about the meaning, consequences, and relevance of polymorphism. Although the language of chemistry is constantly developing, McCrone's working definition noted at the beginning of this section appears to have stood the test of time, and is the one that would be recognized and used by most chemists today.

1.2.2 Some additional adjectival polymorphisms: pros and cons

The expanding research activity on polymorphism has spawned an increasing variety of nomenclature to describe presumably specific or unique phenomena. That new nomenclature is not always justified.

There is no reason to restrict polymorphism to a single compound. Why, for instance, can co-crystals not be polymorphic? Surely among molecular complexes (Pfeiffer 1922; Herbstein 2005), lately reincarnated as co-crystals (Almarsson

and Zaworotko 2004), there are numerous examples of polymorphs that meet McCrone's criteria, as defined in Section 1.2.1. If the composition varies, then clearly they do not meet the criterion of having identical melts and they are not polymorphs; they are something else. Other hitchhikers on the nomenclature bandwagon should no longer be carried. For instance, *structural polymorphism* (e.g., Pravica et al. 2004; Singhal and Curatolo 2004; Piecha et al. 2008; Budzianowski et al. 2010) is simply redundant and belongs in the etymological trash heap. The same applies to *packing polymorphs* (Braun et al. 2008) and *synthon polymorphism* (Babu et al. 2010). And what criteria must a compound meet in order to be classified as a *pharmaceutical polymorph* (Nangia 2008)? Must it be a pharmaceutically active ingredient? Are excipients included? What if the compound is taken off the pharmaceutical market for some reason? Does it no longer qualify as a pharmaceutical polymorph? To quote Stahly (2007):[2]

> There is really no reason to classify organic compounds as "pharmaceutical" or "non-pharmaceutical" in discussing solid properties. Compounds used in the pharmaceutical industry are quite structurally varied; there is not any specific chemical attribute that renders them pharmaceutically active or warrants the term pharmaceutical polymorph.

On the other hand, there certainly are situations where a new term is helpful in recognizing and even describing a particular previously unobserved phenomenon. An example is *isotopomeric polymorphism* (Zhou et al. 2004), describing a change in crystal structure upon changing the isotopic identity of one or more of the atoms in a molecule. While seemingly an isolated incident when initially discovered, at least one other example has been reported (Crawford et al. 2009). There will undoubtedly be many others given the remarkable sensitivity of molecular crystal structure to the positions of hydrogen atoms (Price 2008a; Hughes and Harris 2009).

Perhaps somewhere in between these extremes of appropriate and inappropriate definitions is the case of *tautomeric polymorphism* (Bhatt and Desiraju 2007), particularly of omeprazole. In keeping with the spirit of the McCrone definition alluded to earlier, the appropriate questions to ask would be essentially: (1) Are the crystal structures different? (2) Do they give the same melt? The answers to both are somewhat ambiguous. Bhatt and Desiraju obtained five different forms with varying ratios of two tautomers. Three forms have been patented, distinguishable by their solid-state properties. Do they all give the same composition of tautomers in the melt? As the authors point out, this may be a matter of time, until equilibrium is attained; that also may be a complicating factor. The problem seems

[2] As noted on a monument in Beratzhausen, and a Memorial in Einsiedeln, Switzerland, Paracelsus, sometimes called the father of toxicology, wrote [German: Alle Ding' sind Gift, und nichts ohn' Gift; allein die Dosis macht, dass ein Ding kein Gift ist.] "All things are poison and nothing is without poison, only the dose permits something not to be poisonous." That is to say, substances considered toxic are harmless in small doses, and conversely an ordinarily harmless substance can be deadly if overconsumed. Even water can be deadly if overconsumed.

closely related to dynamic isomerism, also discussed by McCrone (1965). Given the difficulty in defining the limiting conditions, the legitimacy of *tautomeric polymorphism* remains questionable.

Three other adjectival polymorphisms—*conformational polymorphism*, *concomitant polymorphism*, and *disappearing polymorphs*—are discussed in subsequent sections of this volume.

The preceding discussion returns us to the question of *polymorphism in molecular crystals.* McCrone's definition first requires establishing the concept of molecularity, and in those cases the definition works very well. Even though McCrone's definition is still very useful, the last half century has led to a vastly expanded view of solids, which flaunts this concept wonderfully, so that even molecularity is an inherently fuzzy concept (Rouvray 1995, 1997). For instance, are molecular solids limited to neutral molecules? Are metal organic frameworks molecular solids? At what point is a solid no longer molecular?

What excites and motivates many of us about chemistry is the infinite variability that is possible and often observed. That variability defies precise definitions in many cases. In chemistry we use definitions to define essentially ideal cases in order to create a conceptual framework, and we then describe any particular situation as exhibiting or embodying features from more than one of those ideal situations. A classic example is that of the chemical bond—in many cases described as a covalent bond with a certain amount of ionic character. The two ideal states can be used to understand one that contains character of both. All the terms are clear and the meaning is clear. This is the language of chemistry and we can adopt a similar approach in the realm of multiple crystal forms. When a particular situation defies a precise description on the basis of our definitional framework, it does not necessarily warrant the creation of a new descriptive term. The perfectly acceptable alternative for special situations is to describe it as it is; it does not necessarily require an inclusive moniker. In the end, on the issue of nomenclature pragmatism should triumph over dogmatism.

1.2.3 Pseudopolymorphism, solvates, and hydrates

The literature on polymorphism and related phenomena has spawned a number of additional definitions and terms that potentially lead to confusion rather than clarification. The most outstanding of these is *pseudopolymorphism*, whose use was apparently proposed in the current context by Byrn (1982) in a rather limited (but now apparently mostly forgotten (or ignored) sense: "The classification scheme is based on the crystallographic behavior of solvates rather than the stability. Solvates that transform to another crystal form (different X-ray powder diffraction pattern) upon desolvation are *polymorphic solvates*. Solvates that remain in the same crystal form (similar X-ray powder diffraction pattern) are *pseudopolymorphic solvates*" (italics in original).

It is of interest that authors (McCrone 1965; Haleblian and McCrone 1969; Dunitz 1991; Threlfall 1995) who have given serious thought to the definition

of polymorphism and its ramifications almost unanimously argued, strenuously in a number of cases, against the use of the term *pseudopolymorphism*. Typical is Seddon (2004) who argues against the use of the term "pseudopolymorph," since the scientific community gains no new understanding by its introduction, its use is pedagogically misleading, and a long-established and well-understood term "solvate" already exists. In support of Seddon I also pointed out the absurdity of "polymorphs of pseudopolymorphs" for polymorphic solvates (Bernstein 2005). The proponents did not desist, for example, arguing that its long term "wide acceptance" justified continued use (Desiraju 2004; Nangia 2006; Stahly 2007). A more detailed argument against the use of *pseudopolymorphism* was subsequently presented (Bernstein 2011). Even in arguing against its use, for the sake of completeness and to define some phenomena which are not to be considered as polymorphic behavior, it is unfortunately impossible to ignore the term and how it has been used and continues to be misused—*caveat emptor*![3] It is worthy of note that Byrn's scheme as defined previously has not generally been adopted in its original sense by most workers in the field.

McCrone (1965) and Haleblian and McCrone (1969) pointed out that pseudopolymorphism has been used to describe a number of phenomena that are related to polymorphism: among them are desolvation, second-order transitions (some of which may be considered examples of polymorphism), dynamic isomerism, mesomorphism, grain growth, boundary migration, recrystallization in the solid state, and lattice strain effects.

Probably the most common use, particularly prevalent in the pharmaceutical industry (David and Giron 1994; Henck et al. 1997), involves the confusion between solvates (including hydrates) and crystalline materials that do not contain solvent (anhydrates in the case of water). As noted by Byrn (1982), Byrn et al. (1999), Morris (1999), and Griesser (2006), crystal solvates exhibit a wide range of behavior. At one extreme, the solvent is tightly bound, and vigorous conditions are required for the desolvation process. In many of these cases the solvent is an integral part of the original crystal structure, and its elimination leads to the collapse of the structure and the generation of a new structure. At the other extreme are solvates in which the solvent is very loosely bound, and desolvation does not lead to the collapse of the original structure (Van der Sluis and Kroon 1989). Anything between the two extremes is also possible. Threlfall (1995) has noted that since a solvate and an unsolvated crystalline form are constitutionally distinct, they cannot be defined as polymorphs by any definition.

McCrone (1965) and Haleblian and McCrone (1969) proposed a simple experimental test to distinguish between a desolvation phenomenon and a true

[3] A 2016 *SciFinder* search on the term *pseudopolymorphism* showed an annual use of the term with ~285 hits in 2012, rising by about 15 in number per year for the decade preceding that. Specifics of the use were not further investigated.

polymorphic transformation, using the microscope hot stage (see Section 4.2). During heating of a crystalline sample, both a true polymorphic phase transition and a desolvation process will often lead to loss of transmission frequently accompanied by crystal darkening (due to formation of polycrystallites of the product phase). However, if the original sample is placed in a drop of solvent that is immiscible with the (suspected) solvent of crystallization then upon heating the liberated solvent will form an easily observable bubble in the surrounding droplet. No such observation can be made for a true polymorphic transformation. A more sophisticated technique, involving very much the same principle, is measurement by thermogravimetric analysis, which involves following the change in mass (in this case a loss in mass due to loss in solvent) corresponding to the heating process (Gruno et al. 1993; Perrenot and Widmann 1994) (see Section 4.3).

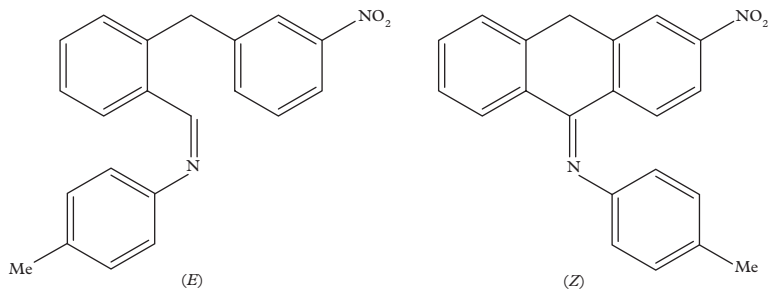
In spite of the objections to the use of pseudopolymorphism to describe solvated structures of a material, the term unfortunately has been used in this particular context, especially in the pharmaceutical industry, both in the characterization (Kitamura et al. 1994; Nguyen et al. 1994; Brittain et al. 1995; Kitaoka and Ohya 1995; Kitaoka et al. 1995; Caira et al. 1996; Gao 1996; Kalinkova and Hristov 1996; Kritl et al. 1996; De Ilarduya et al. 1997; Ito et al. 1997; De Matas et al. 1998) and production/processing aspects (Adyeeye et al. 1995; Hendrickson et al. 1995; Joachim et al. 1995).

McCrone (1965) also noted that second order phase transitions have been termed as pseudopolymorphic. Such transitions are difficult to detect by optical methods, because of the small structural changes that occur; hence, the origin of the prefix *pseudo* sometimes used to describe them. However, the birefringence of the crystals changes during such phase changes (see Section 4.2), so the use of crossed polarizers makes the phase change readily detectable.

A third phenomenon that has been described as pseudopolymorphism is dynamic isomerism (McCrone 1965). This takes us back to the problems defining polymorphism in general, where the questions of degree and time are raised. Dynamic isomers (including tautomers as well as geometric isomers) are generally considered to be chemically different. However, it is not always simple to make a distinction between geometric isomers and conformationally different species. Dynamic isomers exist in both the solid and the molten state, and are in equilibrium over a wide temperature range. Over that range, both isomers are stable in varying amounts depending on the temperature, and in solution, with solvent. Equilibrium between two polymorphs, on the other hand, can occur in the solid state, but upon melting the difference between the two polymorphs disappears. At any particular temperature only one polymorph is the thermodynamically stable one, except at a transition point, where two polymorphs are in equilibrium (see Section 2.2.2).

In principle, the distinction appears rather straightforward. However, a practical example will serve to demonstrate the difficulty. Matthews et al. (1991) described the crystal structures of three crystalline forms of 4-methyl-*N*-(4-nitro-α-phenylbenzylidene)aniline (**1-I**). In solution the material exists as a mixture of

rapidly interconverting stereoisomers with *Z* and *E* configurations, hence dynamic isomers. In the solid state it is trimorphic. The so-called A crystal form has three molecules in the asymmetric unit, all exhibiting the *Z* configuration. The B form, which can be crystallized simultaneously with the A form at 0 °C from ethanol or hexane-ether, has two molecules in the unit cell, both exhibiting the *E* configuration. A third C form, obtained at room temperature from ethanol, also exhibits the *E* configuration. At ambient temperature the latter two forms are converted to A, with the appropriate molecular configurational change from *E* to *Z*.



1-I

While this system falls somewhere on the fuzzy line between polymorphism and dynamic isomerism we agree with McCrone (1965) and Threlfall (1995) that this phenomenon should not be described as pseudopolymorphism.

McCrone (1965) attempted to summarize the distinction using a number of important criteria, and again suggested some rather simple thermomicroscopic tests to determine it. They are worth noting here, since systems of this type have received little experimental attention, and the example cited demonstrates the problems well.

McCrone (1965) notes that polymorphs, existing only in the solid, can convert at least in one direction without going through the melt. On the other hand Curtin and Engelmann (1972) observed that the equilibrium in melt or in solution between the two configurational isomers may be shifted by crystallization or by chemical reaction to form a derivative of one of the isomers. In solution, the two isomers will have different solubilities, in the same way that different polymorphs can have different solubilities (see Sections 3.2 and 7.3.1). The solubility curves may cross, and with a change in temperature the solution can become saturated with one form. This is apparently what happens in the case of **1-I**, as the C form is obtained from the room-temperature crystallization, while at lower temperatures, a mixture of A and B is obtained. Dynamic isomers exist in both the melt and the solid state. Each isomer can exist in polymorphic forms, which is true for forms B and C. Details on the experimental techniques and observations are given in Chapter 4.

The thermomicroscopic differentiation between two phases that are known to be related either by polymorphism or dynamic isomerism is elegantly straightforward. The two phases should be melted side by side between a microscope slide and a cover slip, and then allowed to crystallize. Two possibilities exist for the crystallization events. In the case of polymorphism, the crystal fronts from the two melts will grow at a constant velocity until they come into contact, at which point one phase will grow through the other, due to a solid–solid transformation to the stable phase at that temperature. In the case of dynamic isomerism, the two crystal fronts would slow down as they approach each other, and in the so-called "zone of mixing" (McCrone 1965) a eutectic could appear.

Another suggestion for making the distinction between polymorphs and dynamic isomers is to melt each sample by the equilibrium melting procedure (McCrone 1957), and observe the melt as a function of time. For a polymorphic system, the melting point will not change unless a solid–solid transformation takes place. Such transformations are usually sudden, and the resulting melting point will not change. For the case of dynamic isomers, the melting point of each will decrease gradually with the attainment of equilibrium. The final melting point should be the same for each, since the same equilibrium composition will be attained for both. As the melting point is followed through the eutectic composition, one of the isomers should show an apparent phase transformation. In another test suggested by McCrone two crystals of the same compound suspected of being polymorphs are placed side by side on a microscope slide in a mutually suitable solvent. If they are polymorphs of different thermodynamic stability the more stable one will grow at the expense of the less stable one.

McCrone (1957, 1965) has also given detailed descriptions of the microscopic examinations and phenomena that can be used to distinguish polymorphism from other phenomena that sometimes have been mistakenly labelled as pseudo-polymorphism: mesomorphism (i.e., liquid crystals), grain growth (boundary migration and recrystallization) and lattice strain.

1.2.4 Conventions for naming polymorphs

Part of the difficulty encountered in searching and interpreting the literature on polymorphic behavior of materials is due to the inconsistent labelling of polymorphs. In many cases, the inconsistency arises from lack of an accepted standard notation. However, often, and perhaps more important, it is due to the lack of various authors' awareness of previous work or lack of attempts to reconcile their own work with earlier studies (see, for instance, Bar and Bernstein 1985). While many polymorphic minerals and inorganic compounds actually have different names (e.g., calcite, aragonite, and vaterite for calcium carbonate or rutile, brookite, and anatase for titanium dioxide) this has not been the practice for molecular crystals, which have been labelled with Arabic (1, 2, 3…) or Roman (I, II, III…)

numerals, lower or upper case Latin (a, b, c…or A, B, C…), or lower case Greek (α, β, γ…) letters, or by names descriptive of properties (red form, low temperature polymorph, metastable modification, etc.).

As Threlfall (1995) and Whitaker (1995) have commented, arbitrary systems for naming polymorphs should be discouraged to avoid confusion surrounding the number and identity of polymorphs for any compound. Relative stability and/or order of melting point, as well as a specification of the monotropic or enantiotropic nature of the polymorphic form (see Section 2.2.4) have also been suggested as a basis for labelling (Herbstein 2001) but these do not allow for the discovery of forms with intermediate values, in addition to the fact that small differences in stability or melting point might lead to different order and different labelling by different workers. McCrone (1965) proposed using Roman numerals for the polymorphs in the order of their discovery, with the numeral I specifying the most stable form at room temperature. By Ostwald's rule (Ostwald 1897) (Section 2.3), the order of discovery should in general follow the order of stability. McCrone also supported the suggestion by the Koflers (Kofler and Kofler, 1954) that the Roman numeral be followed by the melting point in parentheses. In fact, the successors of the Koflers at the Innsbruck school have very much followed this practice (Kuhnert-Brandstätter 1971), although in general it has not been adopted by others. The use of melting points is complicated by the fact that while this datum has a clear thermodynamic definition, a number of techniques are employed to determine the melting point (or melting point range, in many cases) so that real or apparent inconsistencies may arise from such a designation (see Sections 4.2 and 4.3).

In view of the body of literature already existing and the questions surrounding the definition of a polymorph it does not appear to be practical to define hard and fast rules for labelling polymorphs. The Kofler method has clear advantages, since the melting point designation may eliminate some questions of identity. But the downside of adopting such an approach is the number of techniques that may be employed to measure a melting point. In addition, in practice many "melting points" are recorded as a range of temperatures, further confusing the issue, as for instance when two ranges overlap. For those studying (and naming) polymorphic systems it is important to be fully aware of previous work, to try to identify the correspondence between their own polymorphic discoveries and those of earlier workers, and to avoid flippancy in the use of nomenclature in the naming of truly new polymorphs.

The problem appears to be particularly egregious in the naming of crystal forms in the patent literature. A perhaps extreme, but nevertheless representative, example is presented in Table 1.1. The fact that virtually all of the named forms were granted patents implies that at least the patent examiners were convinced that the applicant(s) had prepared new and different forms from those in the prior art. Clearly, sorting out any possible identities would be a formidable task, but in a very practical sense it is one that is increasingly faced in pharmaceutical patent litigations (see Chapter 10).

Table 1.1 *Collection of all the names for the various crystal forms in patents and publications of aripiprazole*

Publication	Title	Crystalline forms
Proceedings of the Fourth Japanese–Korean Symposium on Separation Technology (October 6–8, 1996)		Type-I Type-II
Nanubolu et al. (2012)	Sixth polymorph of aripiprazole—an antipsychotic drug	The authors report the existence of the sixth polymorph of aripiprazole (APPZ) as characterized by single-crystal X-ray diffraction and present its structural and lattice energy comparison with five other polymorphs of APPZ in the Cambridge Structural Database (CSD). Incidentally, APPZ with six well-characterized polymorphs happens to be the second most polymorphic system in the CSD after the classic ROY molecule which has a record number of seven characterized polymorphs. The extensive polymorphism in the title compound is attributed to a very high degree of conformational freedom, significant differences in the hydrogen bonding, and the influence of crystal packing effects.
Zeidan et al. (2016)	An unprecedented case of dodecamorphism: the twelfth polymorph of aripiprazole formed by seeding with its active metabolite	A new polymorph of APPZ has been discovered, making it the most polymorphic drug to date with twelve reported anhydrous forms, and a record-breaking ninth olved crystal structure.
Braun et al. (2009b)	Conformational polymorphism in aripiprazole: preparation, stability and structure of five modifications	

continued

Table 1.1 Continued

Publication	**Title**	**Crystalline forms**
Braun et al. (2009a)	Stability of solvates and packing systematics of nine crystal forms of the antipsychotic drug aripiprazole	
Morissette et al. (2004)	High-throughput crystallization: polymorphs, salts, co-crystals and solvates of pharmaceutical solids	
Patent no./company	**Title**	**Crystalline forms/amorphous**
WO2003026659 Otsuka Pharmaceutical	Low hygroscopic aripiprazole drug substance and process for the preparation thereof	Conventional hydrate Hydrate A Conventional anhydrate Anhydrate B Anhydrate C Anhydrate D Anhydrate E Anhydrate F Anhydrate G
WO2004106322 Cadila	Polymorphs of aripiprazole	Polymorph I Polymorph II Polymorph III Polymorph IV
US8008490 Sandoz	Polymorphic forms of aripiprazole and method	Form X Ethanol hemisolvate Methanol solvate
WO2007004061 Medichem	Syntheses and preparations of polymorphs of crystalline aripiprazole	Form J Form L
WO2004083183 Hetero Drugs Limited	Novel crystalline forms of aripiprazole	Form I Form II
WO2005058835 Teva Pharma	Methods of preparing aripiprazole crystalline forms	Form I Form II Form VI Form VIII

Patent no./company	Title	Crystalline forms/amorphous
		Form X Form XI Form XII Form XIV Form XIX Form XX
WO2005009990 Hetero Drugs Limited	Aripiprazole crystalline forms	Form III Form IV Form VI
EP2082735 Helm AG	Amorphous aripiprazole and process for the preparation thereof	Amorphous
WO2006053780 Synthon	Crystalline aripiprazole solvates	Form B (methanolate and hemiethanolate)
WO2006012237 Shanghai Institute of Pharmaceutical Industry	Aripiprazole crystalline forms and associated methods	Anhydrous form
WO2008020453 Unichem Laboratories Limited	A process for the preparation of a novel crystalline polymorph of aripiprazole	Form U
US20160083381 Raqualia Pharma Inc.	Polymorph forms	Form I (L-tartrate salt but inventor calls this salt a polymorph)
WO2006077584 Chemagis	New crystalline forms of aripiprazole	Form AETl Form AETH Form AM2 Form AMI

1.3 Is this material polymorphic?

1.3.1 Occurrence of polymorphism

Perhaps the most well-known statement about the occurrence of polymorphism is that of McCrone (1965): "It is at least this author's opinion that every compound has different polymorphic forms and that, in general, the number of forms known

for a given compound is proportional to the time and money spent in research on that compound." As a corollary to this rather sweeping, even provocative, statement, McCrone noted that "all the common compounds (and elements) show polymorphism," and he cited many common organic and inorganic examples.

These echo similar statements by Findlay (1951, p. 35), "[polymorphism] is now recognized as a very frequent occurrence indeed," Buerger and Bloom (1937), "polymorphism is an inherent property of the solid state and that it fails to appear only under special conditions," and Sirota (1982),

> [polymorphism] is now believed to be characteristic of all substances, its actual non-occurrence arising from the fact that a polymorphic transition lies above the melting point of the substance or in the area of yet unattainable values of external equilibrium factors or other conditions providing for the transition.

Such statements tend to give the impression that polymorphism is the rule rather than the exception. The body of literature in fact indicates that considerable caution should be exercised in making them. It appears to be true that instances of polymorphism are not uncommon in those industries where the preparation and characterization of solid materials are integral parts of the development and manufacturing of products (i.e., those on which a great deal of time and money is spent): silica, iron, calcium silicate, sulfur, soap, pharmaceutical products, dyes, and explosives. Such materials, unlike the vast majority of compounds that are isolated, are prepared not just once, but repeatedly, under conditions that may vary slightly (even unintentionally) from time to time. Similarly, in the attempt to grow crystals of biomolecular compounds, much time and effort is invested in attempts to crystallize proteins under carefully controlled and slightly varying conditions, and polymorphism is frequently observed (Bernstein et al. 1977; McPherson 1982; McPherson and Gavira 2014). Even with the growing awareness and economic importance of polymorphism, many documented cases have been discovered by serendipity rather than through systematic searches. Some very common materials, such as sucrose and naphthalene, which certainly have been crystallized innumerable times at ambient conditions, have not been reported to be polymorphic.[4] The *possibility* of polymorphism may exist for any particular compound, but the conditions required to prepare as yet unknown polymorphs are by no means obvious. Even with the accumulated experience of the past twenty-five years there are as yet no comprehensive systematic methods for feasibly determining those conditions. Moreover, we are almost totally ignorant about the properties to be expected from any new polymorphs that might be obtained.

There have been a number of efforts to provide a statistical basis for the expectation of multiple crystal forms of any particular molecular entity. The true

[4] After nearly a decade of experiments carried out at high pressure, Katrusiak and colleagues succeeded in preparing and determining the crystal structure of a high pressure form of sucrose (Patyk et al. 2012).

occurrence of polymorphism is very difficult to determine and depends to a large extent on the choice of the data sample. This is demonstrated for three attempts summarized in Table 1.2. During the period 1948–1961 McCrone regularly reported the results of crystal growing experiments with approximately 25% of the organic compounds exhibiting polymorphism. A more recent survey of the pharmaceutical compounds in the European Pharmacopoeia yielded 42% polymorphism (Braun 2008). A summary of 248 compounds studied by the commercial analytical consulting firm SSCI with the specific goal of screening for crystal forms yielded 48% exhibiting polymorphism (Stahly 2007).

The difficulty in compiling statistics on polymorphism is evident from two sets of statistics on polymorphism that were recently compiled: (i) from the CSD and (ii) from 157 solid form screens performed at Lilly Company over more than fifteen years of polymorph screenings (Table 1.3) (Cruz-Cabeza et al. 2015). On the one hand, the CSD dataset contains a very large amount of information—much larger than any single group could ever compile—but the degree of form screening for the reported compounds may vary enormously. On the other hand, the Lilly set of compounds is much smaller but all of them have been intensively screened for multiple crystal forms. The statistics on polymorphism together with their 95% confidence intervals are presented in Table 1.3.

From these data 34% of unique compositions in the CSD are polymorphic compared to 25% in the Lilly dataset. When the statistics are broken into different sub-groups of compositions, the results remain quite homogeneous for the CSD dataset but are extremely heterogeneous for the Lilly dataset. This is partly because the Lilly dataset is derived from solid form screenings targeted specifically to identifying commercially viable drug crystal forms, whilst the CSD represents more of a homogeneous representation of all types of compounds.

Table 1.2 *Some early statistics on the occurrence of polymorphism*

Source	Data type	Compounds	Polymorphism occurrence
Microscopy studies by McCrone (1948–1961)[a]	Organic compounds	140	25%
From European Pharmacopoeia (1964–2004)[b]	Single component organic compounds	598	42%
From SSCI polymorph screens of organic compounds (1991–1997)[c]	Organic compounds	245	48%

[a] See text;

[b] Griesser (2011);

[c] Stahly (2007).

Table 1.3 *Occurrence of polymorphism in the CSD and Eli Lilly datasets*

	CSD			Lilly		
Data type	**Unique compositions**	**Pol. Occ. (%)**	**95% C.I.* (%)**	**Unique compositions**	**Pol. Occ. (%)**	**95% C.I.* (%)**
All compositions	8 035	34	(33, 35)	564	25	(21, 29)
Single-component	**5 941**	**37**	**(36, 38)**	**68**	**66**	**(55, 77)**
Neutral multicomp.	1 108	27	(24, 30)	138	13	(7, 19)
Solvates + Co-crystals	721	31	(28, 34)	88	11	(4, 18)
Hydrates	387	20	(16, 24)	50	16	(6, 26)
Salts	986	35	(32, 38)	110	28	(20, 36)
Unhydrated salts	**820**	**37**	**(34, 40)**	**56**	**54**	**(41, 67)**
Hydrated salts	166	28	(21, 35)	54	2	(0, 6)

*Margin of error is calculated within a 95% confidence interval.

The occurrence of polymorphism in single component compounds was found to be 37±1% in the CSD dataset compared to 66±11% in the Lilly dataset. The difference in polymorph occurrence is due in part to the inherent nature of the data. Whilst the CSD dataset contains compounds crystallized at least twice as single crystals suitable for study by X-ray diffraction, the Lilly dataset contains data from extensive polymorph screenings where many crystallization conditions were explored. Moreover, characterization of the forms comprising the Lilly dataset extended beyond single crystal X-ray diffraction, in some cases, increasing the probability of identifying polymorphs.

Polymorphism occurrence for neutral multicomponent systems is 27±3% for the CSD, but only 13±6% for the Lilly dataset. Potential causes for this difference may be i) the inherently different nature of the data and ii) the difficulty to accurately determine stoichiometries in hydrates and solvates. With regard to the different nature of the data, the Lilly dataset of neutral multicomponent systems uniquely contains hydrates and solvates, whilst the CSD dataset contains a broader range of compositions. A further breakdown of the CSD dataset of multicomponent systems into co-crystals (and solvates) and hydrates reveals further differences between these groups. Hydrates appear to be slightly less prone to being polymorphic (20±4%) than co-crystals and solvates (31±3%). Non-solvated salts similarly display a high propensity to polymorphism, that being 37±3% and 54±13% from the CSD and Lilly datasets, respectively.

Many of the attempts to understand the appearance of polymorphism have been based on an assumed (very often hindsight) connection between some molecular property and the propensity for polymorphism, often with contradictory conclusions. For instance, polymorphism has been attributed to conformational freedom in a molecule (Aitipamula et al. 2014), or it has been attributed to conformation flexibility *and* the potential for hydrogen bonding (Ahn et al. 2006). It is claimed that several conformers are available in the crystallization milieu (solution or melt phase) to form different hydrogen bond synthons and close-packing motifs (Nangia 2008). This approach has become textbook dogma, polymorphism being promoted by the fact that drug molecules tend to contain functional groups that are flexible and capable of forming hydrogen bonds (Desiraju et al. 2011). To add to the confusion the *absence* of hydrogen bonding and conformational flexibility have also been attributed to the propensity for polymorphism (Dey and Desiraju 2006).

One of the most enigmatic aspects of polymorphism is how the molecular structure of a compound might relate to its ability to exhibit polymorphism. We recently compiled the statistics to investigate such a relationship (Cruz-Cabeza et al. 2015), as presented in Table 1.4.

It is seen that rigid molecules were found to be as likely to be polymorphic as flexible molecules. As for molecular size, again, small molecules (number (N) of heavy atoms ≤ 18/M_r ≤ 245) were found to be as prone to polymorphism as large molecules, in agreement with previous findings by Sarma and Desiraju (1999).

Table 1.4 *Molecular structure and polymorphism occurrence (adapted from Cruz-Cabeza et al. 2015)*

		Compounds contain property [+]			**Compounds do not contain property [–]**		
Property type	**Property**	***N*[+]**	**Pol. occ. [+] (%)**	**95% C.I. [+] (%)**	***N*[–]**	**Pol. occ. [–] (%)**	**95% C.I. [–] (%)**
Flexibility	R-bonds	4536	38	(37, 39)	1405	36	(35, 37)
	DOFlex	5471	37	(36, 38)	470	40	(38, 42)
Size	M_r ≤ 245	2300	38	(37, 39)	3641	37	(36, 38)
	Heavy atoms ≤ 18	2823	38	(37, 39)	3118	37	(36, 38)
Drug-likeness	Lipinski RO5	4471	36	(36, 37)	1470	41	(40, 42)
HB capacity	HB groups	2991	40	(39, 41)	2950	34	(33, 35)
Chirality	Chiral centre	2083	26	(25, 27)	3858	43	(42, 44)

Most of the molecules in the CSD dataset (4471 out of 5941) could, based on Lipinski's rule of five (RO5) (Lipinski 2004), be classified as drug-like compounds. The difference in polymorphism occurrence found for drug-like and non-drug-like molecules is very small (5%), with non-drug like compounds being found to have a slightly higher occurrence (41±1%). Molecules able to form hydrogen bonds were found to be just 6% more likely to be polymorphic than those that are not able to hydrogen bond.

Finally, chirality was the only molecular property found to be significant in determining the proclivity of a molecule to display polymorphism. The polymorphism occurrence of chiral molecules was found to be only 26±1% compared to a 43±1% of achiral molecules. These statistics for chiral molecules do not change significantly whether or not both enantiomers are present in the same crystal structure. We contrasted this observation with the Lilly dataset and found a similar trend: 60% of chiral compounds were found to be polymorphic compared to 73% of non-chiral compounds.[5]

The original paper should be consulted for a detailed discussion of these statistics. With the growing awareness among chemists of the phenomenon of polymorphism its actual occurrence in any particular system may not be as great a surprise as a generation or two ago. The predicted existence of any particular polymorphic structure for a single compound, the conditions and methods required to obtain it, and the properties it will exhibit are still problems that will challenge researchers for many years to come.

1.3.2 Literature sources of polymorphic compounds

As noted above, the phenomenon of polymorphism is not new to chemistry. Nineteenth century chemists were very much aware of the properties of solids, and in the decades preceding the development of spectroscopic and X-ray crystallographic methods, the characterization of solids was a crucial aspect of the identification of materials. Chemists grew crystals carefully in order to obtain characteristic morphologies and then determined physical properties such as color, interfacial angle, indices of refraction, melting point, and even taste (Schorlemmer 1874; Orndorff 1893; Senechal 1990; Kahr and McBride 1992).

[5] While perhaps anecdotal, the following appears to be a good measure of the state of our knowledge about the "pervasiveness" of polymorphism. In assigning a research project to a graduate student, a research advisor assumes a certain risk that the project will not succeed. One could imagine as a perfectly reasonable project the assignment to prepare and characterize the polymorphic forms of a *single* compound of interest, which is, of course, the practical manifestation of all the quotations on the expectations for polymorphism. Unexpected results can constitute the basis for a PhD thesis, but the absence of results, that is, the inability to obtain *any* polymorphs, would constitute a total failure of the project. This author has yet to encounter an academic research advisor who would be prepared to take the responsibility of assigning such a research project to a PhD student. That is, in spite of the hyperbole of McCrone's statement and the notoriety it has received, and the increasing importance of polymorphism in the market place, there is not sufficient confidence in its veracity to risk the career of a PhD student on any single particular compound.

Being critically observant was essential, for there was little other information to rely on.

A great deal of information on crystalline properties, including polymorphism, was summarized in the five-volume compendium covering over 10 000 compounds by P.H.R. von Groth, published between 1906 and 1919. The first two of these tomes (Groth 1906b, 1908) deal with elements and inorganic compounds, while the last three (Groth 1910, 1917, 1919) are concerned with organic materials. The genesis of this opus is vividly described:

> Groth's most stupendous work was the *Chemische Kristallographie,* five volumes which appeared between 1906 and 1919, comprising in toto 4208 pages and 3342 drawings and diagrams of crystals. The manuscript was written entirely by Groth in his fine hand and corrected over and over again by him until there was hardly a white spot left on the manuscript and again on the galley proofs. Oh for the admirable compositors in the Leipzig printing centers in the days before the general use of typewriters! The volumes contain a review of all crystallographic measurements... Each section is preceded by a survey of the crystal-chemical relations and includes many hints of gaps which should be filled by further work. In many instances Groth doubted the correctness of the work reported in the literature, and wherever possible, he got his pupils, assistants or visiting colleagues to prepare the same substances again, and to recrystallize and re-measure them... Altogether measurements on between 9000 and 10,000 are critically discussed in *Chemische Kristallographie*, an astounding feat considering the small number of the team....

The work thus contains a thorough, checked survey of the physical properties of many of the crystals that had been studied up to its publication. Typical pages of the "crystal-chemical relations" for dimorphic diphenyl malonic anhydride are shown in Figure 1.2, in which the methods for obtaining both structures are described.

das **Diphenylmaleïnsäureanhydrid** = $C_6H_5.C\!=\!\!=\!C.C_6H_5$ (CO.O.CO) und

in der Tat zeigen nun beide Körper eine ähnliche Verwandtschaft in krystallographischer Beziehung wie jene, indem sie die gleiche Symmetrie und sehr nahe übereinstimmende Werte zweier Axen (*a* und *b*) besitzen; die ungesättigte Verbindung existiert aber außerdem noch in einer metastabilen Modification, deren monokline Krystalle sich neben der stabilen in wässeriger Acetonlösung bilden, aber sich sehr bald umwandeln, wenn sie mit Krystallen der stabilen Form in Berührung sind; durch Erwärmung kann die Umwandlung bei jeder Temperatur bewirkt werden, niemals die umgekehrte (Monotropie); die metastabile Modification entsteht außerdem durch Unterkühlen der Schmelze, wenn keine Spur der stabilen vorhanden ist.

Figure 1.2 *A typical entry from Groth's* Chemische Kristallographie. *(a) Textual description of the dimorphic diphenyl maleic anhydride; (b) physical data for the stable modification melting at 155 °C; (c) physical data for the metastable modification melting at 146 °C.*

Diphenylmaleïnsäureanhydrid = $C_6H_5 \cdot \underset{CO \cdot O \cdot CO}{C} = \underset{CO \cdot O \cdot CO}{C} \cdot C_6H_5$.

Stabile Modification.

Schmelzpunkt 155°.

Spec. Gew. 1,340 Drugman[44]).

Rhombisch bipyramidal.

$$a : b : c = 0{,}5176 : 1 : 0{,}7024 \text{ Drugman}^{44}).$$

Aus Aceton entsteht die Combination (Fig. 2575): $m\{110\}$, $o\{111\}$, $q\{011\}$, ebenso aus Benzol, Chloroform, Äther und Alkohol, aus letzterem nach der c-Axe dünn nadelförmig. Einmal wurden aus Aceton kleine oktaëderähnliche Krystalle erhalten, die nur $m\{110\}$ und $q\{011\}$ zeigten; aus etwas harzhaltiger Lösung wurden Combinationen mit untergeordneten Flächen von $x\{112\}$, $y\{122\}$, $c\{001\}$ und $b\{010\}$ beobachtet. Die Krystalle aus Toluol zeigen die Formen (Fig. 2576): $m\{110\}$, $k\{021\}$, $b\{010\}$, untergeordnet: $q\{011\}$, $c\{001\}$, seltener $o\{111\}$; die hier vorhandene Verlängerung nach der a-Axe tritt noch mehr hervor an den Krystallen aus Xylol, welche dieselben Formen, aber mit besser ausgebildetem $o\{111\}$, zeigen. Eine solche nach der a-Axe prismatische Combination mit untergeordnetem $a\{100\}$ hatte früher bereits Jenssen[43]) (l. c. 64) an den von Anschütz und Bendix aus Äther erhaltenen Krystallen beobachtet, ihr aber eine andere Aufstellung gegeben.

Fig. 2575.

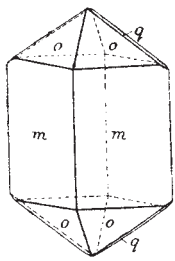
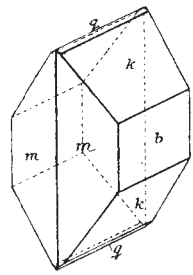


Fig. 2576.



	Berechnet:	Beobachtet: Drugman:	Jenssen:
$m : m = (110) : (1\bar{1}0) =$	—	*54° 44′	54° 42′
$q : q = (011) : (0\bar{1}1) =$	—	*70 10	—
$o : o = (111) : (1\bar{1}1) =$	45° 14′	45 13	—
$o : q = (111) : (011) =$	48 0	48 1	—
$o : m = (111) : (110) =$	33 12	33 15	—
$o : m = (111) : (1\bar{1}0) =$	61 6½	61 7	—
$q : m = (011) : (110) =$	74 41	74 42	—
$k : b = (021) : (010) =$	35 27	35 5 ca.	34 43
$k : m = (021) : (110) =$	68 0½	67 55 »	67 49
$x : o = (112) : (111) =$	19 25	19 13	—
$x : q = (112) : (011) =$	37 23	37 24	—
$y : q = (122) : (011) =$	29 2½	29 2½	—

Keine deutliche Spaltbarkeit.

Doppelbrechung positiv; Axenebene $a\{100\}$, 1. Mittellinie Axe c; Axenwinkel klein.

$\alpha = 1{,}505$ *Li*, 1,511 *Na*, 1,517 *Tl* (alle optischen Angaben von
$\beta = 1{,}505$ ca. » 1,5115 » 1,518 ca. » Drugman).
$\gamma = 1{,}811$ » 1,836 » 1,865 »

44) Drugman, Zeitschr. f. Krystall. 1912, **50**, 576.

Figure 1.2 (Continued)

Metastabile Modification.

Schmelzpunkt 146°.

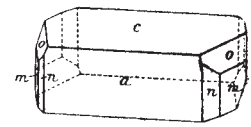
Spec. Gew. 1,345 Drugman[44]).

Monoklin prismatisch.

$$a : b : c = 2{,}5615 : 1 : 2{,}3275; \quad \beta = 101°33' \text{ Drugman}[44]).$$

Diese Modification erhielt Drugman neben der stabilen aus wässeriger Acetonlösung mit den Formen: $c\{001\}$ (oft sehr stark vorherrschend), $a\{100\}$, $m\{110\}$, $o\{111\}$; aus Xylol bilden sich kleine Krystalle der gleichen Form mit $n\{210\}$ (Fig. 2577). Einmal wurde ein Zwilling nach $a\{100\}$ beobachtet.

Fig. 2577.



	Berechnet:	Beobachtet:
$m : a = (110) : (100) =$	—	*68°15′
$a : c = (100) : (001) =$	—	*78 27
$o : c = (111) : (001) =$	—	*64 13
$m : c = (110) : (001) =$	85°45′	85 45
$n : c = (210) : (001) =$	82 50	—
$n : a = (210) : (100) =$	51 25	51 21
$o : n = (111) : (210) =$	24 28	24 17
$o : o_1 = (111) : (\bar{1}1\bar{1}) =$	65 58	65 57
$o : m' = (111) : (\bar{1}10) =$	51 5	51 7
$o_1 : n = (\bar{1}1\bar{1}) : (210) =$	66 21	66 21

Spaltbarkeit nach $a\{100\}$ und $c\{001\}$ vollkommen.

Ätzfiguren auf $c\{001\}$ nach $b\{010\}$ symmetrisch.

Ebene der optischen Axen $b\{010\}$, durch $a\{100\}$ und $c\{001\}$ je ein Axenbild, durch eine Schlifffläche $\| \{101\}$ beide sichtbar; starke Dispersion.

Figure 1.2 (Continued)

A few pages on appear the entries for the description of crystal habit, melting point, solvent, appropriate reference(s), interfacial angles, and indices of refraction, if reported in the literature. Many of the substances had been reported to be polymorphic, and Groth recorded those facts, along with methods for preparing the polymorphs and the original literature references. It is a remarkable work, and one which should be consulted to check for the existence of polymorphism in a specific material, as well as for the source of physical phenomena, once observed, but since forgotten.

A second rich collection of references on the polymorphic behavior of organic materials is the compilation by Deffet (1942). This contains information and references to primary sources on 1188 substances that exhibit polymorphism at atmospheric pressure and another 32 that exhibit polymorphic behavior at elevated pressures. A typical entry contains the number of reported polymorphic forms, their melting points, temperature(s) of transition, crystal system, some physical properties, and literature references, of which there are nearly 1000. Substances are organized by empirical formula with an index organized by compound name (in French).

A third compilation intended to be devoted to polymorphic materials is that of Kuhnert-Brandstätter (1971). The body of this book is an identification table for hot stage studies of pharmaceutical materials (see Sections 4.2 and 7.2), in which entries are arranged by increasing melting point, with eutectic data for mixtures with azobenzene and benzil. There is considerable descriptive detail on the melting behavior and identification and description of polymorphic forms, albeit only microscopic determinations, for approximately 1 000 pharmaceutically important compounds. There is no formula index, and the subject index contains only a partial listing of the compounds included. Nevertheless, the book contains some very useful information about the existence of polymorphism and the characterization of its behavior in many of these commercially important materials. In this context, it is perhaps noteworthy that the Merck Index (2016) describes polymorphic behavior for only fifty-five of over 10 000 entries, many of which appear in the Kuhnert-Brandstätter compilation.

There are a number of additional sources for consultation on information on polymorphism of particular compounds. As noted in the previous section (Table 1.1), from 1948 to 1961, McCrone edited a regular column in *Analytical Chemistry* entitled "Crystallographic Data," in which were published the details on crystal growth, physical properties, and polymorphic behavior of approximately 200 compounds. The series was undertaken at the time "because optical crystallography is neglected as an analytical tool because too few compounds have been described," and with the desire to "…initiate a process which [would] enable a group of crystallographers to complete the tabulation of crystal data for most of the common everyday compounds" (Grabar and McCrone 1950). About 140 of these were organic compounds, and 25% of these exhibited polymorphism. Even in the cases where there is no evidence of polymorphism, these reports contain detailed descriptions of conditions for growth of crystals with well-defined faces, and the characterization of crystal habit very much in the tradition of Groth. It is information that future investigators will be able to utilize for a variety of studies. The need for recording the detailed description of crystal growth, crystal habit, and crystal properties was later echoed in an appeal by Dunitz (1995) to authors of crystallographic structure analyses:

> …please give the color (easy to observe) and melting point of crystals studied (easy to measure); if possible, also the heat of fusion and of any observed phase transitions (only slightly more difficult to measure): report also any "unusual" behavior, any observed change of physical properties or of the diffraction pattern.

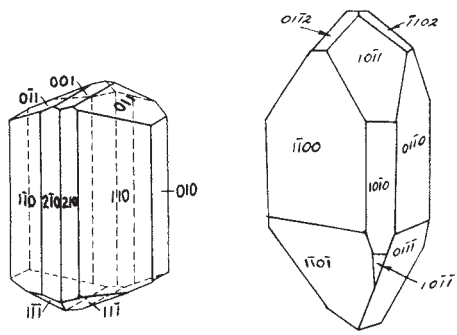
The short reports solicited and edited by McCrone are models of the kind of data that should be required and included in descriptions of crystals and crystal structure reports, even if only in deposited form (Section 1.3.3).

Some additional literature sources should also be consulted to check for earlier reports of polymorphism. The Barker index (Porter and Spiller 1951, 1956; Porter and Codd 1963) made use of the characteristic interfacial angles for purposes of

identification of crystals. The index is based on Groth's earlier compilation (which is organized by chemical composition) and is arranged by increasing interfacial angle within a crystal system. There are some additional compounds, with totals of 2 991 in tetragonal, trigonal, and orthorhombic space groups (Volume I) (Porter and Spiller 1951), 3 572 in monoclinic (Volume II) (Porter and Spiller 1956), and 871 in triclinic (Volume III) (Porter and Codd 1963) space groups. However, the method of arrangement means that polymorphs of a compound crystallizing, say, in monoclinic and orthorhombic space groups requires that the compound be checked in all three volumes.

Another approach was taken by Winchell (1943, 1987), who prepared a compilation of "all organic compounds whose optical properties are sufficiently well known to permit identification by optical methods." The compilation is arranged in the same fashion as the fourth edition of Beilstein's *Handbuch der Organischen Chemie* (Beilstein 1978), and at the time of its publication was meant to include all organic compounds whose indices of refraction had been measured. Since indices of refraction differ among them, polymorphs could be easily recognized by different optical properties. The book does contain references to primary sources and drawings of crystals, as illustrated in a typical entry Figure 1.3.

p-Methylbenzophenone or phenyl *p*-tolyl ketone $[C_6H_5 \cdot CO \cdot C_6H_4(CH_3)]$ has two phases. The stable phase is monoclinic with $a:b:c = 1.012:1:0.412$, $\beta = 95°7'$. Crystals {010} tablets or equant with {110}, {210}, {100}, {011}, {001}, etc. Figs. 60, 61. No distinct cleavage. M.P. 60°. The optic plane is 010 for red to green and normal thereto for blue and violet. $X \wedge c = +37°$. $(-)2E = 49°11'$ Li, 35°15′ Na, 6°55′ Tl, 49°32′ blue. The matastable phase is ditrigonal pyramidal with $c/a = 1.225$. Crystals show both trigonal prisms, {10$\bar{1}$0} and {1$\bar{1}$00}, etc. Fig. 62. M.P. 55°. Uniaxial negative with $N_O = 1.7067$ Li, 1.7170 Na, 1.7250 Tl; $N_E = 1.5564$ Li, 1.5629 Na, 1.5685 Tl; $N_O - N_E = 0.1541$ Na.



Figs. 60, 61. Phenyl-β-tolyl ketone.

Figure 1.3 *Typical entry from Winchell's* Optical Properties of Organic Crystals *for dimorphic* p-*methylbenzophenone (reproduced, with permission).*

Another useful compilation of crystallographic data as a source of examples of polymorphic systems is *NIST Crystal Data* (NIST 2001), which contains the principal crystallographic data on over 237 000 organic and organometallic entries. Each entry contains cell constants, space group, and other crystallographic information and bibliographic citations. In some cases the fact that a crystalline compound is one of a polymorphic system is specifically noted. In other cases the polymorphism may be recognized by the fact that a compound has more than one entry either in the formula index or the compound name index.

In addition to these compilations of crystal data in which instances of polymorphism may be recorded, a number of texts on the subject of the solid-state properties of organic compounds contain many examples of polymorphism. Since these books are based in part, at least, on work by the authors not published elsewhere, they may be considered as primary literature sources. Particularly noteworthy in this regard are the books by McCrone (1957), Kofler and Kofler (1954), and Pfeiffer (1922).

The usual search strategies for information on the preparation and properties, such as use of Chemical Abstracts and Beilstein, can also be useful for determining if a particular compound has been reported to be polymorphic. However, reference to the primary sources on the preparation and the characterization of the compound may reveal unusual behavior (e.g., melting points or colors which differed from one crystallization to the next) which testifies to the possible existence of polymorphic forms, behavior that is not specifically noted in the abstracted material.

1.3.3 Polymorphic compounds in the Cambridge Structural Database

The Cambridge Structural Database (CSD) is the repository for the results obtained from the X-ray crystal structure analysis of organic and organometallic compounds (Allen et al. 1991, 1994; Allen and Kennard 1993; Kennard 1993). As of the May 2016 release, the database contains over 800 000 entries, and as of this date approximately 50 000 structures are added annually. It is now also a depository for crystallographic data that may not be published elsewhere. In the past five decades the database has increasingly influenced the way structural chemists carry out their trade. An enormous amount of geometric and structural information is available in a very short time for searches, correlations, model compounds, packing arrangements, reaction coordinates, hydrogen bonding patterns, and a variety of studies. The rapid increase in the data availability that has been accompanied by increasingly sophisticated software has opened opportunities that could not have been imagined even a quarter of a century ago. Formerly accessible only on mainframes or work stations it has recently become available online.

As the repository for all organic and organometallic crystal structures, the CSD naturally contains entries for polymorphic materials. Each entry in the CSD contains one- (1D), two- (2D), and three-dimensional (3D) information. The 2D information is used to generate the structural formula and chemical connectivity,

which clearly will be the same for polymorphs. The 3D information contains the results of the X-ray structure determination: cell constants, space group, atomic coordinates, and atomic attributes needed to generate the three-dimensional molecular and crystal structures. The 1D data contain bibliographical and chemical information (name and empirical formula), including qualifying phrase(s) such as "neutron study," "absolute configuration," etc. It is here that the CSD notes that the material is polymorphic with a qualifying phrase such as "red phase," "metastable polymorph," or "Form II" *if the author of the primary publication noted this feature or if the abstractors recognized that the structure was one of a polymorphic system.* In many cases note is taken of the fact that this is some special crystal form only when a second (or third, etc.) structure of a polymorphic series is being reported. The first report may not contain such a notation, since the author may not have been aware that the material is polymorphic. (This may be the case for subsequent structure determinations as well. In the early days of the CSD some polymorphic structures were archived with different REFCODEs—the unique identifier for each chemical species. The more sophisticated archiving software used now prevents such duplication and has eliminated many of the older "orphans," but some may still exist.) Once one member of a polymorphic set of structures has been identified care should be taken to extract all entries of that compound. Many, if not most, of these potential pitfalls and problems in the search for true polymorphs in the CSD have been addressed and solved by van de Streek and Motherwell (2005) but the generation and identification of new polymorphs may still be fraught with uncertainty. The absence of a descriptor indicating that a material belongs to a polymorphic system is not a foolproof indication that the material is not polymorphic. Other literature sources should be consulted to make that determination.

An early example of the caution that must be exercised in performing such searches and the numbers obtained was given by Gavezzotti and Filippini (1995). The search was defined for organic compounds (containing only C, H, N, O, F, Cl, or S) and for which the crystal structure of more than one polymorphic form had been determined. A total of 163 "clusters" were obtained, where a cluster is a group of polymorphic crystal structures of the same compound. Of the 163 clusters, 147 contained two structures, thirteen had three, and three had four structures. The authors note that these numbers are "first evidence of the high frequency of polymorphism in organic crystals," although the number of clusters is a relatively small percentage of the entries in the database. The number of these clusters is probably more a measure of certain authors' interest in the particular polymorphic system in question. In a more recent study (Cruz-Cabeza and Bernstein 2014), 1297 polymorphic systems were identified, 89.2% of which have two polymorphs, 8.8% have three polymorphs, and only twenty-six molecules have four polymorphs or more. A more realistic measure (although certainly not precise because of the caveats mentioned above) of the frequency of polymorphism in these compounds would be the fraction of compounds in the database known to be polymorphic, whether multiple structure determinations have been carried out or not.

1.3.4 Powder Diffraction File

The second crystallographic database that can serve as a source of examples of polymorphic structures is the Powder Diffraction File (PDF; Jenkins and Snyder 1996; ICDD 2016). This is the depository for over 500 000 powder diffraction patterns of solids (2015 release) of which more than 250 000 have atomic coordinates, roughly divided into organic, inorganic, and metallic compounds, of which organics are about 98%. Bibliographic searches may be run on compound name or formula, and again, the existence of polymorphism for a particular compound may be recognized by the presence of more than one entry for a compound. An example of identifying polymorphism from the bibliographic entries (formula index and compound name index) of the PDF is shown in Figure 1.4.

1.3.5 Patent literature

As polymorphism has become an increasingly important factor in the commercial aspects of many solid materials, the number of patents relating to the discovery and use of particular polymorphic forms has increased. This is particularly important for pharmaceuticals, pigments and dyes, and explosive materials, which

	Sulphamethylthiazole	$C_{10}H_{11}N_3O_2S_2$	7.80_x	4.34_x	6.80_6	8–521
i	Sulphamidochrisoidine	$C_{12}H_{13}N_5O_2S$	3.86_x	5.13_9	3.27_8	39–1610
o	Sulphamidochrysoidine	$C_{12}H_{13}N_5O_2S$	4.51_x	3.96_8	13.9_5	39–1611
*	β-Sulphanilamide	$C_5H_8N_2O_2S$	6.12_x	3.90_8	4.91_6	41–1909
*	Sulphanilamide	$C_6H_8N_2O_2S$	4.49_g	3.78_g	6.57_g	38–1710
*	Sulphanilamide	$C_5H_8N_2O_2S$	4.47_g	3.70_g	7.82_g	38–1709
o	α-Sulphanilamide	$C_5H_8N_2O_2S$	4.23_x	3.36_x	3.57_7	30–1944
	2-Sulphanilamidopyrimidine Sodium	$C_{10}H_9N_4NaO_2S$	9.16_x	5.17_7	4.06_7	5–112
*	Sulphanilic Acid	$C_6H_7NO_3S$	4.91_x	6.96_5	3.48_2	30–1945
o	Sulphaphenazole	$C_{15}H_{14}N_4O_2S$	4.37_x	7.29_5	3.90_2	30–1946
	Sulphapyrazine	$C_{10}H_{10}N_4O_2S$	5.59_x	7.21_7	4.79_7	5–213
*	Sulphapyridine	$C_{11}H_{11}N_3O_2S$	5.48_x	3.57_5	4.01_5	37–1695
*	Sulphapyridine	$C_{11}H_{11}N_3O_2S$	4.77_x	4.13_5	3.81_8	37–1698
i	Sulphapyridine	$C_{11}H_{11}N_3O_2S$	3.81_x	4.76_7	6.49_5	37–1700
	Sulphasalazine	$C_{18}H_{14}N_4O_5S$	3.77_x	5.73_8	4.28_7	29–1928
	Sulphathiazole	$C_9H_9N_3O_2S_2$	5.81_x	4.12_x	4.02_x	5–206
	Sulphathiazole	$C_9H_9N_3O_2S_2$	5.77_x	4.03_x	4.33_x	29–1930
	Sulphathiazole	$C_9H_9N_3O_2S_2$	5.59_x	5.06_x	4.75_x	29–1931
	Sulphathiazole Sodium Hydrate	$C_9H_8N_3NaO_2S_2{\cdot}1.50H_2O$	6.85_x	4.50_x	3.77_x	8–684
	Sulphathiazole Sodium Hydrate	$C_9H_8N_3NaO_2S_2{\cdot}1.5H_2O$	6.80_x	12.3_3	3.96_8	8–802

Figure 1.4 *Example of the bibliographic entries in the PDF for substances listed by compound name. Each name is followed by the formula and the* d*-spacings of the three strongest diffraction lines, with the relative intensity as a subscript. The last column on the right is the card number in the PDF. Multiple entries with different principle lines are indications of polymorphic systems, for instance the three entries for sulfapyridine, but additional bibliographic information should be obtained from the entries themselves.*

are discussed in Chapters 7–9. Some examples of the role of polymorphism in legal litigation are described in detail in Chapter 10. The patent literature on the U.S. Patents and Trademarks Office site is readily searchable using terms such as "crystal form," "polymorph," etc., and since polymorphic behavior often forms the basis of a patent (as opposed to many journal publications, where it may be peripheral to the main point of the paper) instances of polymorphism are relatively straightforward to locate.

1.3.6 Polymorphism of elements and inorganic compounds

Berzelius (1844) introduced the term "allotropy" as the phenomenon of polymorphism in elements. There has been some debate about the necessity of a special term to designate the polymorphism of elements, as opposed to compounds (Sharma 1987; Reinke et al. 1993), but the term is still introduced in first year chemistry texts, so it has become part of the chemical language. Sharma (1987) has given some examples of allotropism, and Sirota (1982) has noted that "54–55 elements" exhibit the property (Samsonov 1976; Smithells 1976). More complete descriptions can be found in the texts by Wells (1984) and Donohue (1974).

The inorganic equivalent of the CSD is the Inorganic Crystal Structure Database (ICSD) (Bergerhoff et al. 1983; FIZ 2001). This currently contains over 185 000 entries (as of May 2016) with two updates per year, and may be searched in a manner similar to that used for the CSD. Another useful source is the inorganic section of the PDF (Jenkins and Snyder 1996; ICDD 2016). For older references, the first two volumes of Groth (1906b, 1908) are particularly valuable.

1.3.7 Polymorphism in macromolecular crystals

Protein crystal structures are archived in the Protein Data Bank (PDB) (Bernstein et al. 1977; Berman et al. 2003). About 5% of the approximately 124 000 (July 2016) entries (~12 500 proteins, peptides, and viruses, ~900 nucleic acids, ~600 protein/nucleic acid complexes, ~20 carbohydrates) contain the qualifier "form" in the compound name/descriptor field, and most of those refer to polymorphic varieties. In biomolecular crystallography, great efforts are expended varying crystallization conditions in the attempts to obtain single crystals suitable for structural investigations (McPherson 1982, 1989, 1999; McPherson and Gavira 2014). These myriad attempts and the variety of conditions have led to the acquisition of many polymorphic forms, especially for those compounds on which a great deal of work has been done. For instance, the extensively studied lysozyme has entries in the PDB for triclinic, monoclinic, orthorhombic, trigonal, tetragonal, and hexagonal modifications; human hemoglobin has been studied in monoclinic, orthorhombic, and tetragonal modifications. The amount of effort expended in a typical protein crystal structure analysis means that the isolation of crystals and the determination of cell constant and space group is an accomplishment worthy

of publication in and of itself. Thus much of the information on polymorphism in macromolecular structures can be found in the primary literature (King et al. 1956, 1962; Kim et al. 1973; Cramer et al. 1974; McClure and Craven 1974; Falini et al. 1996). One secondary source, which should be of increasing importance as the number of proteins studied increases, is the Biological Macromolecule Crystallization Database and the NASA Archive for Protein Crystal Growth Data (Tung and Gallagher 2009). In 2016 this database contained nearly 43 406 crystal entries from about 2300 biological macromolecules. McPherson (1982) summarized the crystallization procedures for 331 proteins. Of these, twenty-three (or about 7%) were listed as being polymorphic. Another primary source is the citations of the McPherson book (1982); of the nearly 700 citations by early 1998, twenty were for polymorphic systems. For smaller proteins, at least some of the incidents of polymorphism have been included in the abovementioned NIST Crystal Data Compilation.

1.4 Historical perspective

Following the historical development of a particular scientific concept or discipline helps to recall the way certain modes of thinking developed, were debated and accepted as new facts came to light and perhaps were abandoned. Tracing that development serves as a reminder that the field is dynamic, with new techniques and new findings changing our ideas and the problems we are seeking to solve. As in any human activity, knowing where we have come from and where we are helps to define where we have to go, and it is certainly true for the field of polymorphism. An early account may be found in Hartley (1902) and a later one in Verma and Krishna (1966).

Mitscherlich is generally credited with the first recognition of the phenomenon of polymorphism (e.g., Tutton 1911a). Early in his career in 1818 he discovered that crystals of certain phosphates and arsenates were very similar. He termed this phenomenon *isomorphism*, and pursued further investigations with Berzelius in Stockholm on the pairs of salts $NaH_2PO_4{\cdot}H_2O$–$NaH_2AsO_4{\cdot}H_2O$ and $Na_2HPO_4{\cdot}H_2O$–$Na_2HAsO_4{\cdot}H_2O$ and the corresponding ammonium and potassium salts. Among the measurements he carried out were the interfacial angles of the crystals, then a standard technique for characterizing solids (Romé de I'sle 1783; Lima-de-Faria 1990). Mitscherlich (1822) found that the members of the first pair of compounds usually have different crystals, but that the phosphate sometimes crystallizes in the same form as the arsenate. Typical of so many other subsequent discoveries of polymorphism, this one also appears to have been serendipitous:

> Whilst I was still seeking a difference in chemical composition [in the different crystals of the phosphate] I succeeded several times, in the recrystallization of the phosphate, in obtaining crystals having the same form as the acid arsenate. Since I knew

> definitely that there was no difference between the two salts I proceeded with the investigation of this phenomenon, and the whole solution of the acid phosphate crystallized several times in the form of the arsenate.
>
> Hence it is established that one and the same body, composed of the same substances in the same proportions, can assume two different forms. This is easily understood from the atomic theory: different forms can result according as the position of the atoms with respect to one another is changed, but the number of different forms remains quite restricted.

Mitscherlich's mentor, Berzelius, considered the discoveries of isomorphism and *dimorphism*, as it was initially called, "the most important made since the doctrine of chemical proportions, which depends on them of necessity for its further development."

Mitscherlich followed this paper shortly thereafter with another one on the dimorphism of sulfur (Mitscherlich 1823). Actually, others had earlier identified more than one crystal form for a number of materials. Klaproth (1798) had recognized that calcite and aragonite have the same chemical composition and Davy had recognized that diamond was a form of carbon (Encyclopaedia Britannica 1798). This prompted Thenard and Biot (1809) to reach nearly the same conclusion as Mitscherlich, in stating that:

> the same chemical elements combined in the same proportions can form compounds differing in their physical properties either because the molecules of these elements have the intrinsic faculty of combining in different ways or because they acquire this faculty through the temporary influence of a foreign agent which afterwards disappears without destroying itself (Webb and Andersen 1978).[6]

Monoclinic sulfur (in addition to the more common orthorhombic form) had also been recognized and documented by a number of other people (see, e.g., Partington 1952, which also contains many early references to polymorphism and polymorphic materials).

The microscope played a crucial role in research on polymorphism, and as this analytical tool became of wider and more sophisticated use, so polymorphism became the subject of increasing interest and study (Lima-de-Faria 1990; Authier 2013). Frankenheim's (1839) early investigation into the polymorphism of potassium nitrate is one of the classic studies of that period. He demonstrated that phase changes could be brought about by solvent moderation and by physical perturbations of a crystal, such as scratching or physical contact with another polymorph. With a detailed study of the mercuric iodide septum he also established many of the principles still recognized today regarding the nature of polymorphism. Some of these are as follows:

[6] The controversy that arose about the nature of these discoveries and who should get credit for them prompted correspondence, among others, between Berzelius and the pioneering French crystallographer Haüy. Detailed accounts have been given by Amorós (1959, 1978) and Authier (2013).

- Polymorphs have different melting and boiling points and their vapors have different densities.
- The transition from a low temperature form (A) to a high temperature form (B) is distinguished by a specific temperature of transition.
- The low temperature form (A) cannot exist at a temperature above the transition point to form B, but B can exist below the transition point; below the transition point it is a metastable form.
- At temperatures below the transition point, B will transform to A upon contact with A, the transition proceeding in all directions, but with differing velocities.
- In some cases, B can be converted without contact with A by mechanical shock or by scratching.
- Heat is absorbed upon the transition from A to B.

As early as 1835, Frankenheim was particularly concerned with cohesive forces in different states of aggregation, and suggested that in the various solid states of a material the attractions which lead to the aggregation in different solids are different, and are characterized by different special symmetry relations (Frankenheim, 1835).

The first *polarizing* microscope, an instrument that was destined to play such an important role in the development of chemical crystallography in general and polymorphism in particular, was invented by Amici (1844). It was also at about this point that Berzelius (1844), Mitscherlich's early mentor, suggested that the pyrite-marcasite polymorphism of FeS_2 was due to the polymorphism of the sulfur in the two solids, while the iron was the same in the two, although the concept of structure, per se, had not yet really crept into the lexicon of chemical crystallography. As Hartley (1902) pointed out, in spite of the investigation of many polymorphic modifications, the middle decades of the nineteenth century were not noted for any new generalizations in terms of the characterization and understanding of the phenomenon itself.

In the 1870s things started to change rapidly. Mallard (1876, 1879) had been concerned with geometrical crystallography and had considered the structural basis for polymorphism in an 1876 paper. He considered crystals as being built up of minute elementary crystallites that can pack in a number of ways giving rise to different crystal forms. The ideal form is that with the closest packing thereby being the most dense, and different forms have different packing which results in different physical properties such as optical properties and density. He attributed the differences in physical properties to differences in the arrangement of these elementary crystallites. In general, though, he still saw a great deal of similarity in the structures of two forms of the same substance:

> It has been known for a long time that when the same substance displays two fundamentally incompatible forms, often belonging to two different chemical systems,

> these two forms are always only slightly different and the symmetry of the less symmetrical is very similar to that of the other.

As an early pioneer of chemical crystallography, (particularly of organic compounds) Lehmann's PhD thesis, much of which was published in the first issues of *Zeitschrift für Kristallographie* (founded by Groth; Lehmann 1877a, 1877b), already contained some new concepts for polymorphic systems (Lehmann 1891). He characterized two different types of polymorphism. The first, which he termed *monotropic*, involves two forms in which one undergoes an irreversible phase change to the second form. The second form is termed *enantiotropic*, in which the two phases can undergo a reversible phase transition (see Chapter 2). An increase in temperature tends to lead to the transformation to the more stable form.[7] Lehman also showed that many organic compounds crystallize from the melt as monotropic forms, and that these tend to be the less stable form with a lower melting point.[8]

Lehmann further reduced Mallard's "structural crystallites" to be aggregates of "physical molecules." Then the structural crystallites could differ in the number or in the arrangement of the physical molecules of which they were composed, thereby constituting the difference between two polymorphs. These distinctions were then related to the transformation phenomena: an enantiotropic transformation was characterized by Lehmann as a reversible polymerization, that is, with an increase in temperature, elementary particles of a large size were transformed into elementary particles of a smaller size. In a monotropic transition, according to Lehmann, there is no such relationship between temperature and the mode of rearrangement.

The problem of distinguishing between molecular isomerism and polymorphism arose in this period as well. For instance, in a manner similar to Berzelius' arguments about the pyrite-marcasite system, Geuther (1883) postulated that the calcite-aragonite polymorphism arose from the existence of two carbonic acids. Wyrouboff (1890) differed in his view, claiming that polymorphs differ only in their physical properties. Crystals with different molecular isomers would give different products upon reaction, whereas true polymorphs would give the same reaction products. Polymorphic products, according to Wyrouboff, are distinguishable only by

[7] It is remarkable how particular systems attain the status of "classics." Hartley (1902) noted α and β sulfur (transition temperature 95.6 °C), red and yellow mercuric iodide (transition temperature 126 °C), and the four modifications of ammonium nitrate as examples of enantiotropic behavior. These three systems are given as archetypical experiments in Chamot and Mason's (1973) book on chemical microscopy.

[8] It is of interest to note Tutton's optimistic assessment of Lehmann's definition of monotropism and enantiotropism, published just prior to the dawn of the age of structural crystallography: "It thus appears that any general acceptance of Lehmann's ideas will only tend to amplify and further explain the nature of polymorphism on the lines here laid down, the temperature conversion of one form into another being merely that at which either a different homogeneous packing is possible, or that at which the stereometric relations of the atoms in the molecule are so altered as to produce a new form of point-system without forming a new chemical compound" (Tutton 1911b).

their physical properties.[9] He also differed with Lehmann's classification of polymorphs based on monotropic and enantiotropic phase transformations, choosing a scheme based essentially on the physical manifestations of the phase changes. For most materials, labelled heteroaxial by Wyrouboff, the starting crystal loses homogeneity upon transformation, becoming optically clouded and the transformation results in the breaking up of the crystal into many smaller crystallites. The heteroaxial designation results from the lack of any correspondence between axes of the initial and product phases. In the second class, labelled isoaxial, the phase transformation takes place without the crystal losing its optical transparency. If it does break up into smaller crystals they remain parallel to each other and to the axes of the parent crystal.

Following the elaboration of many of the principles of thermodynamics in the latter three decades of the nineteenth century, a major development in polymorphism came with the work by Ostwald (1897) on the relative stability of different polymorphs, and the reason for the mere existence of less stable forms. Among the findings was the fact that unstable polymorphic forms have a greater solubility than the more stable forms in a particular solvent, and that monotropic forms have a lower melting point than enantiotropic forms. Ostwald related these findings to the phenomena of supersaturation and supercooling. The result is Ostwald's so-called "Rule of Steps" or "Law of Successive Reactions," although as Findlay (1951) has pointed out, the designation "law" is not justified since many exceptions are known, but as a guideline or rule of thumb, it is still a useful concept. In Ostwald's words (1897), "…that on leaving any state, and passing into a more stable one, that which is selected is not the most stable one under the existing conditions, but the nearest" (i.e., that which can be reached with the minimum loss of free energy). Groth (1906a) provided an explanation for the phenomenon, which is discussed in detail in Chapters 2 and 3. The phenomenon described by Ostwald is in fact often (unknowingly) observed by synthetic chemists. The first synthesis of a new material with a melting point above room temperature may result in a metastable form, which eventually (either spontaneously or through an intentional recrystallization) will yield a more stable form. The metastable form may not always be recognized or the stable form may not appear immediately—it may take years until the appropriate constellation of conditions exists (Davey et al. 2013). However, once seeds of the more stable form exist in a particular environment, it may be difficult to obtain the metastable form (Dunitz and Bernstein 1995) (see Section 3.5). An example of the stable form crystallizing out of the metastable one over a period of days is shown in Figure 1.5.

Ostwald (1897) was aware of the fact that his "rule" was tenuous, since it was not based on a very large set of observations. In addition, if the metastable region

[9] On first glance this seems consistent with our definition above. However, the topochemical principles, first enunciated by Cohen and Schmidt (1964) were actually developed from the fact that different polymorphs of a substance (*trans*-cinnamic acid) undergo different photochemical reactions, leading to different products (see Section 6.4).