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Article

Common Occurrence of Twisted Molecular Crystal Morphologies from the Melt

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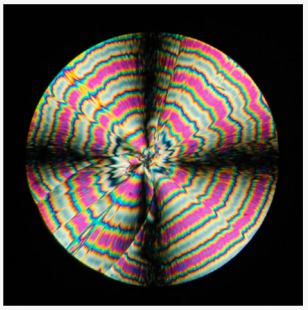
ABSTRACT: Two books that describe the forms of thin films of many molecular crystals grown from the melt in polarized light, *"Gedrillte" Kristalle* (1929) by Ferdinand Bernauer and *Thermomicroscopy in the Analysis of Pharmaceuticals* (1971) by Maria Kuhnert-Brandstätter, are analyzed. Their descriptions, especially of curious morphologies consistent with helicoidal twisting of crystalline fibrils or narrow lamellae, are compared in the aggregate with observations from our laboratory collected during the past 10 years. According to Bernauer, 27% of molecular crystals from the melt adopt helicoidal crystal forms under some growth conditions even though helicoids are not compatible with long-range translational symmetry, a feature that is commonly thought to be an a priori condition for crystallinity. Bernauer's figure of 27% is often met with surprise if not outright skepticism. Kuhnert-Brandstätter was aware of the tell-tale polarimetric signature of twisting (rhythmic interference colors) but observed this characteristic morphology in less than 0.5% of the crystals described. Here, the experience of the authors with 101 arbitrarily selected compounds—many of which are polymorphous—representing 155 total crystal structures, shows an even higher percentage (ca. 31%) of twisted crystals than the value reported by Bernauer. These observations, both positive (twisting) and negative (no twisting), are tabulated. It is concluded that twisting is not associated with molecular structure or crystal structure/symmetry. Rather, these nonclassical morphologies are associated with certain habits with exaggerated aspect ratios, and their appearance is strongly controlled by the growth conditions. Comments are offered in an attempt to reconcile the observations here, and those of Bernauer, the work of seekers of twisted crystals, with those of Kuhnert-Brandstätter, whose foremost consideration was the characterization of polymorphs of compounds of medicinal interest.



INTRODUCTION

During the 1920s,[1] Ferdinand Bernauer (1890–1945) screened 480 organic compounds obtained from colleagues in Germany for their ability to form banded spherulites, radial aggregates with a concentric optical rhythm (progression of interference contrast) in the petrographic microscope, a tell-tale optical morphology that is frequently associated with the growth-actuated twisting of fibrous crystals (typical textures are shown in Figure 1). He concluded that every fourth molecular crystal that can be melted will crystallize under some conditions (temperature, the addition of natural resins) as banded spherulites composed of helicoidal crystals.[2] He published a list of 137 compounds. Of these, 135 form molecular crystals, of which 130 of them form twisted crystals when grown from the melt. The remaining 343 compounds did not form twisted crystals, but Bernauer does not name these substances. It is not clear how many of these compounds did not crystallize from the melt, decomposed, or did not form needle-like crystals, often a prerequisite for twisting. In other words, it is not clear how accurate are the statistics reported by Bernauer. In our experience, contemporary crystallographers greet Bernauer's figure with skepticism.

In 1971, Kuhnert-Brandstätter published another large compendium of observations of crystallization from the melt, *Thermomicroscopy in the Analysis of Pharmaceuticals*.[3] She reported the crystallization of 972 compounds of pharmaceutical interest representing approximately 1284 crystal structures. (The author explicitly identifies distinct polymorphs in some cases, while in others, polymorphism is inferred.) Because the analyses are based wholly on observations in the petrographic microscope, unaccompanied by X-ray diffraction or spectroscopy, her assignments are sometimes confident, and sometimes less so. We used our experience to interpret the number of polymorphs observed according to the descriptions provided by Kuhnert-Brandstätter. We count 1284 but do not claim this number with precision.

Kuhnert-Brandstätter was well aware of the possibility of twisting of fibrous crystals. She stated, "A particularly striking and, at the same time, attractive pattern arises when the phenomenon of fibre twisting occurs ([photo without

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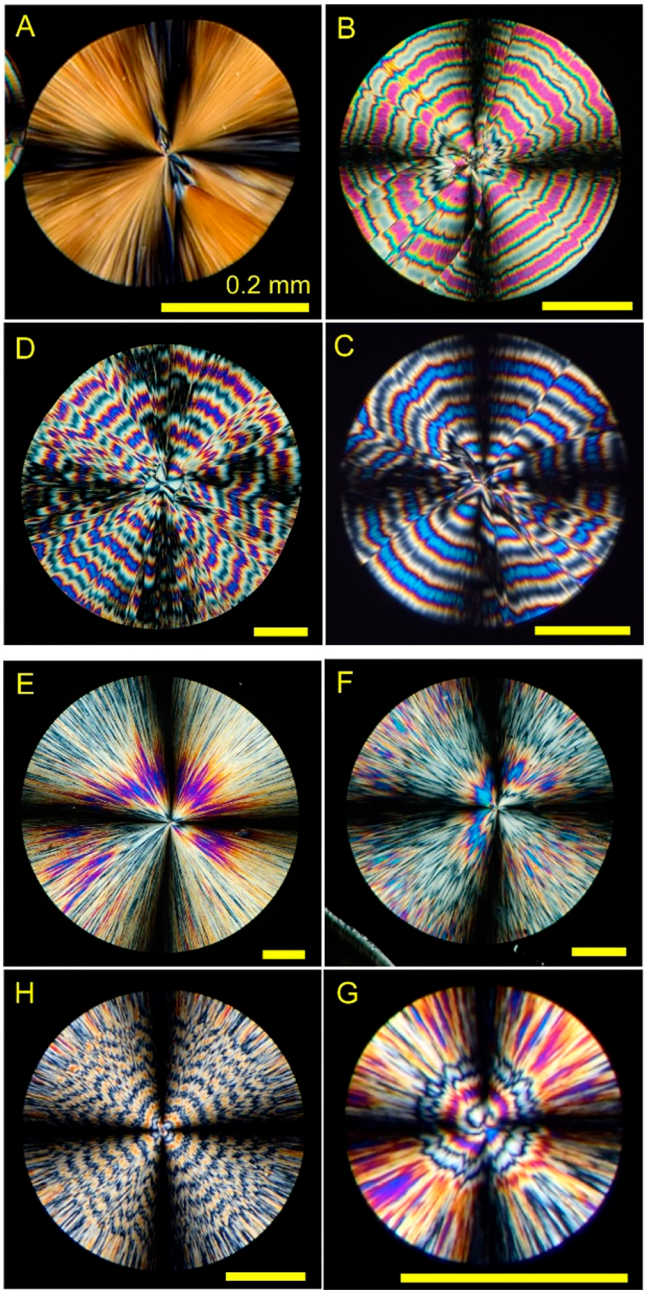

Figure 1. (A–D) Aspirin (**74**). Clockwise from A to D. Spherulites composed of straight fibrils, rhythmic twisted crystals in phase, slightly dephased and further out-of-phase. (E–H) Recorcinol (**32**). Clockwise E–F. Mostly straight crystals, twisted crystals, twisted crystals in the core becoming straight, twisted crystals becoming straight at the perimeter. Black areas around spherulites are uncrystallized supercooled melt. Images edited by M. Ferreira.

caption]).” Kuhnert-Brandstätter noted six examples of fiber twisting for a frequency of 0.47%, a value much lower than that of Bernauer. (And, this value would be halved if all the melted derivatives of the compounds listed are included.)

How to account for the discrepancy between the statistics of Bernauer and Kuhnert-Brandstatter? As one would account for any discrepancy between two experimental scientists, it is best to repeat the experiment or to repeat the experiments as best as you are able.

During the past 10 years, we have been studying the process of crystal twisting and have amassed many observations collected here. Previously,[4] we analyzed growth-induced distortions generally, including bending, twisting, and scrolling of crystals from all types of growth media. Here, we focus only on molecular crystals grown from the melt, the great majority of cases that we have studied. This compendium should identify chemical systems that are attractive to other researchers to advance our collective knowledge of the mechanisms of crystal twisting. We have not reviewed here all twisted molecular crystals observed from the melt, but only those examined in our laboratories. Some other examples not listed below can be found in refs 2, 5–13, among others.

On the other hand, polymers that crystallize as twisted lamellae have been analyzed in considerable detail during the past 70 years, and most recently reviewed by Lovinger.[14] We have emphasized small molecules here, and in the majority of our investigations, in order to balance a subject that curiously oscillated from small molecules in the first half of the 20th Century to polymers exclusively in the second half of the 20th Century.

Our enduring fascination with twisted crystals stems from the classical (pre-quasicrystal) concept of the objects described by the 230 Fedorov groups. Such crystals are characterized foremost by the symmetry operation called a *translation*, which brings in perfect superposition the components. The translation vectors, forming a basis, underlie the lattice and unit cell as organizing ideas in crystallography. If crystals are as commonly helicoidal as the sum would lead us to believe, then we must think a bit differently about what is being grown and designed in considerations of crystal growth and design.[15] Nevertheless, the common occurrence of twisting in molecular crystals may serve to deepen our understanding of the electronic properties of twisted crystals and their applications in the science of twistronics associated with van der Waals nanowires.[16]

EXPERIMENTAL SECTION

Most of the materials were purchased from Sigma-Aldrich, TCI America, or Acros Organics. Four materials (**9**, **10**, **45**, and **59** in Scheme 1) were synthesized (see below). Fluorinated isobenzofurans **112**–**119** and **121** (Scheme 2) were obtained from Prof. J. Michl (University of Colorado, USA), while organic semiconductors **136** and **137** (Scheme 3) were obtained from Prof. Y. H. Geerts (University of Brussels, Belgium).

^{1}H and ^{13}C NMR spectra were recorded on a Bruker AV 500 MHz spectrometer at 500 and 125 MHz, respectively. Chemical shifts are reported in parts per million (ppm) relative to the residual DMSO-d_6 (2.50 and 39.52 ppm for ^{1}H NMR and proton decoupled ^{13}C NMR, respectively). Data are represented as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet), coupling constants (J) in Hertz (Hz), integration.

Synthesis of thiophene-2-carboxamide and thiophene-3-carboxamide (**9** and **10** in Scheme 1, respectively). Thiophenen-2-carboxylic acid or thiophenen-3-carboxylic acid (15.0 mmol) for **9** and **10**, respectively, in $SOCl_2$ (10 mL) was refluxed at 80 °C. After 3 h, the mixture was concentrated by evaporation under reduced pressure and then diluted by anhydrous CH_2Cl_2.[17] The resulting solution was injected dropwise into an aqueous ammonia solution (10.0 mL) in an ice bath. The precipitate was collected by suction filtration, washed with water and hexane, and dried under reduced pressure. *Thiophene-2-carboxamide* (**9**): 70% yield (1.33 g, 10.5 mmol); ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.96 (s, 1H), 7.73 (ddd, J = 7.3, 4.3, 1.2 Hz, 2H), 7.37 (s, 1H), 7.12 (dd, J = 5.0, 3.6 Hz, 1H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 162.91, 140.33, 130.99, 128.68, 127.91. *Thiophene-3-carboxamide* (**10**): 70% yield (1.33 g, 10.5 mmol); ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.13 (dd, J = 3.0, 1.3 Hz, 1H), 7.78 (s, 1H), 7.57 (dd, J = 5.0, 2.9 Hz, 1H), 7.49 (dd, J = 5.0, 1.3 Hz, 1H), 7.23 (s, 1H);

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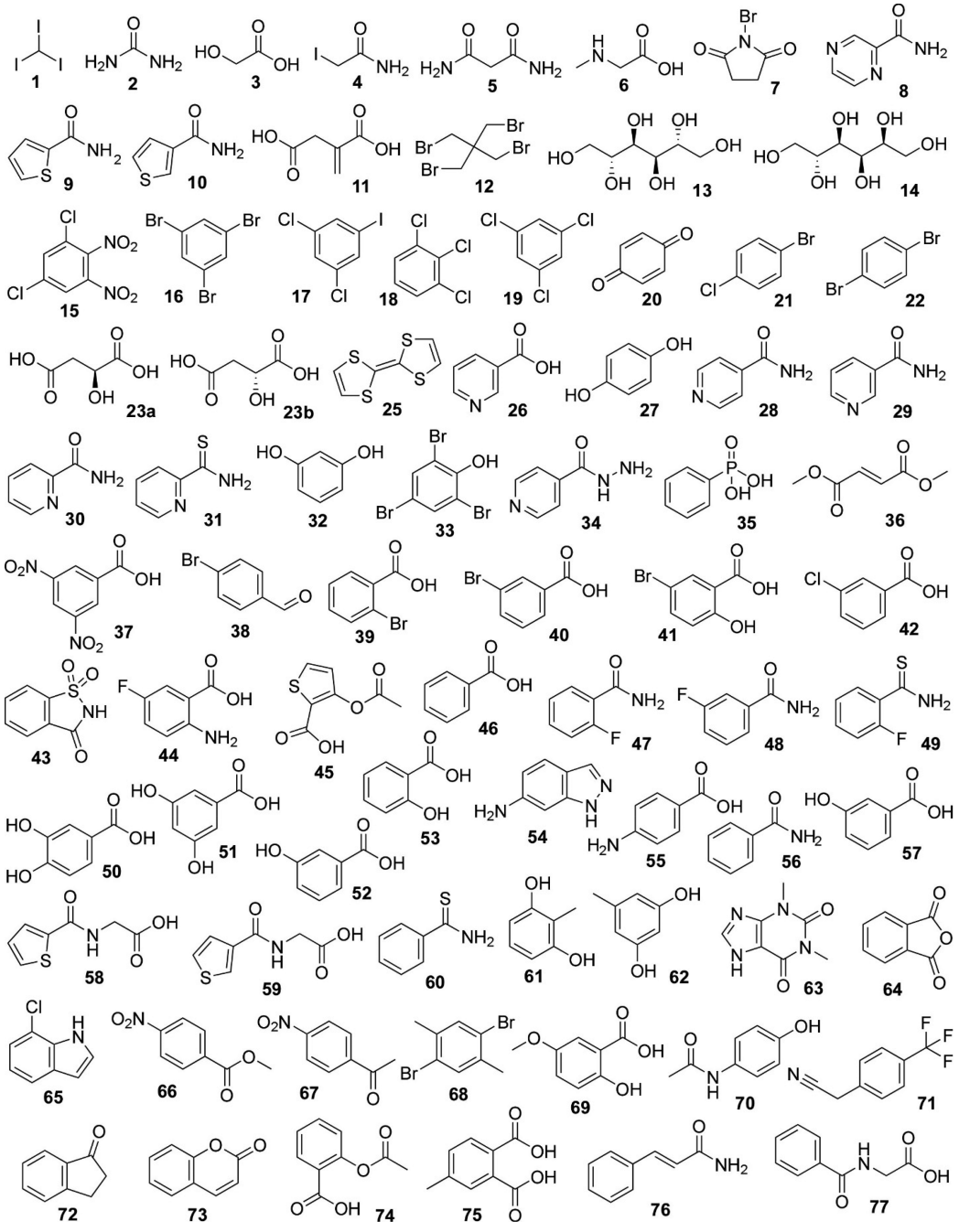
Scheme 1. Molecular Structures of Compounds Shown in Table 1



^{13}C NMR (125 MHz, DMSO-d_6) δ 163.68, 138.01, 129.00, 127.16, 126.56.

Synthesis of 3-acetoxythiophene-2-carboxylic acid (**45** in Scheme 1). One drop of concentrated H_2SO_4 was added to a mixture of 3-hydroxythiophene-2-carboxylic acid (3.50 mmol) and acetic anhydride (10.0 mmol).[18] The reaction was then heated at 80 °C for 1 h. The mixture was poured into ice water (50 mL) and extracted with ethyl acetate (3 × 10 mL). Organic extracts were combined and washed with saturated $NaHCO_3$ solution (2 × 30 mL) and then 1 M HCl solution (2 × 30 mL) until neutral. The organic phase was dried with Na_2SO_4 and concentrated by evaporation under reduced pressure. The resulting residue was purified by silica column chromatography (hexane/ethyl acetate: 1/9). *3-Acetoxythiophene-2-carboxylic acid* (**45**): 80% yield (0.52 g, 2.80 mmol); ^{1}H NMR (500 MHz, DMSO-d_6) δ 13.13 (s, 1H), 7.87 (dd, J = 5.4, 1.8 Hz, 1H), 7.03 (dd, J = 5.4, 1.8 Hz, 1H), 2.26 (s, 3H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 168.22, 161.41, 150.23, 130.80, 124.10, 119.74, 20.56.

Synthesis of *N*-(3-thienylcarbonyl)glycine (**59** in Scheme 1). $SOCl_2$ (1 mL) was added dropwise to the solution of thiophene-3-carboxylic acid (10.0 mmol) in CH_2Cl_2 (20 mL). After 8 h, the mixture was concentrated by evaporation under reduced pressure. The resulting thiophene-3-carbonyl chloride was added dropwise to a 30 mL aqueous solution of glycine (10.0 mmol) and NaOH (40.0 mmol) in an ice bath.[19] After the reaction was stirred overnight at room temperature, 1 M HCl solution was added slowly to the mixture until the pH of the solution was 2. The precipitate was collected by suction filtration, washed with cold water, and purified by silica column chromatography (hexane/ethyl acetate: 1/6). *N-(3-Thienylcarbonyl)glycine* (**59**): 65% yield (1.20 g, 6.50 mmol); ^{1}H NMR (500 MHz, DMSO-d_6) δ 12.58 (s, 1H), 8.66 (t, J = 6.0 Hz, 1H), 8.16 (dd, J = 3.0, 1.3 Hz, 1H), 7.60 (dd, J = 5.0, 2.9 Hz, 1H),

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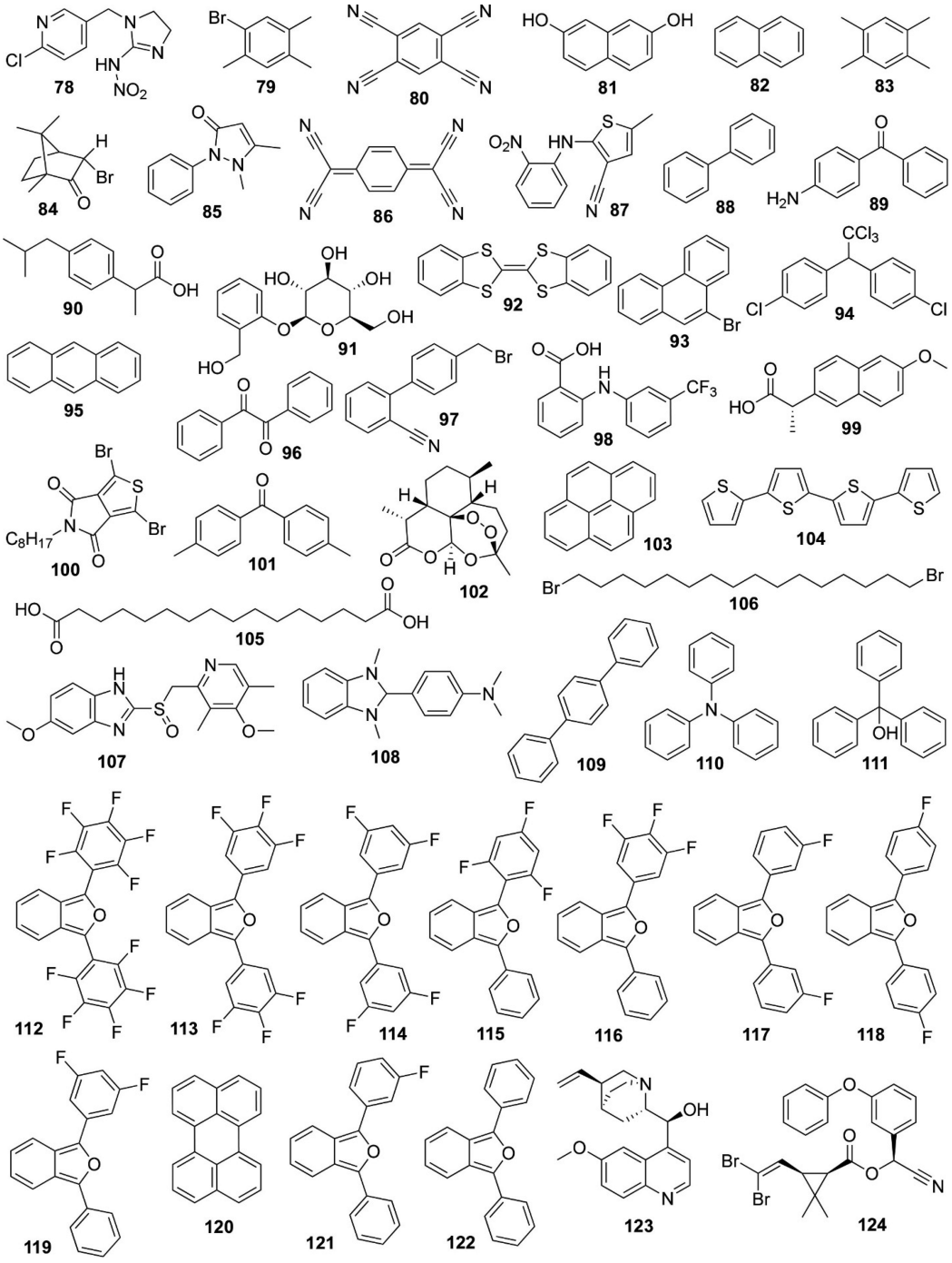
Scheme 2. Molecular Structures of Compounds Shown in Table 1



7.51 (dd, J = 5.1, 1.3 Hz, 1H), 3.89 (d, J = 6.0 Hz, 2H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 171.39, 162.31, 137.27, 129.07, 126.85, 126.74, 40.88.

Several milligrams of each compound listed in Table 1 was sandwiched between two glass slides and melted to form a thin, 1−10 μm, film. If the compound can be cooled without crystallization to room temperature, a 1 mm microscope slide was covered by a 0.1 mm cover glass. If crystallization occurs too quickly just below the melting temperature, a pair of two 0.1 mm slides was used to increase heat dissipation, so as to achieve a supercooled melt. The melts were crystallized in the whole range of temperatures between room temperature (20−25 °C) and the melting point, T_m, using a hot stage or a Kofler bench, or two metal blocks. If crystallization at room temperature did not occur or resulted in large, rapidly growing crystals, crystallization was performed in a refrigerator (8 °C), freezer (0 °C), or between two metal blocks in a box with dry ice (crystallization temperature > −20 °C). All materials were crystallized with and without additives. The most effective additives for inducing twisting include natural resins such as Canada balsam, gum mastic, or Damar gum (aka Dammar crystals), among some others, at loadings of 10−15 wt %.[2] Natural resins are complex mixtures of terpenes, fatty acids, resin acids, and glycerides,[20] extracted from various plants. They can promote the formation of twisted crystals. In specific cases, small molecule additives or synthetic polymers such as polyvinylpyrrolidone (PVP) were used as well. For the purposes of routine screening, we usually used only one additive, mostly Canada balsam. For materials characterized in more detail, several additives were typically used.

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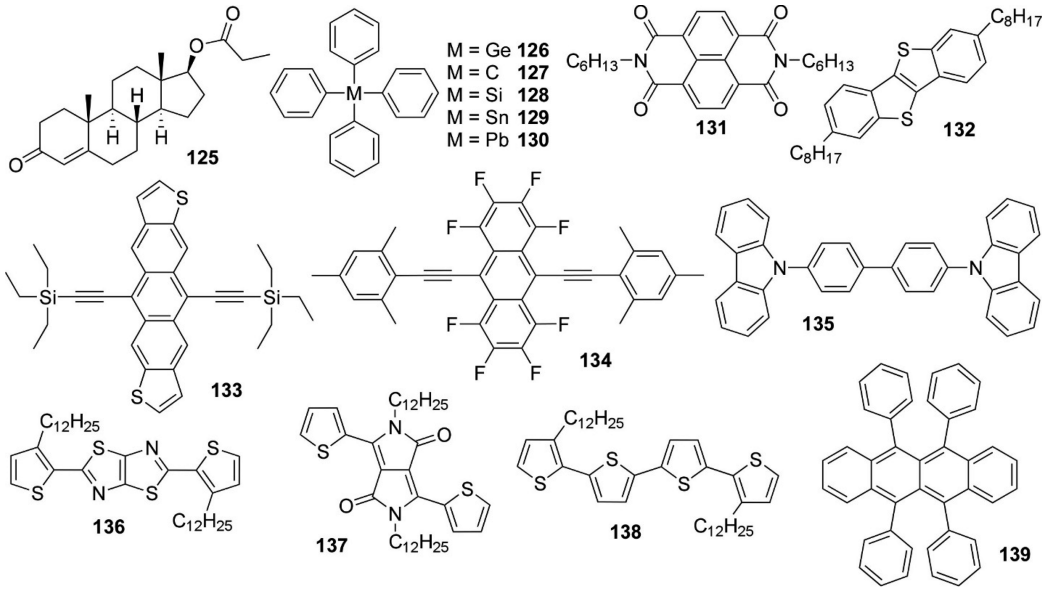
Scheme 3. Molecular Structures of Compounds Shown in Table 1



Single crystals of **10**, **45**, and **59** were prepared in 20 mL glass vials by slow evaporation from their acetone, ethanol, and dimethylformamide solutions, respectively. The X-ray intensity data of single crystals were recorded on a Bruker D8 APEX-II CCD system with the ω scan method at 100 K using graphite-monochromated and 0.5 mm MonoCap-collimated Mo Kα radiation (λ = 0.71073 Å). Structures were solved by intrinsic phasing methods (SHELXT), and the structure models were completed and refined using the full-matrix least-squares methods on F^2. Crystallographic information files (CIFs), including the HKL and RES data, were deposited in the Cambridge Crystallographic Data Centre (CCDC) with nos. 2002874 (**59**), 2002875 (**45**), and 2002876 (**10**).

RESULTS

The results are summarized in Table 1. The number of polymorphs discovered for each compound (N_{total}) is given for reference since the statistical analysis below considered only the number of polymorphs we observed under a given set of conditions, and among those, only suitable polymorphs that under some conditions crystallize as relatively fine fibers (<10−20 μm in width). The number of such polymorphs is indicated by $N_{suitable}$. This limitation is related to the fact that the intensity of twisting decreases as the crystal size increases,[4,21] and twisting in large crystals, with large pitches, is not routinely detected by light microscopy. The minimum detectable twist rate (radians/distance), inverse to the twist period (pitch, P) as the length of a crystal needed for each 180° crystal rotation, is equal to 1−2 mm. We also cannot routinely identify rare cases of tightly twisted crystals with P < 1 μm, below detection by light microscopy. The criteria for counting a polymorph as suitable are somewhat arbitrary, unfortunately, as it is difficult to obtain metric analyses of individual fibrils that are tightly packed.

Crystals are considered twisted if they show a rhythmic progression of interference colors along the growth directions. This is a reliable characteristics of twisted crystals (Figure 1B−G, but not 1A). Rhythmic precipitation[22−24] can masquerade as crystal twisting. In both instances, concentric bands with oscillating linear retardance are the characteristic features. However, these phenomena are distinguishable to the practiced eye equipped with a polarized light microscope. In several cases, twisting was confirmed by using the "sensing the screw" method,[22,25−27] X-ray diffraction analysis, atomic force or electron microscopies. The number of polymorphs with twisted crystals is indicated as N_{twist}.

DISCUSSION

Statistics. Table 1 contains information on 139 compounds, a biased collection because many materials came from the list of twisted crystals of Bernauer.[2] Some materials were analyzed because they were known to form twisted crystals or were isostructural to crystals identified as twisted. Therefore, to make statistically representative sampling, the occurrence of twisted crystals was calculated from 101 materials (155 suitable polymorphs) chosen rather arbitrarily. We did not study a statistically randomized subset of molecules, biased as we were by the availability of compounds in a chemical library collected over decades, we did choose compounds preferentially. We sought compounds with modest melting points below 300 °C, and we eschewed hydrates/solvates and salts, subject to chemical transformations on melting. The fraction of compounds forming twisted crystals with respect to all compounds that can crystallize from the melt in the form of fine fibers 45/101 = 45% is substantially larger than 130/480 = 27% obtained by Bernauer, however, this comparison is not complete because we do not know why twisted crystals were not formed/observed in Bernauer's study. The more correct estimate of the fraction of twisted crystals should come from the ratio between polymorphs showing twisted morphologies and the total number of suitable polymorphs: $\Sigma N_{twist}/\Sigma N_{suitable}$ = 48/155 = 31%. This number is diminished if we consider only polymorphs that can form twisted crystals without additives: $\Sigma N_{twist\ w/o\ additives}/\Sigma N_{suitable}$ = 25/155 = 16%. That means that $\Sigma N_{twist\ w/o\ additives}/\Sigma N_{twist}$ = 25/48 = 52% polymorphs do not require additives for twisting. (Bernauer reported 41/130 = 32% molecular crystals do not need additives to form twisted crystals.) Naturally, we cannot attest to the purity of the compounds used by Bernauer. The purity of starting materials themselves can be important. Bernauer reported twisted crystals of 1,4-benzoquinone, **20**, 3-

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Table 1. Occurrence of Twisting in Molecular Crystals Forming from the Melt[a]

				number of polymorphs[c]				
N	compound	formula	T_m, °C[b]	N_{total}	$N_{suitable}$	N_{twist}	additive[d]	source, ref[e]
1	iodoform	CHI_3	119	1	1	1	**16**	R[28]
2	urea	CH_4N_2O	133	1	1	1	none	FB[28]
3	glycolic acid	$C_2H_4O_3$	75	2	2	1	none	FB[8]
4	iodoacetoamide	C_2H_4INO	100	2	1	0	N/A	R
5	malonamide	$C_3H_6N_2O_2$	173	2	2	1	TA[f]	Tw[8]
6	sarcosine	$C_3H_7NO_2$	210	2	2	0	N/A	R
7	*N*-bromosuccinimide	$C_4H_4BrNO_2$	175	1	1	1	none	R
8	pyrazinamide	$C_5H_5N_3O$	192	4	1	0	N/A	R
9	thiophene-2-carboxamide	C_5H_5NOS	180	1	1	1	CB[g]	R I1
10	thiophene-3-carboxamide	C_5H_5NOS	∼190	1	1	1	CB	R I1
11	itaconic acid	$C_5H_6O_4$	163	1	1	1	none	FB[28]
12	pentaerythritol tetrabromide	$C_5H_8Br_4$	159	1	1	1	CB, GM	FB
13	mannitol	$C_6H_{14}O_6$	168	3	2	2	PVP, **14**[g]	Tw[28,29]
14	sorbitol	$C_6H_{14}O_6$	95	3	1	0	N/A	R
15	1,5-dichloro-2,3-dinitrobenzene	$C_6H_2Cl_2N_2O_4$	97	1	1	1	see text[g]	R[28]
16	1,3,5-tribromobenzene	$C_6H_3Br_3$	122	1	1	0	N/A	R I2
17	3,5-dichloroiodobenzene	$C_6H_3Cl_2I$	57	1	1	1	CB[g]	R
18	1,2,3-trichlorobenzene	$C_6H_3Cl_3$	53	1	1	0	N/A	R
19	1,3,5-trichlorobenzene	$C_6H_3Cl_3$	63	1	1	0	N/A	R I2
20	1,4-benzoquinone	$C_6H_4O_2$	115	1	1	0	N/A	FB
21	1-bromo-4-chlorobenzene	C_6H_4ClBr	66	1	1	0	N/A	R
22	1,4-dibromobenzene	$C_6H_4Br_2$	87	1	1	0	N/A	R
23	D,L-malic acid, **23a**, **23b**	$C_6H_4O_5$	101	2	1	1	none	R[30]
24	D,L-malic acid, **23a**:**23b** = 1:1	$C_6H_4O_5$	132	1	1	0	N/A	R
25	tetrathiafulvalene, TTF	$C_6H_4S_4$	118	2	2	1	none	R
26	nicotinic acid	$C_6H_5NO_2$	237	1	1	0	N/A	R
27	hydroquinone	$C_6H_6O_2$	172	3	2	2	TA[f]	FB[8,28]
28	isonicotinamide	$C_6H_6N_2O$	110	6	2	1	CB, DG[g]	R
29	nicotinamide	$C_6H_6N_2O$	130	8	7	1	none	R
30	picolinamide	$C_6H_6N_2O$	110	2	2	2	CB	R
31	2-pyridine thioamide	$C_6H_6N_2S$	136	2	2	2	CB[h]	R
32	resorcinol	$C_6H_6O_2$	110	3	2	2	TA[f]	FB[8,28,31,32]
33	2,4,6-tribromophenol	$C_6H_6Br_3O$	96	2	1	1	CB	FB
34	isoniazid	$C_6H_7N_3O$	171	3	3	1	none	R
35	phenylphosphonic acid	$C_6H_7O_3P$	163	1	1	0	N/A	R
36	dimethyl fumarate	$C_6H_8O_4$	104	1	1	0	N/A	R
37	3,5-dinitrobenzoic acid	$C_7H_4N_2O_6$	206	2	2	1	CB	R
38	4-bromobenzaldehyde	C_7H_5BrO	57	1	1	0	N/A	R
39	2-bromobenzoic acid	$C_7H_5BrO_2$	149	1	1	1	CB[g]	R
40	3-bromobenzoic acid	$C_7H_5BrO_2$	157	1	1	1	none	FB
41	5-bromosalicylic acid	$C_7H_5BrO_3$	163	2	2	0	N/A	R
42	3-chlorobenzoic acid	$C_7H_5ClO_2$	155	1	1	0	N/A[i]	FB

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Table 1. continued

N	compound	formula	T_m, °C[b]	number of polymorphs[c] N_{total}	$N_{suitable}$	N_{twist}	additive[d]	source, ref[e]
43	saccharin	$C_7H_5NO_3S$	229	2	2	1	none	FB[28]
44	2-amino-5-fluorobenzoic acid	$C_7H_6FNO_2$	182	1	1	0	N/A	R
45	3-acetoxythiophene-2-carboxylic acid	$C_7H_6O_4S$	101	2	2	1	CB	R
46	benzoic acid	$C_7H_6O_2$	122	1	1	1	CB[g]	FB
47	2-fluorobenzamide	C_7H_6NOF	118	2	2	1	none	R I3
48	3-fluorobenzamide	C_7H_6NOF	131	1	1	1	CB	R
49	2-fluorothiobenzamide	C_7H_6NSF	115	1	1	0	N/A	R I3
50	3,4-dihydroxybenzoic acid	$C_7H_6O_4$	221d	1	1	0	N/A	R
51	3,5-dihydroxybenzoic acid	$C_7H_6O_4$	237	1	1	0	N/A	R
52	3-hydroxybenzoic acid	$C_7H_6O_3$	202	2	2	0	N/A	R
53	salicylic acid	$C_7H_6O_3$	159	2	2	1	none	R
54	6-aminoindazole	$C_7H_7N_3$	205	1	1	1	none	R
55	4-aminobenzoic acid	$C_7H_7NO_2$	189	1	1	0	N/A[i]	FB
56	benzamide	C_7H_7NO	127	4	3	1	none	FB I3
57	3-hydroxybenzoic acid	$C_7H_7O_6$	202	2	2	0	N/A	R
58	*N*-(2-thienylcarbonyl)glycine	$C_7H_7NO_3S$	164	2	2	1	none	R I4[28]
59	*N*-(3-thienylcarbonyl)glycine	$C_7H_7NO_3S$	~174	1	1	1	none	R I4
60	thiobenzamide	C_7H_7NS	115	1	1	0	N/A	R I3
61	2-methylresorcinol	$C_7H_8O_2$	117	2	2	1	CB	R
62	5-methylresorcinol, orcinol	$C_7H_8O_2$	111	1	1	0	N/A	R
63	theophylline	$C_7H_8N_4O_2$	273	5	2	0	N/A	R
64	phthalic anhydride	$C_8H_4O_3$	134	1	1	0	N/A	R
65	7-chloroindole	C_8H_6ClN	57	1	1	0	N/A	R
66	methyl-4-nitrobenzoate	$C_8H_7NO_4$	95	2	1	1	CB[g]	R
67	4′-nitroacetophenone	$C_8H_7NO_3$	78	1	1	1	CB	R
68	1,4-dibromo-2,5-dimethylbenzene	$C_8H_8Br_2$	73	2	2	1	CB, GM	R
69	5-methoxysalicylic acid	$C_8H_8O_4$	142	1	1	0	N/A	R
70	acetaminophen	$C_8H_9NO_2$	169	6	6	2	none	R[33]
71	4-(trifluoromethyl)phenylacetonitrile	$C_9H_6NF_3$	48	1	1	0	N/A	R
72	1-indanone	C_9H_8O	39	1	1	0	N/A	R
73	coumarin	$C_9H_6O_2$	71	5	4	2	none	FB[28,34]
74	aspirin	$C_9H_8O_4$	136	3	2	1	**53**, CB, GM[f]	FB[28,35]
75	4-methylphthalic acid	$C_9H_8O_4$	147	1	1	0	N/A	R
76	cinnamamide	C_9H_9NO	149	2	2	0	N/A	R
77	hippuric acid	$C_9H_9NO_3$	188	1	1	1	none	FB I4[23,25,28]
78	imidacloprid	$C_9H_{10}ClN_5O_2$	144	8	3	0	N/A	R
79	5-bromo-1,2,4-trimethylbenzene	$C_9H_{11}Br$	72	1	1	0	N/A	R
80	1,2,4,5-tetracyanobenzene	$C_{10}H_2N_4$	266	1	1	0	N/A	R
81	2,7-dihydroxynaphthalene	$C_{10}H_8O_2$	188	1	1	0	N/A	R
82	naphthalene	$C_{10}H_8$	80	1	1	1	CB	FB
83	durene	$C_{10}H_{14}$	79	1	1	1	GM	FB[28]
84	(+)-3-bromocamphor	$C_{10}H_{15}BrO$	77	1	1	1	CB, GM	FB[28]

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Table 1. continued

N	compound	formula	T_m, °C[b]	number of polymorphs[c]			additive[d]	source, ref[e]
				N_{total}	$N_{suitable}$	N_{twist}		
85	antipyrine	$C_{11}H_{12}N_2O$	114	2	2	1	none	FB
86	tetracyanoquinodimethane, TCNQ	$C_{12}H_4N_4$	295	1	1	0	N/A	R
87	5-methyl-2-[(2-nitrophenyl)amino]-3-thiophenecarbonitrile, ROY	$C_{12}H_9N_3O_2S$	115	12	5	1	none	R[36]
88	biphenyl	$C_{12}H_{10}$	69	1	1	0	N/A	R
89	4-aminobenzophenone	$C_{13}H_{11}NO$	123	1	1	1	CB	R
90	ibuprofen	$C_{13}H_{18}O_2$	77	2	1	1	none	R[37]
91	salicin	$C_{13}H_{18}O$	198	1	1	1	none	R
92	dibenzotetrathiafulvalene	$C_{14}H_8S_4$	241	3	1	1	CB, DG	R
93	9-bromophenanthrene	$C_{14}H_9Br$	62	1	1	0	N/A	R
94	1,1′-(2,2,2-trichloroethane-1,1-diyl)bis(4-chlorobenzene), DDT	$C_{14}H_9Cl_5$	109	2	2	1	none	R[38]
95	anthracene	$C_{14}H_{10}$	216	1	1	1	GM	FB
96	benzil	$C_{14}H_{10}O_2$	95	1	1	1	none	FB
97	4′-bromomethyl-2-cyanobiphenyl	$C_{14}H_{10}BrN$	127	1	1	0	N/A	R
98	flufenamic acid	$C_{14}H_{10}F_3NO_2$	135	9	3	1	none	R
99	naproxen	$C_{14}H_{14}O_3$	153	1	1	1	none	R[37]
100	1,3-dibromo-5-octyl-4*H*-thieno[3,4-c]pyrrole-4,6(5*H*)-dione	$C_{14}H_{17}Br_2NO_2S$	107	1	1	1	none	R
101	4,4′-dimethylbenzophenone	$C_{15}H_{14}O$	92	3	2	0	N/A	R
102	artemisinin	$C_{15}H_{22}O_5$	155	3	2	1	none	R
103	pyrene	$C_{16}H_{10}$	147	3	2	1	CB	R
104	2,2′:5′,2″:5″,2‴-quaterthiophene	$C_{16}H_{10}S_4$	213	2	1	0	N/A	R
105	hexadecanedioic acid	$C_{16}H_{30}O_4$	122	1	1	1	none	R
106	1,16-dibromohexadecane	$C_{16}H_{32}Br_2$	57	1	1	1	CB	R
107	omeprazole	$C_{17}H_{19}N_3O_3S$	156	1	1	0	N/A	R
108	4-(2,3-dihydro-1,3-dimethyl-1*H*-benzimidazol-2-yl)-*N*,*N*-dimethylbenzenamine	$C_{17}H_{21}N_3$	107	2	2	1	CB	R
109	*p*-terphenyl	$C_{18}H_{14}$	213	1	1	0	N/A	R
110	triphenylamine	$C_{18}H_{15}N$	127	1	1	0	N/A	R
111	triphenylmethanol	$C_{19}H_{16}O$	163	1	1	0	N/A	R
112	1,3-bis(perfluorophenyl)isobenzofuran[39]	$C_{20}H_4F_{10}O$	~116	1	1	0	N/A	R
113	1,3-bis(3,4,5-trifluorophenyl)isobenzofuran[40]	$C_{20}H_8F_6O$	216	1	1	0	N/A	R
114	1,3-bis(3,5-difluorophenyl)isobenzofuran[40]	$C_{20}H_{10}F_4O$	~205	1	1	0	N/A	R
115	1-phenyl-3-(2,4,6-trifluorophenyl)isobenzofuran[40]	$C_{20}H_{11}F_3O$	~105	1	1	1	none	R
116	1-phenyl-3-(3,4,5-trifluorophenyl)isobenzofuran[40]	$C_{20}H_{11}F_3O$	~125	2	2	0	N/A	R
117	1,3-bis(3-fluorophenyl)isobenzofuran[40]	$C_{20}H_{12}F_2O$	~140	2	2	1	none	R
118	1,3-bis(4-fluorophenyl)isobenzofuran[40]	$C_{20}H_{12}F_2O$	~111	1	1	0	N/A	R
119	1-(3,5-difluorophenyl)-3-phenylisobenzofuran[40]	$C_{20}H_{12}F_2O$	~100	2	2	1	none	R
120	perylene	$C_{20}H_{12}$	278	2	1	1	CB	R
121	1-(3-fluorophenyl)-3-phenylisobenzofuran[40]	$C_{20}H_{13}FO$	~125	1	1	0	N/A	R
122	1,3-diphenylisobenzofuran	$C_{20}H_{14}O$	129	2	2	0	N/A	R
123	quinidine	$C_{20}H_{24}N_2O_2$	168	2	1	0	N/A	R
124	deltamethrin	$C_{22}H_{19}Br_2NO_3$	98	2	2	1	none	R
125	testosterone propionate	$C_{22}H_{32}O_3$	121	2	2	2	none	Tw[28,40]
126	tetraphenylgermane	$C_{24}H_{20}Ge$	233	1	1	1	PVP	R IS

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Table 1. continued

N	compound	formula	T_m, °C[b]	number of polymorphs[c] N_{total}	$N_{suitable}$	N_{twist}	additive[d]	source, ref[e]
127	tetraphenylmethane	$C_{25}H_{20}$	272	1	1	1	PVP	R I5
128	tetraphenylsilane	$C_{24}H_{20}Si$	236	1	1	1	PVP	R I5
129	tetraphenylstannane	$C_{24}H_{20}Sn$	226	1	1	1	PVP	R I5[22]
130	tetraphenylplumbane	$C_{24}H_{20}Pb$	228	1	1	1	PVP	FB I5[22,28]
131	*N*,*N*′-(1-hexyl)-1,4,5,8-naphthalenetetracarboxydiamide	$C_{26}H_{30}N_2O_4$	208	2	2	0	N/A	R
132	2,7-dioctyl[1]benzothieno [3,2-b][1]benzothiophene, C8-BTBT	$C_{30}H_{40}S_2$	110	2	2	0	N/A	Tw
133	5,11-bis(triethylsilylethynyl) anthradithiophene, TES-ADT	$C_{34}H_{38}S_2Si_2$	133	5	5	0	N/A	R
134	1,2,3,4,5,6,7,8-octafluoro-9,10-bis[2-(2,4,6-trimethylphenyl)ethynyl] anthracene	$C_{36}H_{22}F_8$	267	1	1	1	none	R
135	4,4′-bis(*N*-carbazolyl)-1,1′-biphenyl	$C_{36}H_{24}N_2$	283	3	2	1	none	R
136	2,5-bis(3-dodecyl-2-thienyl)-thiazolo[5,4-d]thiazole[41]	$C_{36}H_{54}N_2S_4$	75	1	1	1	none	Tw
137	2,5-didodecyl-3,6-di(thiophen-2-yl)-2,5-dihydropyrrolo[3,4-*c*]pyrrole-1,4-dione[41]	$C_{38}H_{56}N_2O_2S_2$	127	1	1	1	none	Tw
138	3,3‴-didodecyl-2,2′:5′,2″:5″,2‴-quaterthiophene	$C_{40}H_{58}S_2$	57	1	1	0	N/A	R
139	rubrene	$C_{42}H_{28}$	315	4	2	0	N/A	R

[a]Molecular structures with numbers in the first column corresponding to identifiers in Schemes 1, 2, and 3. [b]T_m – melting point as determined for the most stable polymorph. [c]Number of polymorphs: N_{total} – total number of polymorphs; $N_{suitable}$ – number of polymorphs with fine fibers suited to twisting; N_{twist} – number of polymorphs with twisted morphologies. [d]Additive: None – twisting was observed without additives; CB – Canada balsam; GM – gum mastic; DG – Damar gum; TA – tartaric acid; N/A – not applicable since twisting was not discovered. [e]Source, ref.: FB – compound was reported to form twisted crystals by Bernauer; R – compound was studied by circumstance, mainly determined by availability; Tw – compound was reported to form twisted crystals by other scientists; I1, I2···I5 – families of isostructural compounds. References provide more information. [f]Twisting is at least partially controlled by crystal/additive chemical interactions. [g]Additives responsible for creation of suitable crystal morphologies and fine fibers. This symbol appears if, in the absence of additives, crystal sizes are not suited to twisting and they are straight, whereas in the presence of additives crystals become fine and twisted. It also appears if twisting can be induced by several additives. [h]One polymorph does not require additives to exhibit twisted morphologies, while the second one does. [i]Twisting was reported by Bernauer but not seen here.

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chlorobenzoic acid, **42**, and 4-aminobenzoic acid, **54**. We were not able to twist them, with or without additives.

Molecular Structure. Several mechanisms were suggested to explain crystal twisting,[4] and it is still not clear which of them are relevant in which circumstances. Although we are not aiming to solve this problem now, the data summarized here can help to identify the more probable mechanisms. Twisting does not seem to arise in chemical constitution, a statement supported by the propensity of twisting in different crystal structures formed by the same compound, i.e., in different polymorphs. In Table 1, we identified 40 compounds with two suitable polymorphs ($N_{\text{suitable}} = 2$) and discovered that 12 (30%) of them do not show twisting ($k = 0$), 22 (55%) compounds show twisting for one of the two polymorphs ($k = 1$), and for the remaining 6 (15%) both polymorphs twist ($k = 2$). This analysis included all crystals that can be twisted, with and without additives. If molecular structure is not determinative, then the distribution of twisted crystals in these pairs will follow a probability mass function in a binomial distribution $P(k, n, p) = \frac{n!}{k!\,(n-k)!}p^k(1-p)^{n-k}$.[42] Using the probability of getting twisted crystals obtained above, $p = \Sigma N_{\text{twist}}/\Sigma N_{\text{suitable}} = 0.31$, and the number of polymorphs for each compound $n = 2$, one can calculate $P(0,2,0.31) = 47\%$, $P(1,2,0.31) = 43\%$, $P(2,2,0.31) = 10\%$, respectively. Compare to 30, 55, and 15% found. For this small population, the binomial expectation is roughly followed.

Crystal Structure and Symmetry. The role of crystal structure should be more important, and the simplest check is comparing twisting of materials having comparable X-ray crystal structures but different compositions, i.e., isostructural (same packing and bonding motifs) and isomorphous (in addition to being isostructural, they can form solid solutions in a wide range of compositions) compounds. We can identify five such families in Table 1. *Family I1*. Thiophene-2-carboxamide (**9**) (refcodes TUKPOF and ZAZZEI) and thiophene-3-carboxamide (**10**) (CCDC No. 2002876, synthesized above) are isostructural (space group $Pna2_1$). Crystals from the melt appear identical, and both form banded spherulites only in the presence of resins. *Family I2*. 1,3,5-trichlorobenzene (**19**) (refcode TCHLBZ) and 1,3,5-tribromobenzene (**16**) (refcode TBRMBZ) are isostructural (space group $P2_12_12_1$). Neither twist. *Family I3*. Benzamide (**56**) (refcode BZAMID13), 2-fluorobenzamide (**60**) (refcode BIGSUF), thiobenzamide (**47**),[43] and 2-fluorothiobenzamide (**49**) (refcode XOGRIW) are not strictly isostructural (with the exception of **49** and **60**, space group $P2_1/c$) but share the same molecular packing with parquet-like arrangements of pairs of infinite hydrogen-bonded dimeric or catemeric tapes.[44] Among them, amides form twisted crystals, while thioamides do not. *Family I4*. Hippuric acid, **77** (refcode HIPPAC), and two its isostructural and isomorphous thiophene derivatives **58** (refcode RAVQEM) and **59** (CCDC No. 202874, synthesized above) (space group $P2_12_12_1$) form twisted crystals. However, the propensity to twist decreases sharply in the series: **77** > **58** > **59**. *Family I5*. Tetraphenylmethane, **127** (refcode TEPHME), and its isostructural derivatives, **126** (refcode TEPNGE), **128** (refcode TEPNSI), **129** (refcode TEPNSN), and **130** (refcode TEPNPB) (space group $P\bar{4}2_1c$) from the melt show similar morphologies. All of these compounds form twisted crystals in the presence of PVP, but the propensity to twist is very different: **130** > **129** ≫ **127** > **128** > **126**. In sum, isostructural compounds are correlated with twisting.

Some of the compounds synthesized in this study were intended to exploit isomorphous substitutions common in molecular crystals, such as the size equivalence of the thiophene and phenyl rings as in **77**, **58**, and **59**.[45] All three of these compounds were twisted, affirming that structural constancy leads to dependable chemical and physical consequences, a reliable principle in chemistry. However, changing the conditions of growth in an effort to inhibit twisting in hippuric acid and its derivatives often provoke twisting around some other direction to that first observed.[21,23] The aspirin (**74**) congener, 3-acetoxythiophene-2-carboxylic acid (**45**), while also $P2_1/c$ like the known aspirin polymorphs, was not isostructural with **74**; it had a uniquely shallow *b*-axis. It twisted like aspirin nevertheless. In other words, twisting is so common that, even when the phenomenon is imperfectly encouraged or inhibited, new twisted forms and directions become manifest.

Among the space groups cited in two previous paragraphs, we can find centric crystals, polar achiral crystals, and enantiomorphous crystals, both polar and nonpolar. Other than an absence of cubic crystals, not suitable for crystal optical detection of twisting, symmetry is weakly correlated with twisting. Nevertheless, the *sense* of twisting in positive cases is equal and opposite in enantiomorphs or along enantiotopic growth directions.[35] Additives can also induce twisting via chemical interactions with the crystal. This possibility can be confirmed if the presence of twisting and/or twist sense are very sensitive to the particular additive. For example, the addition of L-tartaric acid produces left-handed helices of one polymorph of resorcinol (**32**) and right-handed helices of another one, while addition D-tartaric acid results in opposite twist senses; racemic tartaric acid does not produce twisted crystals.[8,31] Some examples are shown in Table 1.

We have recently begun to illustrate deviations in the constraints of a lattice when sizes of crystallites are very small.[46,47] In other words, small objects, lacking semi-infinite translations, need not conform to long-range translational symmetry required of semi-infinite crystals. The ubiquity of twisting may well be connected to the intrinsic dissymmetries of small crystals that are somehow preserved by growth on the micron scale.

Growth Environment. As discussed previously,[4,21−23,29,40] twisting depends strongly on growth conditions. There are two major melt crystallization parameters: temperature and additives/impurities. They can affect formation of twisted crystals in several ways.

Temperature can affect dominant growth directions that either actuate or obviate twisting. For example, hippuric acid between 80 and 180 °C forms fibers along [100], while between 60 and 115 °C it grows along [001].[22] Both crystal elongations lead to twisting but pitch varies by 1 order of magnitude.

Both, temperature and additives, can affect thickness of crystallites. Typically, finer crystals form at higher supercooling and higher additive concentration due to stronger branching. Finer crystals are characterized by small pitches.[4,21] Indirectly, additives can reduce the growth rate thereby driving the medium to high undercoolings. In this way, additives can produce twisting by increasing the aspect ratios of fine crystalline fibers. One such example is 1,5-dichloro-2,3-dinitrobenzene, **15**, that without additives does not form fine crystallites and does not exhibit twisting. However, it twists in the presence of CB and GM resins as well as with small

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molecule additives including the following: **1**, **16**, **18**, **19**, **21**, **22**, **77**, **82**, **83**, **110**, 4-bromoaniline, 1,2,4,5-tetrachlorobenzene, and *m*-terphenyl. Twisting was not observed in the presence of **14**, hexachlorobenzene, tetracosane, eicosane, and 2-chloro-4,6-dinitroaniline, but in all these cases the crystals did not form fine fibers. Twisting of **15** also was not observed with additives **39**, **66**, and **67** despite the fact that the crystals were fibrous, but we cannot say why.

Although we focus on crystallization from the melt, twisting is a feature of crystallization from all kinds of growth media.[4] Some materials such as hippuric acid, its size-equivalent congeners **58** and **59**, mannitol, and benzamide can form twisted crystals from the melt as well as from solution and/or vapor phase, indicating that the underlying physical mechanisms at least in a substantial number of cases are material dependent rather than growth medium dependent. The much higher frequency of twisted crystals from the melt stems from the ability to get very fine fibers at a high driving force for crystallization and high homologous temperatures.

While Kuhnert-Brandstätter was aware of twisted forms, she was not looking for them, nor trying to optimize their appearance.[3] The frequency with which she reported twisted crystals is much lower than that reported here and previously.[2] Kuhnert-Brandstätter's aim was the identification of pharmaceutical compounds without the added complications of forms outside of normal crystallographic discourse. As such, she typically cooled slowly from the melt. She did not use additives (growth inhibitors) or drop temperatures precipitously to encourage large undercoolings. A number of compounds we examined with decidedly twisted phases, not difficult to observe, that were also studied by Kuhnert-Brandstätter, include the following: **4**, **13**,[29] **73**,[34] **74**,[35] **77**,[21,23] and **96**.[47] She did not report twisting.

CONCLUSIONS

In 1929, Bernauer showed that 27% of all molecular crystals can grow from the melt as mesoscopic helices, nonclassical morphologies incompatible with ideal 3D periodic crystals. After careful analysis of 101 compounds (155 polymorphs) selected indifferently on the basis of what was available or shared with us, we have concluded that this percentage is even higher, around 31%. Our experience herein and that of Bernauer is quite different from that of Kuhnert-Branstätter. Why? In the words of Thoreau, "Many an object is not seen, though it falls within the range of our visual ray, because it does not come within the range of our intellectual ray, i.e., we are not looking for it. So, in the largest sense, we find only the world we look for."[48] Once attuned to the possibility of seeing rhythmic patterns in the petrographic microscope, you will see them everywhere. Why you see them is another matter still, although it is continually coming into focus.[47,49]

ASSOCIATED CONTENT

Accession Codes

CCDC 2002874−2002876 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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