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Curating Morphological Data: From the Compendium of P. von Groth to the Cambridge Structural Database

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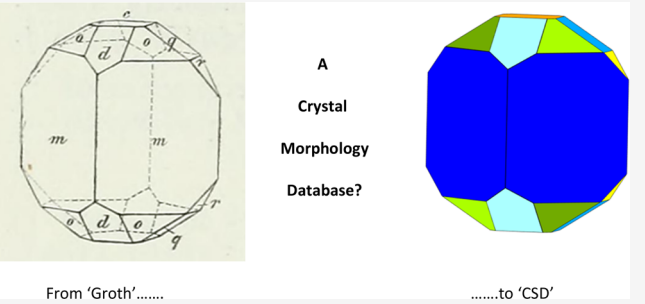
ABSTRACT: Crystal morphology is a significant property in manufactured materials. Related to crystal structure and influenced by environment, manipulating crystal morphology is important for tailoring of product properties to performance and quality control standards. There is a shortage of high-quality morphological data for organic crystals. A largely untapped wealth of such data for over 2000 organic crystals is available in P. von Groth's Chemische Kristallographie, a multivolume reference work, published in the early 20th century. The data are available online, but comparisons with more recent morphological and structural data are not straightforward. Here, the opportunity for a standardized, systematic approach linking Groth's morphology data to crystal structures in the Cambridge Structural Database (CSD) is presented. A method is proposed based on matching unit cells to store morphological data in a standard format—the "morphology.cif". This method is illustrated with four examples: benzophenone, glycine, urea, and α-lactose monohydrate, highlighting the particular challenges associated with polar morphologies. The steps necessary to implement such an approach systematically and hence to make maximum use of Groth's work are discussed.



INTRODUCTION

Understanding, predicting, and controlling the morphology of organic crystals is industrially significant and scientifically challenging. Studies on model systems of smaller organic molecules (molecular mass <200) have additional significance as the "training ground" where scientists learn, experimental techniques and equipment are developed, theories of crystal nucleation and growth are created and tested, and theoretical methods for morphology prediction are developed and refined. Model systems are thus widely studied, and there are many journal articles published each year on such systems. To give just one example, the morphology of benzophenone has been investigated multiple times for over 100 years.[1−4] The variety of ways in which morphological data has been recorded for this compound, and for all other organic compounds, constrains progress.

There is a largely untapped source of data on the morphology of small organic compounds in the form of a reference manual from the early 20th century. This is affectionately known as "Groth" and comprises five volumes of morphology data.[5−9] Paul Heinrich von Groth (1843−1927) was a German mineralogist, whose interest in crystallography led him to found the journal "Zeitschrift fuer Kristallographie" in 1877. In 1883, he was appointed professor of mineralogy at Munich University, where he remained for the next 40 years. He became fascinated by the growing number of organic crystals and specifically in correlations between molecular structure and crystal morphology, devoting 15 years of his working life to the monumental "Chemische Kristallographie", which appeared in five volumes between 1906 and 1919.[5−9]

The books are in German and contain unique, highly detailed morphology information, including over 2000 face-indexed drawings of organic crystals. The work is a compilation of optical crystallographic studies carried out between ∼1840 and 1919, many of which were previously unpublished. The techniques used before the advent of X-rays to understand crystallographic information[10,11] are fascinating, beyond the skills of the modern student of crystallography, and generally not currently taught. The depth and complexity of information that was gleaned from the optical examination of crystal morphology is impressive and

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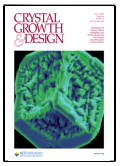

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Table 1. Five Volumes of P. Groth's "Chemische Kristallographie"

volume	I	II	III	IV	V
published	1906	1908	1910	1917	1919
pages	914	930	804	801	1063
figures	390	522	648	828	955
figure numbers	1−389	390−911	912−1559	1560−2387	2388−3342
contents	inorganic, elements, simple compounds	inorganic, salts containing oxygen	organic, aliphatics	organic, one phenyl ring	organic, multiple phenyl rings, heterocycles

valuable. The text is far more than a historical curiosity; it is a wealth of knowledge and understanding from which modern crystal scientists can benefit greatly. Harnessing Groth's wisdom and mapping the morphological information captured within these volumes into current experimental and computational studies would be immensely valuable. Specifically, this could provide the bridge between experimental morphologies from physical crystals and morphologies predicted from crystal structure information.

This contribution contains a historical overview of the different ways of describing morphologies of organic crystals. The methods used by Groth and in the Cambridge Structural Database (CSD) are presented and compared in this context. The scope and structure of Groth's work are described, followed by a description of how relevant data are stored and displayed in the CSD. A generic methodology that describes the steps involved in matching an entry in Groth to a CSD entry is presented and then illustrated using four worked examples: benzophenone, glycine, urea, and α-lactose monohydrate.

Describing Morphology: Symmetry v. Shape. For Groth, the symmetry of crystals was of primary importance. The 32 crystallographic point groups were established theoretically in the 19th century. Instruments such as the optical goniometer were developed to determine interfacial angles of crystalline minerals to within the nearest minute (1/60th of a degree). The deduction of point group symmetry, unit cell angles and relative dimensions, and indexing of crystal faces from optical measurements became routine for crystalline minerals. The rapid development of synthetic organic chemistry in the second half of the 19th century included the widespread use of crystallization for purification. This created the opportunity to apply these theoretical and experimental tools to the growing number of known organic crystals. Groth set out to summarize this knowledge within his monumental work from 1906 to 1919.[5−9]

Thereafter, X-ray crystallography began to supersede optical methods for studying organic crystals, revealing space groups, absolute unit cell dimensions, and confirmation of molecular structure from atom positions. Early examples include the crystal structure of hexamethylene-tetramine,[12] followed by CSD entries dated from 1936 with atomic coordinates for organic molecules (METALD, PHTHCY01, RESORA). As X-ray methods became more automated and routine, the quality of data on the external morphology of crystals declined. More recently, with increasing interest in crystal morphology, more publications now include crystallographic descriptions of morphology as determined in an X-ray diffractometer. This varies from describing the crystallographic orientation of, e.g., the needle axis to indexing faces. There is no requirement to include such information and no standard format for doing so.

Currently, the shapes of crystals are often reported without reference to their symmetry, using descriptive terms such as needles, plates, prisms, or blocks. Images of crystals, full-size or from optical or scanning electron microscopes, are also often presented in the literature without symmetry information. Noncrystallographic information may also be quantitative, for example, in average aspect ratios derived from image processing of crystal ensembles. As Groth himself points out,[10] confusion may arise if specific crystallographic terms (e.g., "prismatic") are used when describing shapes noncrystallographically.

How "Groth" Is Organized. Groth's work was published by W. Engelmann, Leipzig in five volumes, as summarized in Table 1. Within volumes III, IV, and V, there are 2431 figures depicting the morphology of over 2000 organic crystals. Less detailed information is provided on more than 1500 further compounds.

The entries are grouped chemically. Each chapter contains a short overview which includes information on polymorphism, a phenomenon receiving much less attention at the time of Groth than it does today. Each entry gives a point group, unit cell dimensions, Miller indices of observed faces, measured interfacial angles, and one or more labeled drawings of observed crystals. Unit cell dimensions are expressed as ratios, with $b = 1$, which were calculated from interplanar angles. Additional information may include melting point, density, refractive indices, and electrical properties. Each volume contains two indexes, one for chemical name (in German) and one for chemical formula. Chemical isomers are identified clearly within each relevant chemical formula entry.

Notably, Groth usually presents only one morphology for each material. This is a representative morphology selected by Groth to illustrate the symmetry and shape of the material. Groth gives only scant details about how crystals were prepared—typically only the solvent is mentioned. Variations in crystal shape with solvent are described, and occasionally additional figures are given. Further information on crystal growth conditions may be available in the references provided by Groth. Room temperature and the absence of impurity effects are assumed. Supersaturation is not discussed, although given the requirement for good quality crystals for accurate measurements, it is likely to be low. Axiomatic to Groth's approach is that external factors such as solvent do not alter crystal symmetry.

How Relevant Data Are Organized within the CSD. Each crystal structure in the CSD is identified by a unique reference code, which ultimately is linked to a unique crystallographic information file—".cif". The format of this ".cif" has been agreed internationally,[13] and each file contains sufficient data to specify the crystal structure and how it was determined. The CSD rests entirely on this common data format, which in turn rests on a continued consensus between equipment manufacturers, publishers, and scientists to use only this file structure.

The CSD is the repository of all organic crystal structure determinations, which may include multiple determinations of the "same" crystal structure (i.e., the same molecule packed in the same way), which may have different axis settings or unit cell choices. When seeking to correlate crystal structures with

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morphology, or any other physical property, the "best representative" crystal structure has to be identified.[14] Polymorphism poses an additional and related challenge. Sometimes polymorphs are easy to distinguish, for example if they have different space groups. Sometimes they are not, particularly if different axis settings or unit cell choices have also been used.

Noncrystallographic descriptions of crystal shape are sometimes included with the CSD entry, in the "habit" field, accessed via Display/More Information/Structure Information. There is currently no facility within the CSD for recording experimental crystallographic information about morphology.

How Morphologies Are Displayed within "Groth". Figure 1 shows the morphology of Benzophenone as presented by Groth.[9] Since there were then no X-ray data available, different conventions to those we have become used to have been employed. A standard projection is used, with the viewing direction close to the *x* axis as shown. The *z* axis is tilted slightly toward the viewer, and the *y* axis is tilted slightly downward so that in this case (001)—labeled "*c*" in Figure 1—is just visible. The point group is identified by name (in German) in the text. Corresponding unit cell data and Miller indices are identified in the text. Groth uses italicized lowercase letters to identify morphological forms comprising symmetry-related faces. For example, the two largest forward-facing faces in Figure 1 are both labeled *m* and belong to the same "form", {110}. Throughout the five volumes of Groth's work,[5−9] these letters always refer to the same form—so, for example, *m* always refers to {110}.

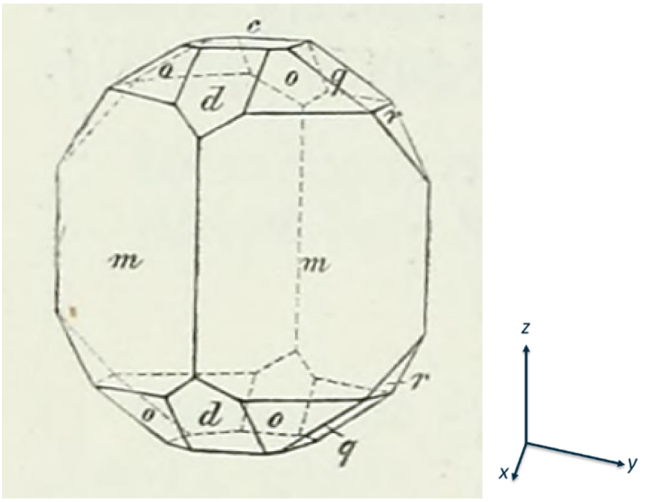

Figure 1. Morphology of benzophenone from Groth,[5] with crystallographic axes added.

How Morphologies Are Displayed within "Mercury". Although the CSD does not currently house experimental crystallographic data on morphology, it does provide options for predicting morphology. The Mercury software provided by the Cambridge Crystallographic Data Centre (CCDC)[15] includes the display of the morphologies predicted using two different methods, both of which may be calculated using the CSD-Particle/Morphology options from the main menu. Further details are provided in Chapters 25.2 and 25.3 of the Mercury User Guide, accessed from the "help" function on the far right of the top toolbar. The Bravais Friedel Donnay Harker (BFDH) method[16] uses only the unit cell and space group to calculate the *d*-spacing for each set of Miller indices. Center-to-face distances are assumed to be proportional to the reciprocals of *d*-spacings, giving a rapid prediction of morphology. One consequence of this method is that faces with the same *d*-spacing will show the same size and shape in the BFDH prediction even if they are not related by the symmetry of the crystal structure. The resulting shapes are thus centrosymmetric. Each crystal structure gives rise to only one morphology prediction according to the BFDH method.

More recently, an alternative method, "Visual Habit" (VH),[17] has been incorporated into the Mercury software. This takes account explicitly of the crystal structure, to calculate morphologies based on attachment energy. There are three different force fields, two options for calculating electrostatic energies, as well as an option to select the limiting radius for the calculation. Hence, each crystal structure gives rise to several morphology predictions according to the VH method. This more sophisticated method still assumes a center of symmetry.[17] Both methods are entirely based on the crystal structure, taking no account of external factors such as solvents. Examples of both predicted morphologies are included for benzophenone (BPHEN012) in Figure 2.

The output from both methods is a "morphology.cif" file that can be displayed and manipulated within the "Mercury" software, with many attendant advantages:

- Images can be rotated to obtain a visual match with other data.

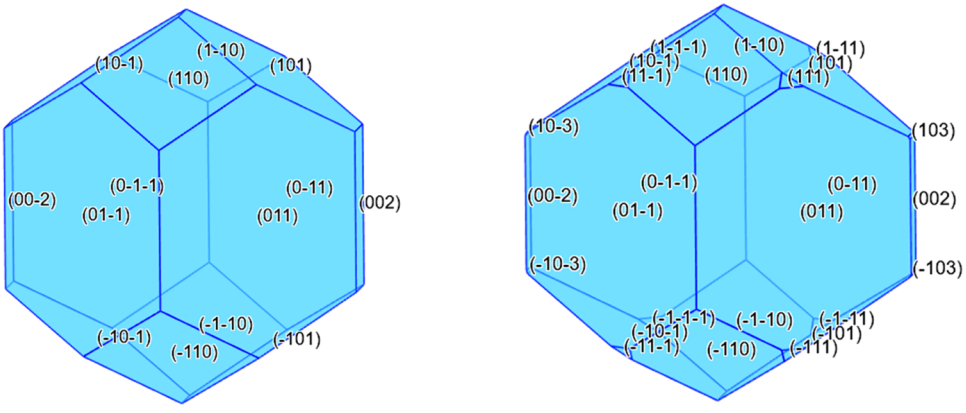

Figure 2. Predicted morphologies of benzophenone (BPHENO12): BFDH (left); Visual Habit (VH, right), as displayed using default settings in the Mercury software.

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- Faces are indexed automatically, allowing for systematic absences.
- Faces and symmetry elements can be displayed simultaneously.
- Faces and molecules can be displayed simultaneously.
- The displayed morphology is linked implicitly to a specific unit cell in the CSD.

The following manipulations are also possible but not routine:

- Faces can be colored individually.
- Morphologies can be exported from Mercury as "morphology.cifs"
- "morphology.cifs" can be modified using a simple text editor.
- Edited morphologies can be imported back into Mercury and displayed.
- Symmetry relationships between faces, although not explicit, can be deduced.

The "morphology.cif" is a standardized way of recording morphology that ties it to a unit cell. Neither the "morphology.cif", or anything else, is recognized as a definitive way of representing morphology data, either predicted or determined experimentally, and there is no other recognized standard for this.

MATCHING GROTH MORPHOLOGY DATA TO A CSD ENTRY

Literature studies including links between the data in Groth for individual compounds and their crystal structures have spanned several decades.[4,18] There is no agreed protocol for carrying out and reporting such comparisons. Here, a general method for matching data in Groth to CSD data is proposed and illustrated. For the most part, this is an objective, detailed exercise in applying basic chemical and crystallographic principles. The key subjective step is in deciding which unit cell (of several that may be available for each compound) in the CSD matches the unique unit cell for that compound in Groth.

1. Access the Groth data—either hard copies of volumes III, IV, and V, or via the links given in the references to the digitized versions online.[7−9]
2. Is there an entry in Groth for the compound? Select the volume (III, IV, or V for organic compounds) based on chemistry and check the formula index. Check that matching entries are for the desired chemical isomer. Check that the entry has a picture of the morphology. Summarize any information on polymorphism.
3. What are the corresponding entries in the CSD? Use the formula search within Conquest. Check which hits refer to the same chemical isomer. Check how may polymorphs are present and find the best representative structure[14] for each one. Use the CSD Core/Subsets/Best Representatives/Best Room Temperature option available in CSD version 5.45.
4. Match unit cells: check all polymorphs in Groth against the selected polymorph entries in CSD. Match first by point group, then angles (if monoclinic or triclinic), then $a/b/c$ ratios. If a match is not found, consider impact(s) of systematic absences or alternative axis settings. Save the corresponding morphology.cif.
5. Rotate the morphology to the standard projection used in Groth. Edit the morphology.cif by trial and error to obtain a visual match to the figure(s) in Groth. Color the symmetry-related faces. Save the revised morphology.cif using a different file name, to clarify that it has been edited.

Matching by point group requires an understanding of how the German descriptions used by Groth are related to the numerical description of point groups and the space groups to which they correspond. This is illustrated in Table 2 for the 11 most common space groups in the CSD.[19]

Table 2. Point Group Nomenclature for Common Space Groups

system (German)	class (German)	point group symbol	common space groups	polar faces
triklin	asymmetriche	1	$P1$	all
	pinakoidal	$\bar{1}$	$P\bar{1}$	none
monoklin	sphenoïdisch	2	$P2_1$, C2	some
	domatisch	m	Cc	some
	prismatisch	$2/m$	$P2_1/c$, $P2_1/a$, $P2_1/n$, $C2/c$	none
rhombisch	bisphenoïdisch	222	$P2_12_12_1$	some
	pyramidal	$mm2$	$Pna2_1$	some
	bipyramidal	mmm	$Pbca$, $Pnma$	none

Using this table, point groups of crystals, as expressed in Groth[5−9] (columns 1 and 2) can be translated into more common symbols in use today (column 3). Typically, each point group can arise from several different space groups, and only the most common ones are given here in column 4. The symmetry of the point group also dictates whether polar faces may be present. Polar faces are parallel pairs of faces on opposite sides of the crystal, sometimes referred to as "Friedel Pairs", that are not related by symmetry. The possibility of polar faces appearing is summarized in column 5. Further details are given in International Tables for Crystallography Vol I p739 Table 3.2.2.2.[20]

One consequence of this procedure is that the faces identified within Groth are represented based on the matching unit cell from the CSD. This greatly simplifies the presentation and storage of the results, as well as enabling future comparisons. The procedure is demonstrated here for four examples.

LINKING GROTH TO CSD: FOUR EXAMPLES

The four examples presented here are benzophenone, glycine, urea, and α-lactose monohydrate. They have been chosen to cover a range of point groups and illustrate the opportunities and challenges in working with data from Groth. The relevant data from Groth and the corresponding data from the matched unit cell in CSD are presented in Table 3, followed by further details and illustrations for each material.

Example 1: Benzophenone. Benzophenone, $C_{13}H_{10}O$, contains more than one phenyl ring, so is found in Groth Volume V.[9] The index shows three chemical isomers; benzophenone is easily recognized. Two polymorphs of benzophenone are described: a metastable "probably monoclinic" form with no further details and an orthorhombic stable polymorph with a full morphological description. The point group for the orthorhombic form is "rhombisch bisphenoïdisch", corresponding to "222" (see Table 2). A Conquest search of the CSD based on the chemical formula $C_{13}H_{10}O$ gave 17 hits, 5 of which were chemical isomers. Three of the remaining 12 entries are the metastable monoclinic polymorph. The stable, orthorhombic form has space group $P2_12_12_1$ (no. 19). The

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Table 3. Data from Groth[3,5] for the Four Examples

	benzophenone	glycine	urea	α-lactose monohydrate
		Groth		
name (German)	Benzophenon	Glycocoll Amidoessigsäure	Carbamid Harnstoff	Lactose-Monohydrat, Michzucker-Monohydrat
Groth volume	V[9]	III[7]	III[7]	III[7]
Groth pages	88, 102−103	92, 98−99	539	450
Groth figure(s)	2486	989, 990	1352	1264
class (German)	rhombisch	monoklin	tetragonal	monoklin
symmetry (German)	bisphenoïdisch	prismatisch	skalenoëdrisch	sphenoïdisch
unit cell: *a*	0.8511	0.8523	1	0.3677
unit cell: *b*	1	1	1	1
unit cell: *c*	0.6644	0.453	0.8333	0.2143
unit cell: *β*	90°	111° 38 1/2′	90°	109° 47′
		CSD		
matching REFCODE	BPHENO12	GLYCIN02	UREAXX23	LACTOS03
polymorph	orthorhombic	*α*	polymorph I	n/a
point group	222	2/*m*	$\bar{4}2m$	2
space group	$P2_12_12_1$	$P2_1/c$	$P\bar{4}2_1m$	$P2_1$
unit cell: *a*	0.6427	0.426	1	0.3681
unit cell: *b*	0.8507	1	1	1
unit cell: *c*	1	0.456	0.8315	0.2232
unit cell: *β*	90°	111.70°	90°	109.77°

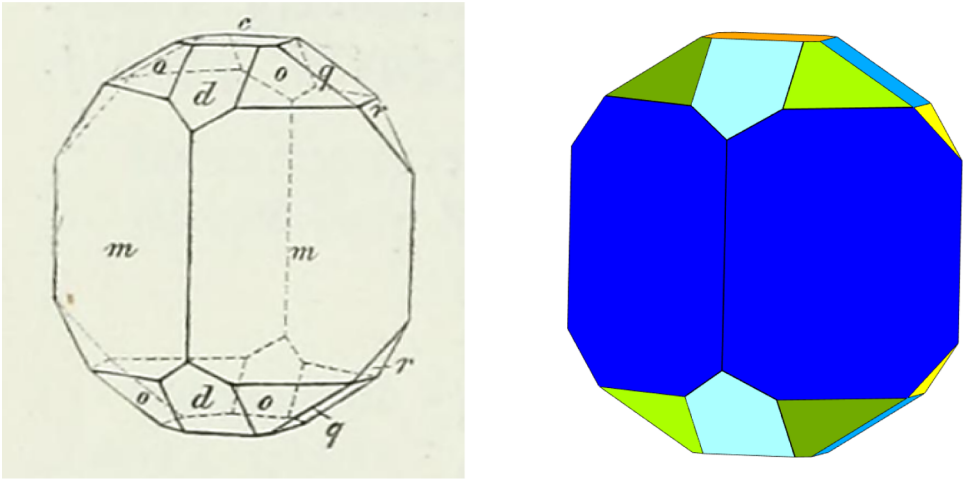

Figure 3. Experimental morphology of benzophenone from Groth[9] (left) and as displayed within Mercury after unit cell matching (right).

corresponding point group (Int. Tables Vol 1 (2016) page 273)[20] is "222", which agrees with Groth.[9] The earliest two structures for the stable, orthorhombic form (BPHENO01, BPHENO10) are from 1968 and lack hydrogen coordinates. The ratios of the unit cell dimensions are $a/b/c$ = 0.85:1:0.65, matching the unit cell ratios given in Groth. The other seven entries for the orthorhombic crystal structure share a different axis setting, with $a < b < c$. After adjusting for this, the unit cell dimensions are similar. BPHENO12 was selected as the "best representative" crystal structure.[14]

The image in Figure 3 (right) was obtained starting from the "morphology.cif" for the BFDH prediction for BPHENO12. The image was orientated and the center-to-face distances were edited by trial and error in a text editor to obtain a good visual match with the figure in Groth, shown in Figure 3 (left).[9] Faces were colored individually to show symmetry relationships. The output was saved as a revised morphology.cif which is presented in Figure 4. The REFCODE is given in the first line, followed by the space group, symmetry operator, and unit cell parameters. The last seven lines of this file identify the seven sets of Miller indices ("forms") that are present in Figure 3, together with their center-to-face distances. Table 4 shows how the face labels and colors link to the Miller indices based on the BPHENO12 unit cell.

Visual comparison of the experimental (Figure 1) and predicted (Figure 2) morphologies of benzophenone suggests that they look similar. All three morphologies are dominated by four large faces, identified as {110} and *m* in Groth;[9] compared with {011} in Mercury—the difference is consistent with the axes swap. Figure 3 (right) distinguishes between {111} and $\{\bar{1}11\}$, which are not related by symmetry in this point group. Groth[9] comments that the morphology shown in Figure 3 (left) should also have made this distinction, as other studies on this material did; - here this is essential in assigning the correct point group.

The first line identifies the crystal structure used to generate the morphology. The file can be saved, with the default name BPHENO12-Morphology.cif, differentiating it from the crys-

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data_BPHENO12
_symmetry_cell_setting              orthorhombic
_symmetry_space_group_name_H-M      'P 21 21 21'
_symmetry_Int_Tables_number         19
_space_group_name_Hall              'P 2ac 2ab'
loop_
_symmetry_equiv_pos_site_id
_symmetry_equiv_pos_as_xyz
1 x,y,z
2 1/2-x,-y,1/2+z
3 -x,1/2+y,1/2-z
4 1/2+x,1/2-y,-z
_cell_length_a                      7.7378(2)
_cell_length_b                      10.2421(3)
_cell_length_c                      12.0395(3)
_cell_angle_alpha                   90
_cell_angle_beta                    90
_cell_angle_gamma                   90
_cell_volume                        954.146
loop_
_exptl_crystal_face_index_h
_exptl_crystal_face_index_k
_exptl_crystal_face_index_l
_exptl_crystal_face_perp_dist
0 1 1 10
1 1 1 15
1 1 0 15
1 1 -1 15
2 0 0 16
1 0 1 16
1 0 2 16.5
```

Figure 4. "morphology.cif" for benzophenone as displayed in Figure 3 (right).

Table 4. Labeling of the Crystal Faces of Benzophenone, as Displayed in Figure 3

letter	color	M	form	center-to-face distances
m	dark blue	4	{011}	10
d	light blue	4	{110}	15
o	light green	4	{111}	15
*o**	dark green	4	$\{\bar{1}11\}$	15
q	mid blue	4	{101}	16
c	orange	2	{100}	16
r	yellow	4	{102}	16.5

tallographic information file. This file does not record the orientation of the view or the colors of the faces in Figure 3 (right). The point group and the multiplicity of each form are not given, although these can be deduced from the space group using, for example, International Tables Vol 1. (2016).[20] More importantly, the file does not reference the source of the center-to-face distances for the seven faces listed.

Example 2: Glycine. Glycine, $C_2H_5O_2N$, appears in Groth Volume III.[7] There is no mention of polymorphism. There are two images showing the same faces but in different proportions; both are reproduced in Figure 5. The corresponding point group (see Table 2) is $2/m$. The CSD contains 143 crystal structure determinations for glycine, covering 4 polymorphs. The thermodynamically stable γ-polymorph was first reported in 1954,[21] long after Groth's studies. GLYCIN02 was selected as the best representative crystal structure for the α polymorph.

The point group ($2/m$) and the monoclinic angle (111.70°) match the Groth entry,[7] but the unit cell ratios are 0.426:1:0.456, with the *a* repeat differing by a factor of 2. Examination of Int. Tables Vol A. (2016) p. 255[20] indicates that this is due to a halving of both the *b* and *c* repeats in Groth.[7] This explanation is that Groth[7] identifies *b* faces as {010}, and *c* faces as {001} but does not observe *a* faces. In space group $P2_1/n$ (no. 14, cell choice 2) both (010) and (001) are systematically absent, so faces *b* and *c* would be labeled {020} and {002}, respectively. Hence, the *b* and *c* repeats are both halved but the *a* repeat is not. This illustrates the general point that (010) and (020) faces cannot be distinguished by direct morphological observation and that Groth[5−9] had no way of knowing about these systematic absences. Matches for the two images in Groth[7] were obtained by editing the morphological.cif as before and are shown in Figure 5 and Table 5, including the corresponding center-face distances. The two morphologies, which were both obtained from aqueous solutions, differ in shape but display the same faces with the same symmetries.

Example 3: Urea. Groth[7] identifies one polymorph of urea in Vol. III. The point group is $(\bar{4}2m)$, corresponding to the unusual (for CSD) tetragonal space group $P\bar{4}2_1m$. There are 63 crystal structures for urea in the CSD: a matching unit cell was found for UREAXX23, denoted "polymorph I". Figure 6 shows the morphology from Groth[7] matched within Mercury by manipulation of the "morphological.cif", with further details in Table 6.

Groth[7] comments that {001} sometimes appears as well. Similar experimental morphologies have been reported in crystals grown from the vapor.[22] Neither predictive method (BFDH, VH) distinguishes between the four {111} faces shown here and their four Friedel pairs $\{\bar{1}\bar{1}\bar{1}\}$. More sophisticated methods based on surface relaxation[23] or different partial charges in solution[17,22] gave satisfactory matches to experimental morphologies. These options are not available within the Mercury software.

Example 4: α-Lactose Monohydrate. Groth[7] identifies one polymorph, giving Figure 1264, as reproduced in Figure 7a on the left. A matching unit cell was found for LACTOS03 and used to generate Figure 7b, with further details in Table 7. The predicted morphologies using the BFDH and VH methods are also shown in similar orientations in Figure 7c,d.

The Friedel pairs (020) and $(0\bar{2}0)$ both appear in the experimental morphology, but (020) is much larger. These two faces are not related by symmetry because they are both perpendicular to the 2-fold rotation axis along *y*, which is the only symmetry element in this point group. Groth identifies this nonequivalence elegantly by labeling one face as *b* and the other as *b*′. Similarly, two light blue {110} faces are larger than two pink $\{1\bar{1}0\}$ faces and are labeled *m* and *m*′, respectively. The largest faces are the two violet $\{0\bar{1}1\}$ faces, labeled *q*′ in Groth;[7] their two Friedel pairs, $\{01\bar{1}\}$ do not appear at all. In this example, the only two Friedel pairs that appear and are related by symmetry are the red "*a*" faces (100) and $(\bar{1}00)$.

The resultant polar morphology is similar to that described more recently[24] as "tomahawk", with consistent Miller indices. This morphology was obtained at lower ($S < 2$) supersaturations, changing to a more extreme needle morphology at higher ($4 < S < 5$) supersaturations.[24] This is consistent with the possibility that the well-defined morphologies reported in Groth[5−9] were generally obtained at low supersaturations. The "tomahawk" morphology and associated surface properties of α-lactose monohydrate are integral to its function as the standard carrier for inhaled active pharmaceutical ingredients (APIs).

The predicted morphologies shown in Figure 7c,d are very different from the experimental morphology, partly because they

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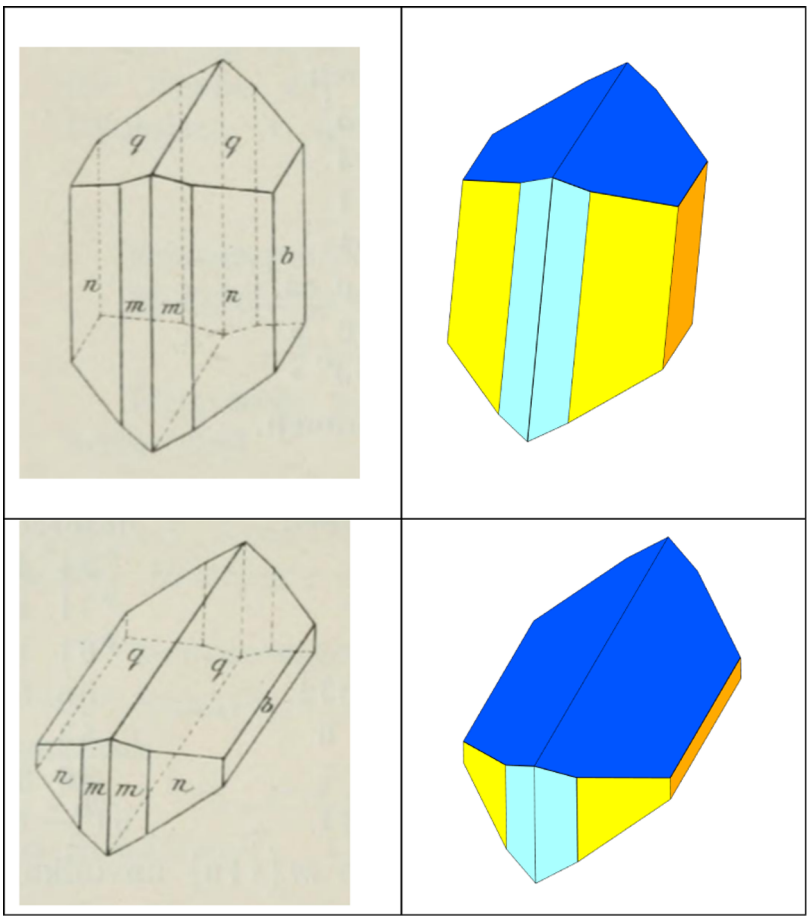

Figure 5. Experimental morphologies of α-glycine: Groth[7] (left) and as displayed in Mercury after unit cell matching (right).

Table 5. Labeling of Crystal Faces for α-Glycine, as Displayed in Figure 5

letter	color	M	form	center-to-face distances	
		top	bottom		
b	orange	2	{020}	16.7	21
q	royal blue	4	{011}	17	10
m	light blue	4	{110}	17	27
n	yellow	4	{120}	16	25

are centrosymmetric. Neither predictive method simulates this polar morphology. This is the same issue as was noted previously for urea, but with more severe consequences in this example. It is not clear from the images based on prediction (Figure 7c,d) which Friedel pairs are related by symmetry. The introduction of a center of symmetry effectively changes the point group of the predicted morphologies from "2" to "2/*m*".

DISCUSSION

Four aspects of this study are considered separately here. First, a standard way of recording morphological data is proposed, including suggestions for how morphological data is visualized. Second, the prospects for extending the approach illustrated here to the entirety of Groth's compendium are compared with the potential benefits. Third, pathways for adding more morphological data are suggested. Finally, appropriate treatment of polar faces is recommended.

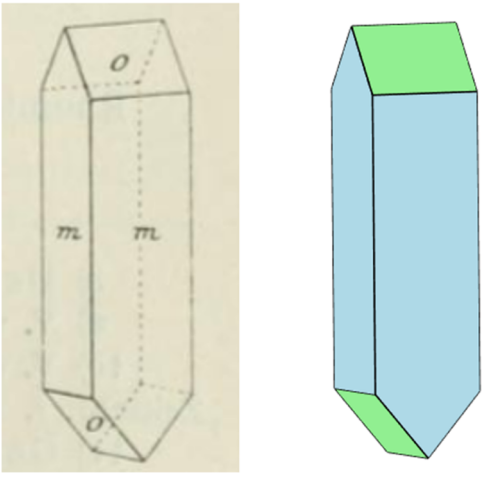

Figure 6. Groth's[7] experimental morphology of urea, original (left) and as reproduced in Mercury after unit cell matching (right).

Table 6. Labeling of the Crystal Faces of Urea, as Displayed in Figure 6

letter	color	M	form	center-to-face distances
m	light blue	4	{110}	2
o	light green	4	{111}	5

A Standard Way to Record and Morphological Data?

The CSD rests on the crystallographic information file (".cif");

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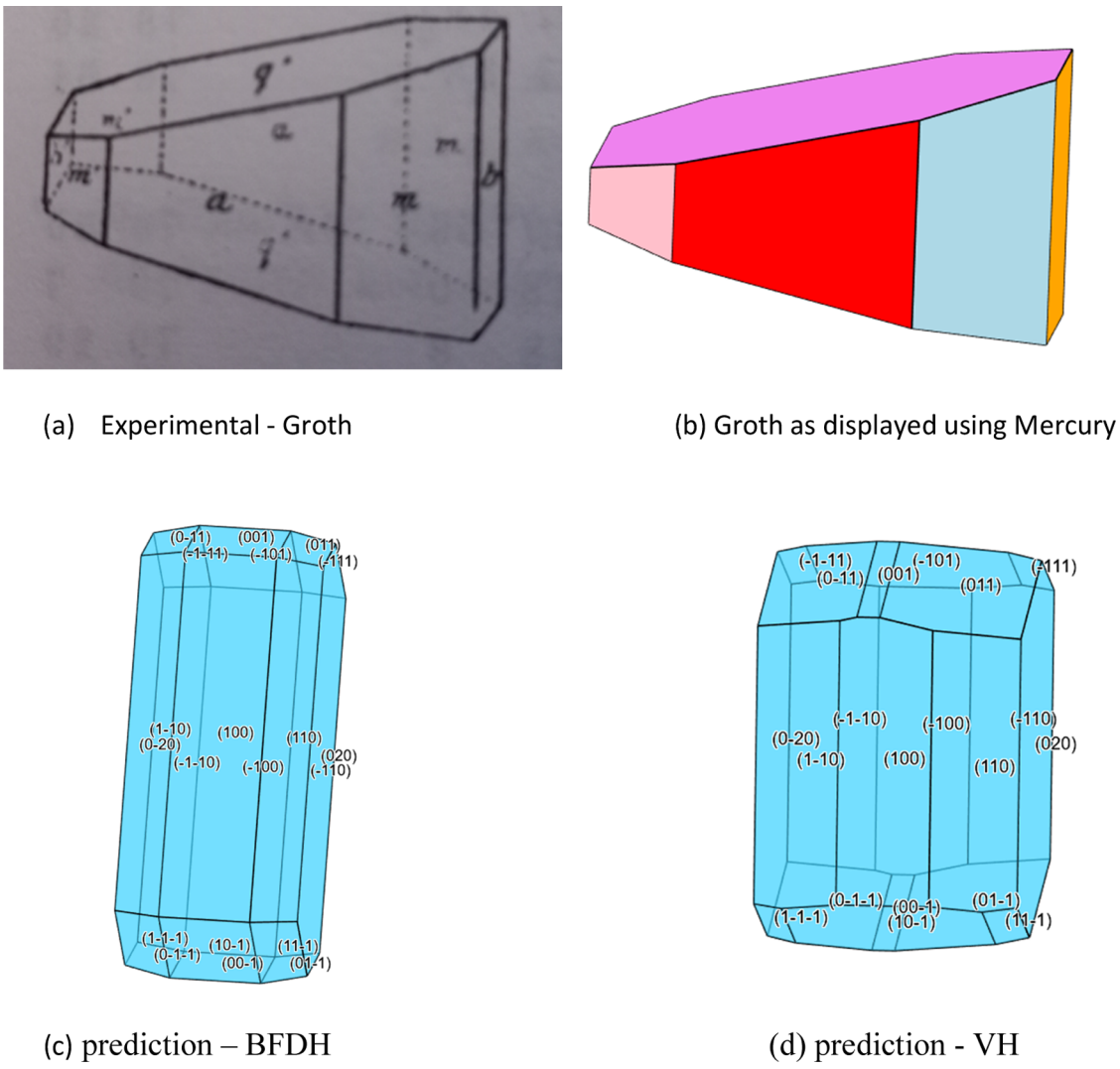

Figure 7. Morphologies of α-lactose monohydrate: (a) from Groth;[7] (b) as displayed in Mercury after unit cell matching procedure (c) as predicted by BFDH, and (d) as predicted by VH

Table 7. Labeling of Faces for the Experimental α-Lactose Monohydrate Morphologies Displayed in Figure 7a,b

letter	color	M	form	center-to-face distances
q'	violet	2	$\{0\bar{1}1\}$	1.5
a	red	2	{100}	2
b	orange	1	{020}	3.5
m	light blue	2	{110}	2.5
m'	pink	2	$\{1\bar{1}0\}$	3
b'	(not shown)	1	$\{0\bar{2}0\}$	5

the standard format for crystal structure data, which has been adopted by academics, equipment manufacturers, and publishers of scientific journals.[13] A morphology database requires a similar standard format for morphological data. This could be the "morphology.cif", as shown in Figure 4. One addition is essential—the source of the center-to-face distances at the end of the file must be identified. Currently, there is no place in the "morphology.cif" to identify where these data came from. In performing this study, the authors achieved this by careful naming of different "morphology.cif"s from the same crystal structure as they were saved.

There is a further opportunity here to learn from Groth[5−9] about how to visualize morphologies. Groth[5−9] adopted a standard orientation and labeled faces so that symmetry-related faces were instantly recognizable. Both these features have been incorporated manually in the representations of Groth's morphologies[7,9] in Mercury shown here (Figures 3 and 5−7). These features could be incorporated as defaults when displaying morphologies, both predicted and measured, in computer programmes such as Mercury.

Linking Groth's Data to the CSD. The four examples shown here illustrate unambiguous unit cell matching, given due regard to point group symmetry, axes swaps, and systematic absences. It is expected that this will also be the case for most of the 2000 other experimental morphologies of organic materials within Groth.[7−9] Linking these morphologies to the CSD is achievable. The procedure described here is cumbersome, and there may be several opportunities for automation. Industrial consortia such as the Emerging Technologies Consortium (ETC) could assist here, as they have done in the past in supporting developments in crystal science.[25]

The benefits of such a database would include ready access to valuable data on individual materials, many of which are important industrially and/or widely studied in academia. A

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database would also allow statistical studies on the prevalence of certain types of faces, including polar faces. Moreover, it would provide a testbed for evaluating the performance of predictive methods such as BFDH and VH. In this study, both these predictive methods worked well for benzophenone but not for α-lactose monohydrate. A further 2000 examples would identify what determines when these methods work well, highlighting opportunities for future development of predictive capability. This will give greater confidence and direction in using morphology prediction for other materials.

Create Pathways for Inputting Morphological Data. In some academic and pharmaceutical laboratories, it is already common practice to record some morphological data in the single-crystal diffractometer at the same time as determining the crystal structure. Sometimes this information is used for adsorption corrections. A standard format for recording such information, such as the "morphology.cif" could be helpful here, particularly if adopted by equipment manufacturers. Could a suitable light source/laser be incorporated into a single-crystal X-ray diffractometer, enhancing simultaneous crystal structure and crystal morphology determination? It is probable that crystals suitable for single-crystal studies are grown at low supersaturations, like those studied by Groth. Their morphologies may be similar to those obtained from crystallizations that are controlled by seeding to keep supersaturations low for morphological control.[26]

For other experimental morphologies, one approach would be to follow the example of Groth by including a field in the "morphology.cif" for a literature reference, where further details on the crystallization conditions are recorded. Consideration could also be given to the output of morphological data. For example, shape factors and aspect ratios could be calculated, for comparison with similar data used elsewhere.[25]

Treat Polar Morphologies Appropriately. Polar morphologies are accessible for any crystal structures lacking a center of symmetry, as explained in Table 2, including enantiopure crystal structures. Groth[5−9] identifies polar faces clearly and elegantly using a simple apostrophe. Over 100 years later, identifying polar faces in morphology drawings from Mercury (Figures 2 and 7) is not straightforward, relying on users' knowledge of space groups and point groups. Explicit recognition of predicted morphologies with altered crystal symmetries seems advisable. A database of experimental polar morphologies may in time facilitate consensus on the best way to predict them.

CONCLUSIONS

To paraphrase Olga Kennard, could the collective use of morphological data lead to the discovery of new knowledge that transcends the results of individual experiments?[27] A prerequisite is to record morphological data: center-to-face distances linked to a unit cell and space group in a standard data format. The "morphology.cif" is waiting patiently to be recognized as this standard. The work of Groth contains a valuable morphological database of over 2000 organic compounds.[7−9] These data could be converted into "morphology.cif" format, given careful matching of unit cells. The four examples presented in this study involved several manual interventions that could be automated to rapidly include many more materials.

The examples presented have illustrated the possibility of linking Groth's extensive database to prediction based on the structures in the CSD. The display of morphological data within Mercury can be enhanced using the general learning from Groth about standard projections and how to label faces. This would increase the power of Mercury in teaching and communicating about morphology. A morphology database would benefit both students and researchers by allowing better comparison of different methods of morphology prediction, encouraging better predictive methods, and "transcending the results of individual experiments."

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Notes

The authors declare no competing financial interest.

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