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On the Validity of Wallach's Rule: On the Density and Stability of Racemic Crystals Compared with Their Chiral Counterparts

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Abstract: Wallach's 1895 rule (Wallach, O. *Liebigs Ann. Chem.* **1895**, *286*, 90–143) states that racemic crystals tend to be denser than their chiral counterparts. Although this rule has not gone unchallenged, it has nevertheless given rise to the fairly widespread notion that a collection of right- and left-handed objects can be packed more tightly than a collection of homochiral ones. To test the rule we have identified, with the help of the Cambridge Structural Database, 129 pairs of corresponding racemic and chiral crystals. The quantity $\Delta(\%) = 100[(V/Z)_A - (V/Z)_R]/\{0.5[(V/Z)_A + (V/Z)_R]\}$, where A and R refer to the chiral and racemic crystals and (V/Z) is the molecular volume, is +0.56(22)%, an inconclusive result. When the sample is divided into two subpopulations, one containing achiral molecules and rapidly interconverting enantiomers (group I, 64 pairs) and the other containing resolvable enantiomers (group II, 65 pairs), Δ(%) is reduced to +0.20(34)% for group I and increased to +0.92(29)% for group II. This difference in behavior can be attributed to statistical bias in the group II population, since this can contain pairs in which the racemic crystal is markedly more stable than the chiral one (obtainable by crystallization of resolved material) but no pairs in which the racemic crystal is markedly less stable. A similar bias contributes to the apparent greater thermodynamic stability of the racemic crystals in the thermodynamic data collected for 36 pairs of racemic and chiral crystals by Jacques, Collet, and Wilen (Jacques, J.; Collet, A.; Wilen, S. H. *Enantiomers, Racemates and Resolutions*; Wiley: New York, 1981; pp 93–100). The thermodynamic argument given by these authors for the greater stability of racemic crystals is shown to be fallacious. Nevertheless, apart from the bias inherent in all comparisons of racemic/chiral pairs of resolvable enantiomers, there may also be a genuine tendency for racemic crystals to indeed be more stable (and denser) than their chiral counterparts. This need not be a consequence of any special kinds of interactions between opposite enantiomers but could result merely from the additional possibilities for favorable packing arrangements in racemic space groups compared with chiral ones. The possible role of kinetic factors in crystal nucleation and growth from racemic solutions is also discussed.

Is the observation that crystals of D,L-alanine are denser than crystals of L-alanine a happenstance or does it exemplify a general rule? Do the molecules in a racemic crystal tend to be more tightly packed than in a corresponding crystal composed of homochiral molecules? This question has been a subject of desultory speculation since at least 1895, when Wallach formulated and answered it—on the basis of eight pairs of densities—in the affirmative.[1] Although Wallach's rule has certainly not gone unquestioned,[2] it has nevertheless given rise to the widespread notion that heterochiral molecules pack together more efficiently than do homochiral molecules.[3] This surmise raises two questions. Are racemic crystals[4] generally more stable than their chiral counterparts, as stated, for example, by Jacques, Collet, and Wilen?[5] And is this greater stability reflected in a greater density of the racemic crystals? In this paper we begin by examining the second question on the basis of data culled from the Cambridge Structural Database.[6] We find a small but significant increase in average density for racemic crystals composed of enantiomers that can be resolved chemically (two-component systems in phase-rule parlance), but no significant difference in density for those pairs where the chiral crystal is composed of achiral molecules or ions, or where the enantiomers interconvert rapidly (one-component systems). As we shall argue, this result can be attributed to the existence of statistical bias in the first collection of racemic/chiral pairs but not in the second. We then reexamine the thermochemical data of Jacques, Collet, and Wilen[7] and show that their sample of racemic/chiral pairs is affected by a similar bias; their thermodynamic arguments about the relative stabilities of enantiomers and racemic crystals are shown to be erroneous. Finally, we consider other arguments for the generally greater stability of racemic crystals over their chiral counterparts.

Densities

Wallach based his 1895 rule on the densities of eight pairs of compounds, and one of those pairs was an exception. Jacques, Collet, and Wilen[8] summarize the data available in 1898, when the densities for 12 pairs of optically active and racemic compounds

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(1) Wallach, O. *Liebigs Ann. Chem.* **1895**, *286*, 90–143. "Hieraus ist ersichtlich, dass nur bei dem zuletzt gennanten Körper keine Aenderung des Volumes zu bemerken ist. In allen übrigen Fällen findet die Vereinigung der optisch isomeren Körper zu einer krystallisierten racemischen Verbindung unter Kontraction statt."

(2) See especially: Jacques, J.; Collet, A.; Wilen, S. H. *Enantiomers, Racemates and Resolutions*; Wiley: New York, 1981; pp 23–31.

(3) Statements of Wallach's rule appear in several classic textbooks. Consider the following excerpt from p 574 of *Basic Principles of Organic Chemistry* by J. D. Roberts and M. C. Caserio (Benjamin: New York, 1964). "The racemic tartaric acid has a noticeably higher melting point and lower solubility than the separate component enantiomers, which means that the racemic acid has the more stable crystal structure. In other words, the 1:1 mixture of enantiomers gives a stronger packing than either enantiomer separately. This is analogous to the observation that right- and left-handed objects usually can be packed in a box better than all right- or all left-handed objects." In the 1977 edition of the same text, however, the extrapolation from the specific example of tartaric acid to a general rule is absent. Consider also several statements from pp 44–45 of *Stereochemistry of Carbon Compounds* by E. L. Eliel (McGraw-Hill: New York, 1962). "It may happen that in a crystal each enantiomer has a greater affinity for molecules of the same kind than for molecules of the other enantiomer. ... A rather more common situation than that described above is that the molecules of one enantiomer have a greater affinity for those of the opposite enantiomer than for their own kind. ... Racemic compounds have lower enthalpies than pure enantiomers."

(4) In this paper we use the term "racemic crystal" to describe any crystal whose space group includes improper symmetry elements (symmetry elements of the second kind), i.e., centers of inversion, mirror planes, glide planes, and alternating (rotation-inversion) axes. Thus we apply the term not only to most racemates—or "racemic compounds" as they have been dubbed (ref 2, p 4)—but also to crystals built from achiral molecules. [The qualifier "most" is needed because a racemate or racemic compound is usually defined as a crystalline addition compound containing both enantiomers in equal amounts. Since a racemate or racemic compound is occasionally found to crystallize in a chiral space group (see ref 14), it is not necessarily a racemic crystal in our parlance. Indeed, such a racemate can occur in chiral and achiral polymorphic forms, as it does in the case of methylsuccinic acid (DLMSUC). According to the definition used here, only one of the two polymorphs of methylsuccinic acid would be a racemic crystal.] In the latter context we would imply the existence of another polymorphic form with a chiral space group. Racemic mixtures of enantiomeric chiral crystals are here referred to as "conglomerates".

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were known. Four of the 12 pairs were exceptions to Wallach's rule. The average $|\Delta(\%)|$[9] for these 12 pairs is +1.9(4)%,[10] but the average $\Delta(\%)$ is only 0.9(7)%. Since crystal densities cannot be measured by standard methods (e.g., flotation) to better than ca. 1% without heroic efforts, the error in the *difference* of two densities is likely to be ca. 1.4%, i.e., nearly as large as a typical value of $|\Delta(\%)|$.

Crystallographic measurements of unit cell dimensions yield much more precise measurements of molecular volumes than do other methods; errors are typically less than 0.15%. Jacques, Collet, and Wilen[8] list densities calculated from crystallographic data for 14 pairs of structures. The average $\Delta(\%)$ is −1.2(9)%, with nine of the 14 racemic crystals being *less dense* than their chiral counterparts. In another recent compilation, Mason[11] lists 14 pairs that partially overlap with the aforementioned list, the average $\Delta(\%)$ being +2.2(13)% with five of the racemates less dense than their chiral counterparts. Mason concludes that "the rule has many exceptions and expresses only a general trend".

The availability of the Cambridge Structural Database[6] (hereafter, the CSD) now makes it possible to examine a much larger number of pairs of racemic and corresponding chiral crystals. Identification in the CSD of such pairs of compounds is problematic, however, because the members of the pair are sometimes linked to the same reference code and sometimes not; the structures of L- and D,L-alanine, for example, have different REFCODEs, as do the members of all other pairs of amino acid structures.

Our searches were made on the January 1989 version of the CSD. Entries were eliminated if coordinates were lacking, if the crystallographic R factor was >0.15, or if error or disorder flags had been set. Two subfiles were created. One contained the entries for the 65 space groups that contain only proper symmetry operations, i.e., rotations. About 20% of the entries in the CSD fall into these 65 space groups. The second subfile contained the entries in the remaining, achiral space groups. The two subfiles were then sorted according to chemical composition and compared. Sets of structures having the same chemical composition were identified as potential matches if both subfiles were represented. Information (REFCODE, formula, chemical name, space group, Z, unit cell dimensions, and temperature) for each of the entries in the set was then printed.

The possible matches were investigated individually; the original literature was consulted in all cases. Pairs of structures having the same REFCODEs were easy to identify; pairs of corresponding structures having different REFCODEs were not. The compound names in the file are those given by the authors in the original publications rather than those derived from the nomenclature rules set by the IUPAC or Chemical Abstracts. Some of the given names are misleading and others are incorrect. In several instances the members of an apparent pair turned out to be diastereomers, even though they appeared in the CSD under the same REFCODE.

It was important to resolve space group ambiguities. Space group pairs differing only by the presence or absence of an inversion center (e.g. $P1$, $P\bar{1}$; $C2$, $C2/m$; and the like) were given special scrutiny. For some such pairs the two reported structures were essentially the same although described in terms of different space groups and/or slightly different cell dimensions. In other cases the two structures were clearly distinct although sometimes closely related.

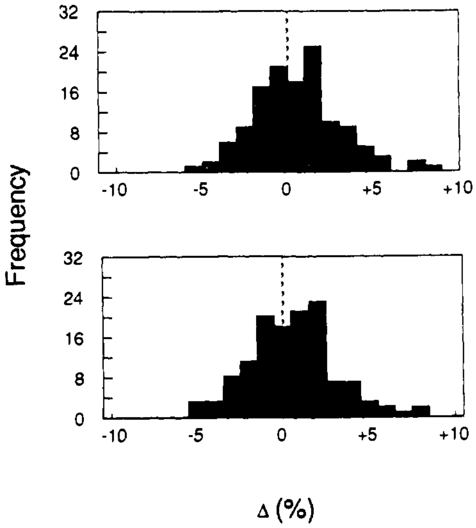

Figure 1. Distributions of sample points for bin sizes of $\Delta(\%) = 1$ and two choices of bin boundaries for all 129 pairs of structures.

Finally, the temperatures at which the structures were determined were compared. If the temperatures differed by more than 5°, the pair was not included in the final tabulation. Structures of crystals grown as stable phases at higher temperatures and then studied as metastable phases at lower temperatures were, however, retained.

The quantity $\Delta(\%)$[9] was calculated for each pair of structures. For structures determined more than once to a similar level of precision, an average V/Z value was used. If the ratio of the estimated standard deviations (hereafter, esds) of the cell dimensions of two determinations was greater than five, the less precise V/Z value was discarded. For $|\Delta(\%)| > 5\%$, the low-density structure was checked for the possible presence of solvent molecules that might have been overlooked.

The final list contains 129 structure pairs. Because of polymorphy, 10 substances appear in two pairs and one appears in three pairs. The procedure described above yielded 124 of these pairs. Two more had a member flagged in the CSD as being disordered but were included because the disorders were minor and carefully described; i.e., there was no doubt that the space groups were correct. Three structures not yet entered in the CSD were also included.[12] Of the 126 pairs archived in the CSD, 66 have the same REFCODE and 60 have different REFCODEs.

Our list of structure pairs is probably incomplete; some REFCODE matches may have been overlooked.[13] More im-

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(5) Reference 2, p 28. "In other words, the free energy for the 'reaction'

D-crystal + L-crystal → racemic compound

is almost always negative".

(6) Allen, F. H.; Kennard, O.; Taylor, R. *Acc. Chem. Res.* **1983**, *16*, 146–153.

(7) Reference 2, pp 94–95.

(8) Reference 2, p 29.

(9) $\Delta(\%) = 100(\rho_R - \rho_A)/[0.5(\rho_R + \rho_A)]$ or, what is equivalent, $\Delta(\%) = 100[(V/Z)_A - (V/Z)_R]/\{0.5[(V/Z)_A + (V/Z)_R]\}$, where R refers to the racemate and A to the enantiomer (i.e., the "antipode"), and where ρ is the density, V is the volume, and Z is the number of formula units in the unit cell. The value of $\Delta(\%)$ should be significantly positive if Wallach's rule holds.

(10) The numbers in parentheses are the estimated standard deviations of the means.

(11) Mason, S. F. *Molecular Optical Activity and the Chiral Discriminations*; Cambridge University Press: Cambridge, 1982; p 171.

(12) For the pair designated Thioph6, the chiral structure has been described briefly (Kwiatkowski, S.; Syed, A.; Brock, C. P.; Watt, D. S. *Synthesis* **1989**, 818–820); a full description of both structures is in press (*Acta Crystallogr., Sect. B*). Reports of the structures of the $P3_121$ and $C2/c$ forms of ZZZKPE are likewise in preparation (Brock, C. P.; Simpson, G. H.; Fu, Y., 1991).

(13) Too late for inclusion in this study was the structure analysis of the elusive anhydrous D,L-glutamic acid (Schweizer, W. B. Unpublished results), which has $V/Z = 152.4$ Å^3 compared with 159.5 Å^3 for the α form (Lehmann, M. S.; Nunes, A. C. *Acta Crystallogr.* **1980**, *B36*, 1621–1625) and 155.0 Å^3 for the β form of L-glutamic acid (Lehmann, M. S.; Koetzle, T. F.; Hamilton, W. C. *Cryst. Mol. Struct.* **1972**, *2*, 225–233). The $\Delta(\%)$ values are then +0.046 (α form) and +0.017 (β form). Depending on the conditions, crystallization of racemic solutions of glutamic acid can yield crystals of the enantiomers, of the racemate as a monohydrate, of the anhydrous racemate, or, often, as mixtures of several forms (Dunn, M. S.; Stoddard, M. P. *J. Biol. Chem.* **1937**, *121*, 521–529). This dependence on conditions of crystallization suggests that kinetic, as well as thermodynamic, factors are operative. The thermodynamic transition point between the monohydrate and the anhydrous crystal forms of the racemate are 20.3 °C (Ogawa, T. *J. Chem. Soc. Jpn., Ind. Chem. Sect.* **1949**, *52*, 71–72; *Chem. Abstr.* **1951**, *45*, 1860g).

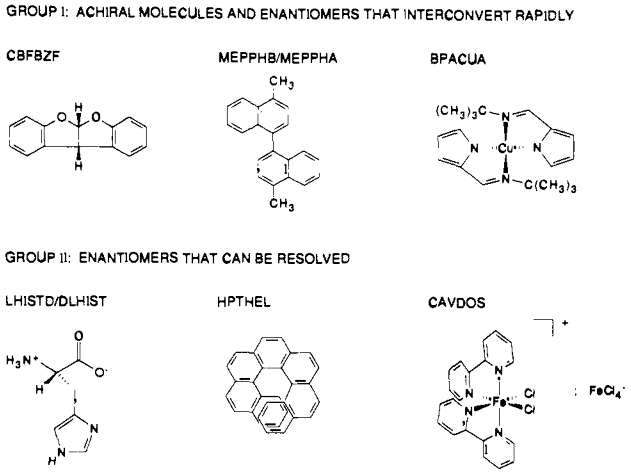

Figure 2. Examples of molecules or ions that form group I and group II pairs.

portantly, our search procedure would not have found pairs in which the racemic compound happens to crystallize in a chiral space group.[14]

A list of the REFCODEs and $\Delta(\%)$ values is given in Table I. Full literature citations, chemical names (as given in the CSD), and line drawings have been deposited.

Results of CSD Search

Two histograms of the distribution of the 129 pairs are shown in Figure 1. The number of pairs is not large enough to yield a smooth distribution; the appearance of the histograms depends on the choices of bin size and boundaries. Both representations, however, show a hint of bimodality. For these reasons, significance estimates based on the normal distribution have to be taken with reserve.

The average value $\langle\Delta(\%)\rangle$ for the 129 pairs is +0.56(22)%; the median value is +0.64%. The esd of an individual value of $\Delta(\%)$ is less than 0.25%, and the esd of the distribution itself is 2.5%. The esd of the average has been reduced by about a factor of 4 compared with previous results,[8] largely because of the ca. 10-fold increase in the number of pairs.

The average value of $\Delta(\%)$, which should be positive if Wallach's rule is true, is only 2.5 times its esd. Regardless of numerical significance tests, this deviation from zero is hardly large enough to be convincing, but it is too large to ignore. It is about half the value calculated from the data available at the turn of the century.

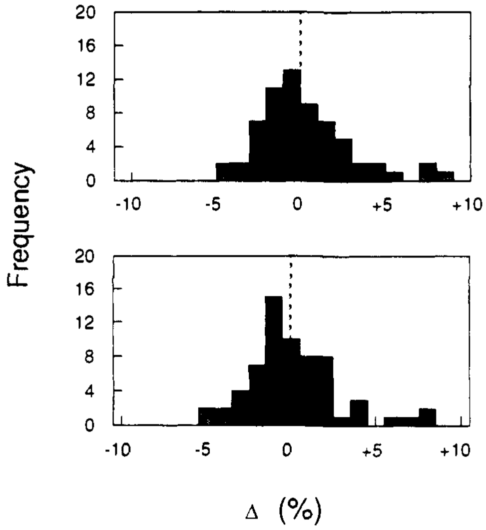

Figure 3. Distributions of sample points for bin sizes of $\Delta(\%) = 1$ and two choices of bin boundaries for the 64 pairs of structures of achiral molecules and ions and of enantiomers that interconvert rapidly.

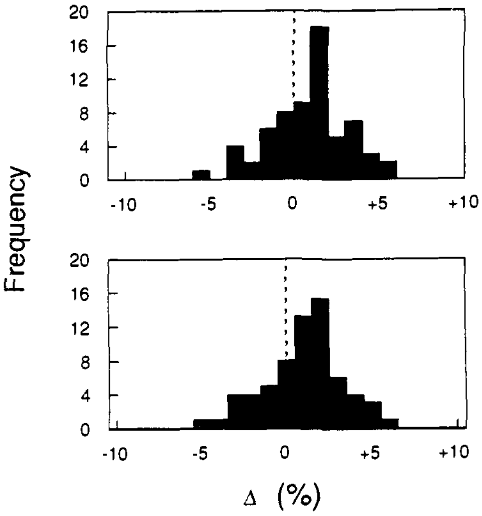

Figure 4. Distributions of sample points for bin sizes of $\Delta(\%) = 1$ and two choices of bin boundaries for the 65 pairs of structures of resolvable enantiomers.

The hint of bimodality in the distribution prompted us to ask whether the sample might be usefully divided into two populations. One way of dividing the sample is to distinguish between pairs that should be classed as polymorphs and those that should not.[15] The first class (see Figure 2) contains molecules[16] that are essentially achiral[17] [e.g., dibenz[*a,h*]anthracene (DBNTHR)], as well as molecules that interconvert between enantiomeric conformations rapidly in solution or in the melt at the temperature of crystallization [e.g., glycine (GLYCIN), 4-hydroxybiphenyl (BOPSAA), and 1,1'-binaphthyl (BNPHTA/BINAPH)]. For compounds in this first class, the solid–liquid phase diagram is that of a one-component system, and the different phases are polymorphs.[18] The second class (see Figure 2) contains enantiomeric molecules for which the rate of interconversion is slow relative to the rate of crystallization, e.g., molecules that contain "asymmetric carbon atoms" or are locked in a chiral conformation [such as heptahelicene (HPTHEL)]. For pairs in this class, the solid–liquid phase diagram is that of a two-component system; the two enantiomers as well as the racemic crystal must be con-

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[14] Although crystallization in a chiral space group of a racemic compound formed from resolvable enantiomers is thought to be rare (ref 2, p 17), we came across the following examples (names as given in the CSD): BIJVEV (*rac*-3,3'-biindan-1-one, $P2_12_12_1$)); CEHBUM (*rac*-3-methoxy-18-methylestra-1,3,5(10)-trien-17-one, $P2_12_12_1$); CUMFEV ((+,−)-*rel*-(1*R*,3*S*,3'*S*)-3,3'-di-*tert*-butyl-1,1'-spirobiindan, $P2_12_12_1$); DCPENT (D,L-2,4-dicyanopentane, $P4_1$); DLMSUC (D,L-methylsuccinic acid, $P2_1$); FAXMIA (*rac-trans*-2-hydroxy-2-methyl-4-(*p*-methoxyphenyl)-3,4-dihydro-2*H*,5*H*-pyrano-[3,2-*c*][1]benzopyran-5-one, $P2_12_12_1$); SSESOX (D,L-1,4-diphenyl-1,4-dithiabutane 1,4-dioxide, $P2_12_12_1$).

[15] McCrone, W. C. In *Physics and Chemistry of the Organic Solid State*; Fox, D., Labes, M. M., Weissberger, A., Eds.; Interscience: New York, 1965; Vol. II, pp 725–767. According to McCrone, polymorphs are different solids that melt to give the same liquid.

[16] The term "molecule" as used here should also be understood to include ions [e.g., dichlorobis(2,2'-bipyridine)iron(III) (CAVDOS)], sets of ions [e.g., piperidinium 1-piperidinecarbodithiolate (PIPPTC)] and sets of molecules [e.g., D,L-methylsuccinic acid (DLMSUC)], and repeating units in network solids (e.g., the SiO_2 unit in quartz).

[17] In chiral structures (e.g., quartz, $NaClO_3$) built from essentially achiral units, the optical activity is a consequence of the packing arrangement only. Individual crystals containing such building units may be optically active, but once the crystal is dissolved, melted, or sublimed, the optical activity is lost. The sense of the optical rotation of any one crystal depends on accidents of growth. [It has recently been reported (Kondepudi, D. K.; Kaufman, R. J.; Singh, N. *Science* **1990**, 975–976) that crystallization of stirred $NaClO_3$ (aq) solutions produces crops of nearly homochiral crystals.]

[18] In phase-rule terminology, two species in chemical equilibrium are considered to form a single component. For example, see: Berry, R. S.; Rice, S. A.; Ross, J. *Physical Chemistry*; Wiley: New York, 1980; p 869.

Table I. List of Pairs of Chiral and Racemic Structures

	achiral structure			racemic structure			
REFCODE(s)	space grp	V	Z	space grp	V	Z	Δ (%)
	Group I: Achiral Molecules and Ions; Enantiomers That Racemize Rapidly						
ATCPEN	$P2_1$	329	2	$P2_1/c$	661	4	−0.45
BACVOQ	$P2_12_12_1$	4709	4	$P2_1/n$	4799	4	−1.89
BANGOM	$P2_1$	571	2	$P2_1/c$	1144	4	−0.17
BARWUM	$P2_12_12_1$	1696	4	$P2_1/c$	3274	8	3.54
BAZKUI	$P2_12_12_1$	2489	4	$P2_1/c$	2507	4	−0.72
BIGTIU	$P2_12_12_1$	1806	4	$P2_1/c$	1809	4	−0.17
BNPHTA/BINAPH	$P4_12_12$	1427	4	$C2/c$	661	2	7.62
BOPSAA	$P2_12_12_1$	1743	8	$P2_1/a$	877	4	−0.63
BPACUA	$P4_12_12$	1847	4	$P\bar{1}$	950	2	−2.83
CBPACU/BENJAF	$P22_12_1$	1127	2	$P2_1/n$	2297	4	−1.89
CBFBZF	$P2_12_12_1$	1042	4	Cc	516	2	0.96
CEBKEZ	$P2_12_12_1$	1284	4	$Pbca$	2536	8	1.25
CEMDON	$P2_12_12_1$	1678	4	$P\bar{1}$	844	2	−0.59
CIFLEI/CIFLIM	$I4_1$	696	2	$P2_1/c$	2808	8	−0.86
CIVTUW	$P2_12_12_1$	1292	4	$P2_1/n$	1341	4	−3.72
CLBZAM	$P2_12_12_1$	753	4	$P2_1/n$	762	4	−1.19
CLPHTE	$P2_12_12_1$	1343	4	$P2_1/n$	1372	4	−2.14
COSALP	$P2_12_12_1$	1575	4	$P2_1/n$	1565	4	0.64
COYMOS	$P2_12_12_1$	995	4	$P2_1/n$	990	4	0.50
DAZABZ	$P2_1$	524	2	$P2_1/c$	1048	4	0.00
DBNTHR	$P2_1$	712	2	$Pcab$	1444	4	−1.39
DEFDUN	$P2_12_12_1$	805	4	$P2_1/c$	809	4	−0.50
DETBAA	$P2_1$	1886	8	$R\bar{3}$	1429	6	−1.02
DETBAA	$P2_1$	1886	8	$C2/c$	495	2	−4.86
DIKYEB	$P2_12_12_1$	1516	4	$Pbcm$	1525	4	−0.59
DLMSUC	$P2_1$	623	4	$P\bar{1}$	618	4	0.81
DLMSUC	$P2_1$	623	4	$C2/c$	632	4	−1.43
DMFUSC	$P2_12_12_1$	1588	4	$Pna2_1$	1588	4	0.00
DMFUSC	$P2_12_12_1$	1588	4	$P2_1/c$	1596	4	−0.50
DMNPYO	$P4_12_12$	745	4	$Pbca$	1514	8	−1.60
DOCWEX	$P2_12_12_1$	4340	4	$C2/c$	4285	4	1.28
DPHETH	$P2_12_12_1$	1690	4	$Pbcn$	5103	12	−0.65
DPIPDS	$P2_12_12_1$	1280	4	$P2_1/c$	1278	4	0.16
FAJTIT	$P2_1$	1378	4	$P2_1/n$	1345	4	2.42
FAKHUU	$P2_1$	944	2	$P2_1/c$	3786	8	−0.26
FAKHUU	$P2_1$	944	2	$P2_1/n$	1857	4	1.66
FEFSAK	$P2_12_12_1$	957	4	$P2_1/c$	919	4	4.05
FESKAP	$P2_12_12_1$	1850	4	$P2_1/c$	1888	4	−2.03
FIKFIO	$P2_12_12_1$	2608	8	$P2_1/c$	1231	4	5.76
FOBBIH	$P4_32_12$	2035	4	$P2_1/c$	2032	4	0.15
FOJMOG	$P2_1$	1245	2	$Pccn$	2558	4	−2.69
GLYCIN	$P3_1$	236	3	$P2_1/n$	310	4	1.28
GLYCIN	$P2_1$	157	2	$P2_1/n$	310	4	1.28
HETPAL	$P2_12_12_1$	1181	4	$P2_1/a$	1193	4	−1.01
HGEXAN	$P2_1$	613	2	$P2_1/c$	1197	4	2.39
HMCTST	$P4_1$	1623	4	$P2_1/c$	1659	4	−2.19
MABZNA	$P2_12_12_1$	5363	16	$P\bar{1}$	1364	4	−1.72
MABZNA	$P2_12_12_1$	5363	16	$P2_1/c$	1348	4	−0.54
MABZNA	$P2_12_12_1$	5363	16	$P\bar{1}$	1375	4	−2.52
MBPHOL	$P2_12_12_1$	1426	4	$C2/c$	1394	4	2.27
MEPPHB/MEPPHA	$P4_12_12$	1634	4	$C2/c$	752	2	8.29
MGXPCO	$P2_12_12_1$	2609	4	$P2_1/c$	2641	4	−1.22
MMANCN	$P1$	486	2	$C2/c$	986	4	−1.43
MOFORM	$P2_12_12_1$	874	4	$P2_1/c$	1347	6	−2.71
MOFORM	$P2_12_12_1$	874	4	$P2_1/a$	459	2	−4.91
MOPBZA	$P2_1$	784	2	$P2_1/c$	1566	4	0.13
NBZANO	$P2_12_12_1$	1364	4	Pc	669	2	1.92
OCHTET	$P6_1$	1676	6	$Fdd2$	535	2	4.33
OCHTET	$P6_1$	1676	6	$P2_1/c$	519	2	7.36
PHGQUO	$P2_12_12_1$	1220	4	$Pnam$	2539	8	−3.98
PHTHCU	$P2_12_12_1$	3821	4	$P\bar{1}$	1850	2	3.22
PIPPTC	$P2_1$	2739	8	$Pbc2_1$	2673	8	2.44
PTCDEC	$P2_12_12_1$	983	4	$P2_1/c$	960	4	2.37
TBTMER	$P2_12_12_1$	1590	4	$P2_1/c$	1561	4	1.84
	Group II: Enantiomers That Can Be Resolved						
ABINOS/ABINOR	$P2_12_12_1$	613	4	$P2_1/c$	609	4	0.65
ACACCT/ACACCR	$P2_1$	1806	4	$P2_1/c$	1714	4	5.23
ALFUCO/ADLFUC	$P2_12_12_1$	734	4	$P2_1/c$	717	4	2.34
APHAMA/APALAM	$P2_1$	599	2	$P2_1/n$	1190	4	0.67
BAGMOL/BAGMUR	$P2_1$	1941	4	$P2_1/n$	1919	4	1.14
BAKVIS/BAKVOY	$P2_1$	1905	4	$P2_1/n$	1910	4	−0.26
BALSAI/CADINC	$P2_12_12_1$	1586	4	$P2_1/n$	1592	4	−0.38
BBHDPQ/BRHPQU	$P2_12_12_1$	1846	4	$P2_1/c$	1894	4	−2.57
BILTIZ/BILTEV	$P2_12_12_1$	1796	4	$P2_1/c$	1781	4	0.84

Table I (Continued)

REFCODE(s)	achiral structure			racemic structure			Δ (%)
	space grp	V	Z	space grp	V	Z	
BUFFIR/COBXAS	$C2$	811	2	$P2_1/c$	1650	4	−1.71
BUHCIQ/BABCUC	$P2_1$	698	2	$Pbca$	2814	8	−0.78
BXGLPR/BXCGPL	$P4_32_12$	3119	8	$Pbc2_1$	3067	8	1.68
BZMPIZ/CDBMPI	$P2_1$	884	2	$P2_1/a$	1724	4	2.52
CAPMSU/CXPMSO	$P2_12_12_1$	844	4	$P2_1/c$	833	4	1.31
CAVDOS	$P2_12_12_1$	2580	4	$Pccn$	2529	4	2.00
CENCOC/CLECOC	$P2_1$	1150	4	$P2_1/c$	1151	4	−0.09
CHDECL/CBXODL	$P2_12_12_1$	1312	4	$P2_1/c$	1264	4	3.73
COBDEC	$P2_1$	1985	4	$P2_1/a$	1966	4	0.96
CULGEV/CULGIZ	$P2_12_12_1$	958	4	Cc	461	2	3.83
DECMIH/DECMED	$P2_12_12_1$	1767	4	$P2_1/c$	1795	4	−1.57
DESWED/DESWAZ	$P2_12_12_1$	1752	4	$Pbcn$	1696	4	3.25
DFBPAC/FBPACR	$P2_1$	432	2	$Pna2_1$	877	4	−1.49
DKSBTR/SBTARK	$C222_1$	1697	4	$Pca2_1$	1749	4	−3.02
DPESCU/RPESCU	$P2_12_12_1$	2611	4	$P2_1/n$	2530	4	3.15
DUBFIP/CIBZIW	$P2_12_12_1$	2097	4	$P2_1/n$	2170	4	−3.42
EBPVPO/BZPPBA	$P2_1$	1577	4	$P2_1/c$	1549	4	1.79
FAXMEW/FAXMAS	$P2_12_12_1$	1629	4	$P2_1/n$	1600	4	1.80
FEFUMR/FECAFA	$P2_12_12$	1566	6	$Pccn$	1022	4	2.13
FEGHAA/DLMAND	$P2_1$	749	4	$Pbca$	1557	8	−3.86
GLYALB/GLYDLA	$P2_12_12_1$	696	4	$P2_1/c$	674	4	3.21
GPTANI	$P2_12_12_1$	3796	8	$Pnna$	1867	4	1.65
HPHENA/ZZZUJZ	$P3_121$	2252	6	$P4_2bc$	2978	8	0.82
HPTHEL	$P2_1$	1949	4	$P2_1/c$	1935	4	0.75
ICRFRB/ICRFRA	$P2_1$	657	2	$P\bar{1}$	647	2	1.53
JAMINE	$P2_12_12_1$	1873	4	$P\bar{1}$	923	2	1.45
LALNIN/DLALNI	$P2_12_12_1$	430	4	$Pna2_1$	425	4	1.17
LASPRT/DLASPA	$P2_1$	269	2	$C2/c$	538	4	0.00
LCARVX/CARVOX	$P2_1$	994	4	$P2_1/c$	978	4	1.62
LEUCIN/DLLEUC	$P2_1$	748	4	$P\bar{1}$	366	2	2.16
LHISTD/DLHIST	$P2_1$	359	2	$P2_1/c$	678	4	5.73
LHISTD/DLHIST	$P2_12_12_1$	713	4	$P2_1/c$	678	4	4.96
LMETON/DLMETA	$P2_1$	748	4	$P2_1/a$	749	4	−0.13
LMETON/DLMETA	$P2_1$	748	4	$I2/a$	741	4	0.94
LNLEUC/DLNLUA	$C2$	384	2	$P2_1/a$	748	4	2.64
LPYGLU/PYRGLU	$P2_12_12_1$	1784	12	$P2_1/a$	575	4	3.36
LSERIN/DLSERN	$P2_12_12_1$	451	4	$P2_1/a$	455	4	−0.88
LTYROS/DLTYRS	$P2_12_12_1$	851	4	$Pna2_1$	838	4	1.54
LVALIN/VALIDL	$P2_1$	617	4	$P2_1/c$	588	4	4.81
MBABIQ	$P2_12_12_1$	1563	4	$Pna2_1$	1570	4	−0.45
MPOSAC/MXPHAC	$P4_12_12$	2092	8	$P2_1/c$	1029	4	1.64
NMLALA/RMNALA	$P2_12_12_1$	943	4	$P2_1/n$	903	4	4.33
OCTPIN/RCLOTH	$P2_12_12_1$	1743	4	$Pna2_1$	1800	4	−3.22
OPADNA/OPADNB	$P2_1$	470	2	$P2_1/n$	962	4	−2.31
OPTCET/OPDDTE	$P2_12_12_1$	1511	4	$P\bar{1}$	1488	4	1.53
PNPSXI/NPHTNS	$P2_12_12_1$	2050	4	$P2_1/c$	2071	4	−1.02
PPRHCM/PRCOUM	$P2_1$	1494	4	$P2_1/n$	1468	4	1.76
PROPDD/PROPOL	$P2_1$	831	2	$P2_1/c$	1601	4	3.74
SULPIA/PYMSBZ	$P2_12_12_1$	3355	8	$P\bar{1}$	840	2	−0.15
Thioph6	$P2_12_12_1$	1326	4	$P2_1/c$	1309	4	1.29
TMPYRO/RTMPRO	$P2_1$	513	2	$P2_1/c$	2162	8	−5.22
TNAPHB/TNAPHC	$P2_1$	588	2	$Pca2_1$	1194	4	−1.52
VALEHC/DLVALC	$P2_1$	399	2	$P2_1/c$	788	4	1.26
ZEGGEX/ZEGGIB	$P1$	998	2	$P\bar{1}$	994	2	0.40
ZZZKPE	$P3_121$	988	6	$Pbca$	1293	8	1.86
ZZZKPE	$P3_121$	988	6	$C2/c$	1335	8	−1.33

sidered as distinct compounds rather than as polymorphs.[19]

The 129 pairs were thus separated into two groups (see Table I) according to the rates of racemization: group I, achiral molecules and ions and enantiomers that interconvert rapidly; group II, enantiomers that can be resolved. Most questions concerning the assignments could be resolved by consulting the original literature.[20,21]

The 64 pairs in group I have $\langle \Delta(\%) \rangle = +0.20(34)\%$, i.e., not significantly different from zero. Two histograms of the distribution (Figure 3) show that there are several apparent outliers having $\Delta(\%) > 5\%$; the median of the distribution, $\Delta(\%) =$

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(19) Strictly speaking, solvated crystals of achiral molecules contain two components, and solvated crystals of resolvable enantiomers contain three. This complication does not, however, affect the phase diagrams in any way that is important to the argument presented below.

(20) Only two assignments (BPACUA, a pseudotetrahedral Cu(II) complex, and CBPACU/BENJAF, a dinuclear complex containing two five-coordinate Cu(II) ions) presented problems. Both were assigned to group I because Cu(II) complexes usually cannot be resolved (see: Hathaway, B. J. In *Comprehensive Coordination Chemistry*; Wilkinson, G., Gillard, R. D., McCleverty, J. A., Eds.; Pergamon: Oxford, 1987; Vol. 5, pp 596–619).

(21) Although DACWUZ [(η^6-mesitylene)(2,3,5-η^4-3a,4,6,7,7a-pentahydro-4,7-methano-1*H*-inden-5-yl)osmium(II) hexafluorophosphate; Bennett, M. A.; McMahon, I. J.; Pelling, S.; Robertson, G. B.; Wickramasinghe, W. A. *Organometallics* **1985**, *4*, 754–761] is reported to occur in chiral and racemic space groups (space groups $P2_1$ and $P2_1/a$), we decided to omit it from our tabulations. Both crystal structures have been determined, but, as the authors state, the structure of the chiral form is defined only poorly by the available data; the esd's of some of the atomic coordinates are greater than 0.05 Å. The reported positions of most of the atoms correspond closely to the centrosymmetric space group $P2_1/m$ so that there is a possibility that both enantiomers are present, perhaps in different regions of the crystal. Moreover, we do not know whether the enantiomers are isolable (although the molecule does appear to be rigid on the NMR time scale), so it is not clear whether the pair should be assigned to group I or group II.

−0.36%, is actually negative.[22]

The value of $\langle\Delta(\%)\rangle$ for the 65 pairs of structures in group II is +0.92(29)%, i.e., 3.2σ above zero. If the distribution were normal, the probability that this result is due to chance would be less than 0.002. The histograms of the distribution (see Figure 4) are skewed so that the median value of 1.26% is larger than the average. The value of $\langle\Delta(\%)\rangle$ found in this study for group II is similar to that calculated from the data available in Wallach's time. All of the pairs in Wallach's original list, of course, contain resolvable enantiomers.

The reason for the small but significant difference in the average densities of the two samples cannot possibly be that the molecules in group II are "more chiral" than those in group I. Chirality is a geometric property, and molecules that racemize rapidly are not necessarily "less chiral" than those that racemize slowly. We believe that the difference between the two samples results mainly from a thermodynamic factor that leads to a bias in the selection of pairs in group II but not in group I.

In group I (the achiral molecules and rapidly interconverting enantiomers), the racemic and chiral crystals compete, so to speak, on equal terms. Depending on the relative stabilities of the possible solid phases, crystallization from solution leads sometimes to one and sometimes to more than one crystalline form. If two or more crystal forms are obtained, they must be of roughly equal stability;[23] the enthalpies of polymorphic forms of molecular crystals rarely differ by more than a few hundred cal mol^{-1}. Any crystalline form markedly less stable than its competitors is likely to be unobtainable.

For noninterconverting enantiomers (group II) the situation is quite different. A racemic solution may yield a racemic crystal, a racemic conglomerate of chiral crystals, or a mixture of both, depending on their relative stabilities. In contrast, crystals obtained from an enantiomerically pure solution must be chiral. Thus, even if the racemic crystal is much more stable than its chiral counterpart, the latter can always be obtained in principle by resolution prior to crystallization.[24] On the other hand, if the racemic crystal is much less stable than its chiral counterpart, it disappears from the phase diagram. In this case, the crystalline product obtained from the racemic solution is the eutectic, i.e., the conglomerate containing equal amounts of the enantiomeric chiral crystals. Thus the group II sample is statistically biased. It contains pairs for which the racemic crystal is markedly more stable than the chiral crystal and also pairs for which the stabilities of the racemic and chiral crystals are similar, but there are *no pairs for which the racemic crystal is much less stable than the chiral crystal.* This asymmetry in the phase relationships of a system of noninterconverting enantiomers is illustrated in Figure 5.[25] Thus, in group II, pairs in which the racemic crystal is

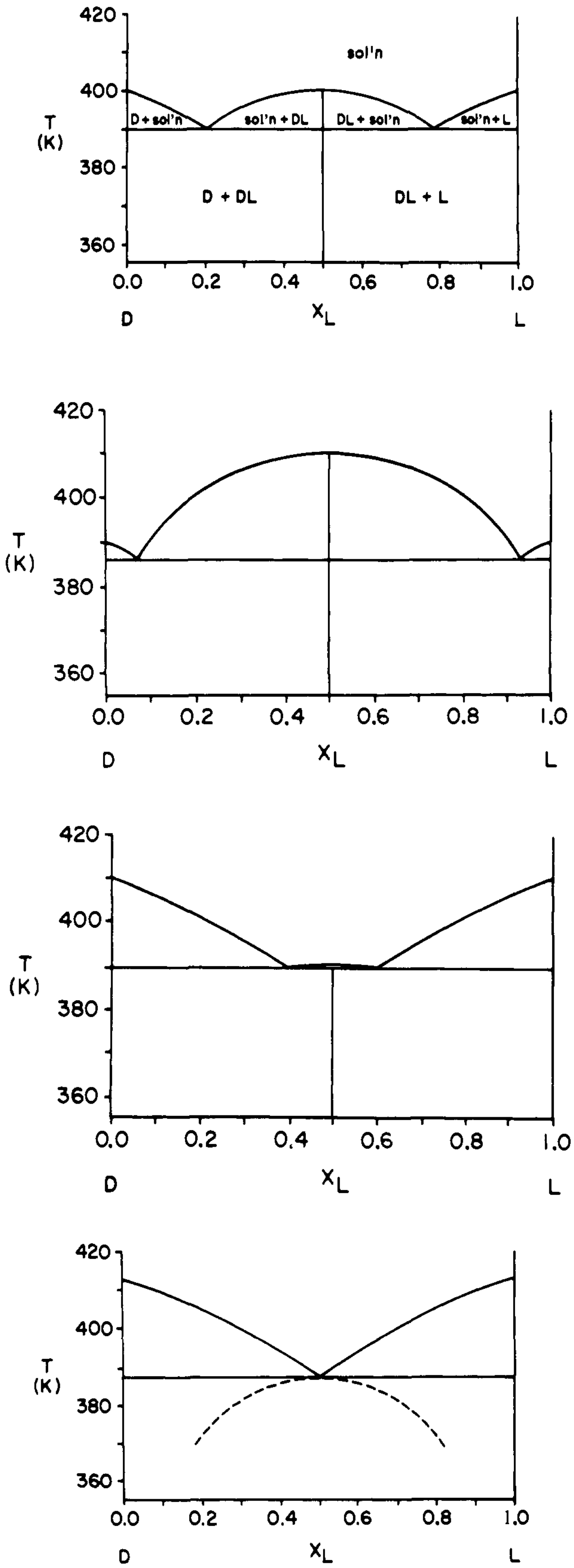

Figure 5. Ideal solid–liquid phase diagrams calculated from the simplified Schröder–van Laar and Prigogine–Defay equations, assuming (a) T_{fus} = 400 K and ΔH_{fus} = 7.0 kcal/mol for both the chiral and racemic phases; (b) T_{fus} = 390 K and ΔH_{fus} = 6.0 kcal/mol for the chiral phase and T_{fus} = 410 K and ΔH_{fus} = 8.0 kcal/mol for the racemic phase; (c) T_{fus} = 410 K and ΔH_{fus} = 8.0 kcal/mol for the chiral phase and T_{fus} = 390 K and ΔH_{fus} = 6.0 kcal/mol for the racemic phase; and (d) T_{fus} = 412.5 K and ΔH_{fus} = 8.8 kcal/mol for the chiral phase and T_{fus} = 387.5 K and ΔH_{fus} = 4.2 kcal/mol for the racemic phase.

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(22) The statistical distributions for both group I and group II samples are so irregular and dependent on accidents of choice (why a particular compound was chosen for detailed crystal structure analysis) that it would be dangerous to draw too dogmatic conclusions from them. In particular, our use of probabilities derived for normal distributions in discussing distributions that deviate very far from normal may be open to criticism, so that our deductions from them need to be viewed with some reservation. Note that in Figures 3 and 4 the distributions for groups I and II are both strongly skewed—and in opposite directions. Thus, although the mean Δ(%) is smaller for group I than for group II, the four largest positive values (8.29%, 7.62%, 7.36%, 5.76%) are all in group I, and the largest negative value (−5.22%) is in group II.

(23) Kinetic effects play a role (see, for example, ref 13), but they are unlikely to favor a phase that is thermodynamically disfavored to a large extent. If crystals of the two members of the pair were grown at very different temperatures but studied at similar temperatures, one is almost certainly metastable with respect to the other, but there are only a few such pairs in the list.

(24) The second sample (group II) contains many pairs for which the chiral crystals were derived from natural products and the racemic crystals from synthetic material.

(25) The melting point curves for the enantiomers were calculated from the simplified Schröder–van Laar equation (see ref 2, pp 46–47),

$$\ln x = (\Delta H_{\text{fus}}^{A}/R)(1/T_{\text{fus}}^{A} - 1/T_{\text{fus}})$$

and the melting point curves for the racemic crystals were calculated from the Prigogine–Defay equation (see ref 2, pp 374–375):

$$\ln 4x(1-x) = (2\Delta H_{\text{fus}}^{R}/R)(1/T_{\text{fus}}^{R} - 1/T_{\text{fus}})$$

energetically favored are more likely to occur than pairs in which the racemic crystal is disfavored.

Insofar as tighter crystal packing can be expected to run parallel to thermodynamic stability,[26] the racemic crystals should then tend to be more dense than their chiral counterparts, as is observed. Thus, although Wallach's rule seems to hold for the group II sample, this may be a result of bias in the sample. At the very least, the basis for the belief that a collection of right- and left-handed objects related by improper symmetry operations can be packed more efficiently than a collection of congruent objects needs to be reexamined.

Comparison of Melting Points and Heats of Fusion for Racemic and Chiral Pairs

At the melting point of a crystal, the solid and liquid phases are in equilibrium: $\Delta G_{fus} = \Delta H_{fus} - T_{fus}\Delta S_{fus} = 0$. If the molecules or ions are achiral or if the enantiomers interconvert rapidly, the chiral and racemic crystals are in equilibrium with the *same* liquid phase at their respective melting points. If, however, interconversion is slow, the chiral and racemic crystals give *different* liquids on melting: the chiral crystal is in equilibrium with enantiomerically pure liquid while the racemic crystal is in equilibrium with a 1:1 mixture of enantiomers. The 1:1 liquid has an additional mixing entropy of $R \ln 2$ with respect to the enantiomerically pure liquid. As the two crystalline solids have zero mixing entropy,[27] it follows that melting of the racemic crystal is associated with an entropy increase of $R \ln 2$, or about 1.4 cal mol^{-1} K^{-1}, as compared with the crystalline enantiomer. Essentially the same entropy increase occurs on melting the racemic conglomerate since the same 1:1 liquid phase is produced and since the mixing entropy of the crystalline conglomerate resulting from the mixing of macroscopic crystals is virtually zero. More precisely, this entropy of mixing is $(N_{xtal}/N_0)R \ln 2$, where N_{xtal} is the number of crystals per mole of material and N_0 is Avogadro's number. Even for a microcrystalline sample N_{xtal}/N_0 is less than 10^{-12}; this entropic term is thus far too small to be detectable.

There appears to be considerable confusion about this point. For example, Jacques, Collet, and Wilen argue that the conglomerate has $R \ln 2$ lower entropy than the racemic crystal because formation of the former from the racemic liquid involves a separation of the enantiomers into two phases, whereas no phase separation is necessary for the formation of the racemic crystal. It is then inferred that "all other things being equal, conglomerates have an initial handicap of 0.4 kcal mol^{-1} (i.e., $RT \ln 2$ with T = 300 K) relative to racemic compounds".[28] Two crucial points have been neglected, namely, that the three solids (crystalline enantiomer, crystalline conglomerate, and racemic crystal) all have essentially the same entropy and that differences in entropy due to mixing are too small to measure except for systems that are disordered at the molecular level (i.e., disordered crystals, solid and liquid solutions, and gases).

Thus, the crystalline conglomerate mixture has not only the same enthalpy as the corresponding homochiral material but also essentially the same entropy—and hence the same free energy. The difference in melting behavior between the homochiral crystals and the conglomerate arises only from the differences between the liquids with which they are in equilibrium at their respective melting points (see Figure 6). Since the racemic crystal and the conglomerate are in equilibrium with the same racemic liquid at their respective melting points, their relative stabilities are governed only by enthalpy differences. Figure 6 shows that even if the chiral crystal is less stable than the corresponding racemic one, it may have a higher melting point. If the racemic and chiral crystals are equally stable, the racemic crystals and the 1:1 conglomerate will melt at about the same temperature.[29] If the racemic crystal is appreciably less stable, it will melt at a lower temperature than the conglomerate, in which case it may be unobtainable and so will disappear from the phase diagram.

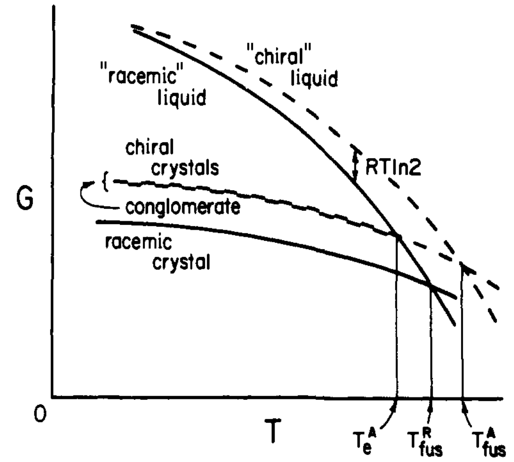

Figure 6. Schematic free energy vs temperature curves for chiral and racemic crystals of resolvable enantiomers.

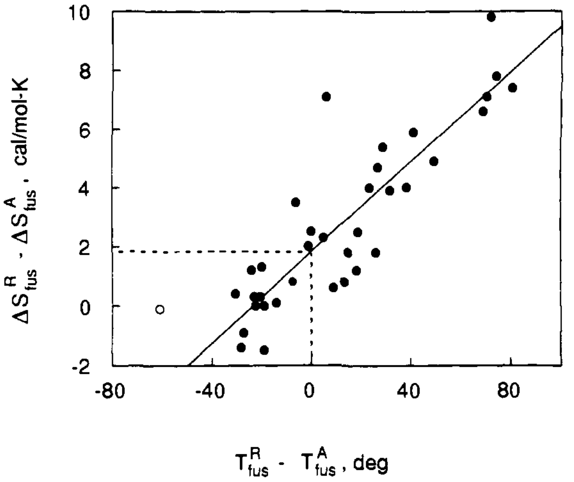

Figure 7. Plot of $\Delta(\Delta S_{fus})$ vs $T_{fus}^R - T_{fus}^A$ based on the data collected by Jacques, Collet, and Wilen for 36 pairs of chiral and racemic solids.[7] The two pairs shown as open circles contain a member having $|\Delta H_{fus} - T\Delta S_{fus}| > 0.1$ kcal mol^{-1} and were omitted from the regression calculation.[30]

The book by Jacques, Collet, and Wilen contains a list[7] of ΔH_{fus}, ΔS_{fus}, and T_{fus} values for 36 pairs of chiral and racemic crystals, all involving resolvable enantiomers (our group II). The average melting points, T_{fus}, and enthalpies and entropies of fusion, ΔH_{fus} and ΔS_{fus}, are 405 K, 7.54 kcal mol^{-1}, and 18.5 cal mol^{-1} K^{-1} for the racemic crystals and 395 K, 6.26 kcal mol^{-1}, and 15.7 cal mol^{-1} K^{-1} for the enantiomers. The racemic crystals thus seem to be more stable than the enantiomers, as was concluded by Jacques, Collet, and Wilen.[7] The extrapolation from the specific list of pairs to a general rule is, however, invalid. The list is biased, and indeed, *any* such list of pairs is necessarily biased. The racemic crystals will always *appear* to be more stable on average because

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(26) For polymorphic materials at sufficiently low temperatures, where the entropic term becomes unimportant, the relative free energies of polymorphs must be in the same order as the internal crystal energies. The form that is stable at low temperature tends to have the highest density (Richardson, M. F.; Yang, Q.-C.; Novotny-Bregger, E.; Dunitz, J. D. *Acta Crystallogr.* **1990**, *B46*, 653–660).

(27) Since the entropy of all ordered crystals is zero at 0 K (a statement of the third law of thermodynamics), it follows that the *configurational* entropy of ordered crystals is zero at all temperatures.

(28) Reference 2, p 30. Essentially the same argument is given by Collet, A. In *Problems and Wonders of Chiral Molecules*; Simonyi, M., Ed.; Akadēmiai Kiadō: Budapest, 1990; pp 91–109.

(29) If the racemic and chiral crystals are equally stable, the melting point of the former is close to the eutectic temperature T_e^A of the enantiomers (see Figure 5d), which can be calculated, assuming ideality, from the simplified Schröder–van Laar equation (see ref 25) by setting $x = 0.5$ so that

$$T_e^A = [(1/T_{fus}^A) + (R \ln 2)/(\Delta H_{fus}^A)]^{-1}$$

For crystals having $T_{fus}^A \cong 400$ K and $\Delta H_{fus}^A \cong 7$ kcal mol^{-1}, the eutectic temperature T_e^A is about 30 K lower than T_{fus}^A, the melting point of the homochiral crystals.

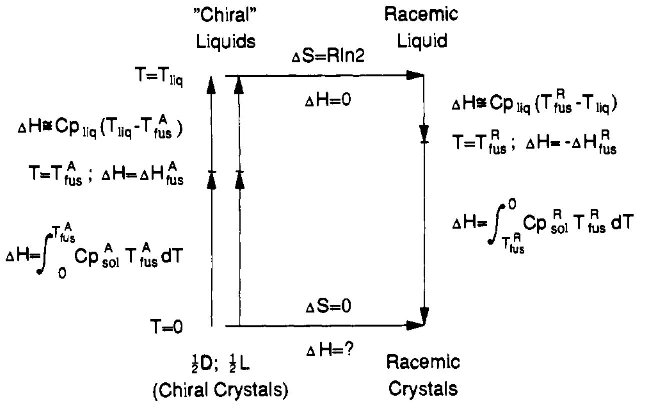

Figure 8. Thermodynamic cycle for a system of noninterconverting enantiomers that allows estimation of ΔH for the following reaction: $^1/_2$ mol of D-crystals + $^1/_2$ mol of L-crystals → 1 mol of racemic crystals. Both the chiral and racemic crystals are assumed to be perfectly ordered so that the entropy of each is zero at $T = 0$ K.

the pairs in which they are markedly less stable are absent.

A plot of the values of $\Delta(\Delta S_{\mathrm{fus}}) = \Delta S_{\mathrm{fus}}{}^{\mathrm{R}} - \Delta S_{\mathrm{fus}}{}^{\mathrm{A}}$ against $\Delta T = T_{\mathrm{fus}}{}^{\mathrm{R}} - T_{\mathrm{fus}}{}^{\mathrm{A}}$ from the aforementioned list is shown in Figure 7. Consideration of the thermodynamic cycle shown in Figure 8 leads to the relationship

$$\begin{aligned}\Delta(\Delta S_{\mathrm{fus}}) = \Delta S_{\mathrm{fus}}{}^{\mathrm{R}} - \Delta S_{\mathrm{fus}}{}^{\mathrm{A}} &\cong R \ln 2 + (\mathrm{Cp_{liq}} - \mathrm{Cp_{sol}}) \ln (T_{\mathrm{fus}}{}^{\mathrm{R}}/T_{\mathrm{fus}}{}^{\mathrm{A}}) \\ &\cong R \ln 2 + [(\mathrm{Cp_{liq}} - \mathrm{Cp_{sol}})/T_{\mathrm{fus}}{}^{\mathrm{A}}]\,\Delta T\end{aligned}$$

if the melt is ideal and the heat capacities for the chiral and racemic crystals are approximately equal. Since $T_{\mathrm{fus}}{}^{\mathrm{A}}$ does not vary too much from compound to compound in the sample, the plot of $\Delta(\Delta S_{\mathrm{fus}})$ vs ΔT should be approximately linear with an intercept of $R \ln 2$. The regression for 34 of the 36 pairs[30] of values given by Jacques, Collet, and Wilen gives a reasonable correlation ($R^2 = 0.77$) with an intercept of 1.82 (25) cal mol^{-1} K^{-1} = $R \ln$ [2.5 (3)] (see Figure 7). The slope of the least-squares line is 0.077 (8) cal mol^{-1} K^{-2}, which gives a value of $\mathrm{Cp_{liq}} - \mathrm{Cp_{sol}} = 30$ (3) cal mol^{-1} K^{-1} for the average $T_{\mathrm{fus}}{}^{\mathrm{A}} = 395$ K. The quality of the correlation is, of course, limited by the assumption that $\mathrm{Cp_{sol}}{}^{\mathrm{R}} = \mathrm{Cp_{sol}}{}^{\mathrm{A}}$ and by the variation in $T_{\mathrm{fus}}{}^{\mathrm{A}}$, as well as by the accuracy of the ΔS_{fus} values.

Since the reactants and products melt to form the same liquid, an estimate of the enthalpy change ΔH_{rac} for the reaction

$$\tfrac{1}{2} \text{ mol of D-crystals} + \tfrac{1}{2} \text{ mol of L-crystals} \rightarrow 1 \text{ mol of racemic crystals}$$

can be obtained from the quantity $-\Delta(\Delta H_{\mathrm{fus}}) = -[\Delta H_{\mathrm{fus}}{}^{\mathrm{R}} - \Delta H_{\mathrm{fus}}{}^{\mathrm{A}}]$. A major source of error in this estimate is neglect of the term that brings the two ΔH_{fus} values to a common temperature: $(\mathrm{Cp_{liq}} - \mathrm{Cp_{sol}})(T_{\mathrm{fus}}{}^{\mathrm{R}} - T_{\mathrm{fus}}{}^{\mathrm{A}})$, where the value of $\mathrm{Cp_{sol}}$ is for the crystal with the lower melting point. The value $\Delta(\Delta H_{\mathrm{fus}})$ is also a rough estimate of the free energy change ΔG_{rac} for the reaction as long as ΔS_{rac} is small, as it should be if neither crystal is disordered. The value of ΔG_{rac} is the vertical distance between the free energy curves shown in Figure 6 for the chiral and racemic crystals.

We might then expect a reasonable correlation between the values of $\Delta(\Delta H_{\mathrm{fus}})$ and $T_{\mathrm{fus}}{}^{\mathrm{R}} - T_{\mathrm{e}}{}^{\mathrm{A}}$ (see Figure 9), where $T_{\mathrm{e}}{}^{\mathrm{A}}$ is estimated from the simplified Schröder–van Laar equation. Only two pairs have $T_{\mathrm{fus}}{}^{\mathrm{R}}$ lower than the estimated $T_{\mathrm{e}}{}^{\mathrm{A}}$. For one of these pairs the data ($T_{\mathrm{fus}}{}^{\mathrm{R}}$, $\Delta H_{\mathrm{fus}}{}^{\mathrm{R}}$, $\Delta S_{\mathrm{fus}}{}^{\mathrm{R}}$) are internally inconsistent,[30] and for the other ($T_{\mathrm{fus}}{}^{\mathrm{R}} - T_{\mathrm{e}}{}^{\mathrm{A}}$) is only −2°. The regression line can be made to pass through the origin by adding a correction term of (−0.023 kcal mol^{-1} K^{-1})($T_{\mathrm{fus}}{}^{\mathrm{R}} - T_{\mathrm{fus}}{}^{\mathrm{A}}$) to the $\Delta(\Delta H_{\mathrm{fus}})$ values (see Figure 9b). This correction term is comparable to the value of 0.030 kcal mol^{-1} K^{-1} for $\mathrm{Cp_{liq}} - \mathrm{Cp_{sol}}$ obtained from the slope of the regression line shown in Figure 7. This correlation shows that for $\Delta(\Delta H_{\mathrm{fus}}) = 0$, the fusion point of the racemic crystals is close to the eutectic temperature, that is, typically some 20–30° lower than the fusion point of the corresponding pure enantiomers. For a racemic crystal to melt at a *higher* temperature than the pure enantiomer, it would need to have ΔH_{fus} higher by something of the order of at least 1 kcal/mol.

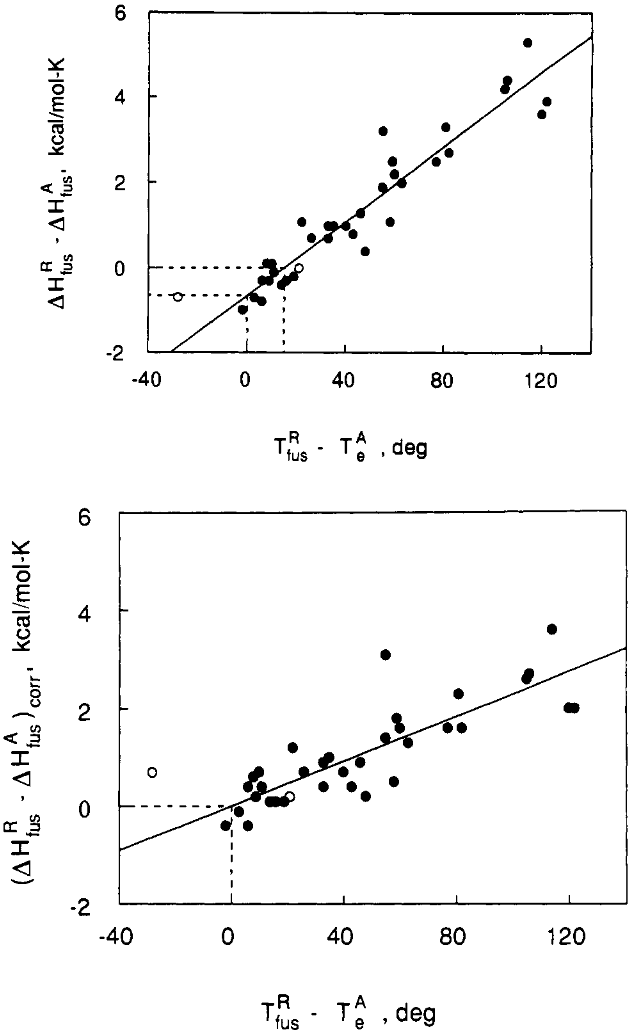

Figure 9. (a) Plot of $\Delta(\Delta H_{\mathrm{fus}})$ vs $T_{\mathrm{fus}}{}^{\mathrm{R}} - T_{\mathrm{e}}{}^{\mathrm{A}}$ based on the data collected by Jacques, Collet, and Wilen for 36 pairs of chiral and racemic solids.[7] The two pairs shown as open circles contain a member having $|\Delta H_{\mathrm{fus}} - T\Delta S_{\mathrm{fus}}| > 0.1$ kcal mol^{-1} and were omitted from the regression calculation.[30] (b) A correction term, (−0.023 kcal mol^{-1} K^{-1})($T_{\mathrm{fus}}{}^{\mathrm{R}} - T_{\mathrm{fus}}{}^{\mathrm{A}}$), has been added to the $\Delta(\Delta H_{\mathrm{fus}})$ values to force the regression line to pass through the origin.

Once it is recognized that all lists of *pairs* of resolvable enantiomers are biased toward greater stability of the racemic crystal, its (on average) ca. 1% greater density can be interpreted as evidence to support the supposition that packing efficiency is correlated with stability.[31,32] Conversely, the members of the group I pairs have, on average, equal densities, and they are approximately equally stable.[33]

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[30] Two of the sets of values given in the table on pp 94–95 of ref 2 are inconsistent and were therefore omitted from the regression calculation. For the racemate of N,N'-bis(α-methylbenzyl)thiourea $|\Delta H_{\mathrm{fus}}{}^{\mathrm{R}} - T\Delta S_{\mathrm{fus}}{}^{\mathrm{R}}| = 0.51$ kcal mol^{-1}, and for the racemate of *trans-exo*-1,5-dichloro-11,12-di(hydroxymethyl)-9,10-dihydro-9,10-ethanoanthracene $|\Delta H_{\mathrm{fus}}{}^{\mathrm{R}} - T\Delta S_{\mathrm{fus}}{}^{\mathrm{R}}| = 0.24$ kcal mol^{-1}. For all other entries in the table $|\Delta H_{\mathrm{fus}} - T\Delta S_{\mathrm{fus}}| < 0.12$ kcal mol^{-1}.

[31] Thermal expansion coefficients of molecular crystals typically correspond to a ca. 1% increase in the crystal volume for a ca. 100 °C increase in the temperature.

[32] The estimated standard deviation of the distribution exceeds 2% so that in any given pair the more stable crystal may be the less dense. Certain kinds of interactions, such as hydrogen bonds, may systematically favor more open structures.

Crystallization from a Racemic Solution or Melt

The belief that racemic crystals are more tightly packed and more stable than their chiral counterparts has been largely based on comparisons of properties of pairs of chiral and racemic structures. We have shown that such comparisons are necessarily affected by statistical bias. The presence of this bias reduces the logical force of the argument, but it is still possible that the conclusion is correct, i.e., that there is an intrinsic preference for the racemic over the chiral crystal. Such a preference would be expressed, for example, if crystallization from a racemic solution or melt were more likely to produce racemic than chiral crystals, i.e., if formation of a conglomerate were relatively rare. Indeed, there are persistent (although hardly conclusive) reports that crystallization from a racemic solution or melt produces racemic crystals far more often than conglomerates.[34] Only about 10% of such crystallizations are supposed to lead to conglomerates.[35]

More persuasive evidence for the predominance of racemic over chiral crystals comes from tabulations[36] of space group frequencies. Only a few space groups account for most observed crystal structures, the preferred ones being overwhelmingly racemic: $P\bar{1}$, $P2_1/c$ (and its centered equivalent $C2/c$), and $Pbca$. Together these four space groups account for two-thirds of all organic crystal structures. The chiral space groups are less common; they account together for only 20% of the structures in the CSD,[37] and many of those are of chiral natural products or resolved enantiomers. The vast majority of crystallizations from racemic solutions lead to racemic crystals.

For a crystal composed of homochiral molecules, only 65 space groups—the ones that exclude improper symmetry operations such as inversion and reflection—are available. In crystallization from a racemic solution or melt, all possible arrangements compatible with these 65 space groups[38] are available for packing the molecules as are *also* arrangements in the remaining 165 racemic space groups. It seems likely that the best of many possible racemic packing arrangements is to be preferred to the best of fewer possible chiral arrangements. As Kitaigorodskii has pointed out in his analysis of crystal packing,[39] organic molecules crystallize preferentially in the space groups that allow close packing of triaxial ellipsoids, especially the space groups $P2_1/c$ and $P\bar{1}$, which together account for more than half of all known organic crystal structures. Besides, glide reflection is preferable to pure reflection, screw rotation is preferable to pure rotation, and the combination of glide reflection and screw rotation is preferable to either individually.[36c] Crystallographic rotation axes and mirror planes lead to energetically unfavorable mutual orientations of juxtaposed polar groups of neighboring molecules related by these symmetry elements; the preferred space groups avoid these unfavorable interactions and allow more favorable orientations to be achieved by combining the pure point group symmetry operations with translational displacements of the molecules. The extra possibilities for using inversion centers and glide reflections could well lead to a preference for racemic space groups over chiral ones.[40]

Thus the tendency seen in Figure 9 for $\Delta(\Delta H_{\mathrm{fus}})$ and $\Delta(\Delta T_{\mathrm{fus}})$ to be positive may not be completely attributable to bias, but it may also reflect a real preference for the racemic crystal over the conglomerate, and similarly for the tendency of the racemic crystals to have slightly higher densities.

As far as the kinetic argument is concerned, it is easy to imagine that crystallization from a racemic solution or melt could have very different effects on the rate of formation of nuclei of critical size for racemic and chiral crystals and on the growth of these crystals. In the process of forming a viable nucleus of the chiral crystal, only half of the molecules that arrive on the surface of the subcritical cluster are suitable for its development. The presence of molecules of the "wrong" enantiomer will thus inhibit formation of the nucleus and possibly also of the growth of the crystal. A molecule arriving at the "wrong" site on the surface of a racemic subcritical cluster need only "slide" into a "right" site; it need not be replaced by another molecule of opposite chirality. Insofar as there are growing faces involving intermolecular interactions that are the same for both enantiomers, e.g., interactions between achiral groups such as aromatic systems, the presence of the wrong enantiomer in the racemic solution could act as a "tailor-made" impurity—in the sence of Leiserowitz, Lahav, and their colleagues[41]—in the growth of the chiral crystal but not of the racemic crystal. There is also the problem of overcoming the concentration gradients that must be set up during nucleation and growth of the chiral crystals. These factors might well explain the relative infrequency of conglomerates, even if they were of comparable thermodynamic stability to the corresponding racemic crystals.

As far as the practical problem of enantiomer separation is concerned, the relative rarity of conglomerate formation notwithstanding, it is always worth trying crystallization as the simplest method of effecting a separation of enantiomers.[42,43] A possible procedure would be roughly as follows: On crystallization of the racemic solution, determine whether racemic or chiral crystals have been obtained (morphology, space group,[44] etc.). A quick and convenient, but not necessarily foolproof,[45] method requires only the determination of melting points.[46] Compare the melting points of two powdered samples, one prepared from a single crystal, the other from a collection of several crystals. If the two melting points are the same, racemic crystals have been obtained; if the melting point from the single crystal is higher, the conglomerate has been obtained. Once a single crystal has

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(33) Few direct comparisons of packing energy and density are available. For the group II pair BAGMOL/BAGMUR, the racemic product, obtained by irradiation of the chiral starting material (Ohashi, Y.; Yanagi, K.; Kurihara, T.; Sasada, Y.; Ohgo, Y. *J. Am. Chem. Soc.* **1982**, *104*, 6353–6359), is estimated to have a PPE (packing potential energy) (Gavezzotti, A. *J. Am. Chem. Soc.* **1983**, *105*, 5220–5225) of -90 kcal mol^{-1} compared with -83 kcal mol^{-1} for the chiral crystal (Uchida, A.; Dunitz, J. D. *Acta Crystallogr.* **1990**, *B46*, 45–54). The $\Delta(\%)$ value is $+1.14$ (see Table I).

(34) (a) Coquerel, G.; Bouaziz, R.; Brienne, M.-J. *Chem. Lett.* **1988**, 1081–1084. (b) Coquerel, G.; Bouaziz, R.; Brienne, M.-J. *Tetrahedron Lett.* **1990**, *31*, 2143–2144.

(35) Reference 2, p 81.

(36) (a) Mighell, A. D.; Himes, V. L.; Rodgers, J. R. *Acta Crystallogr.* **1983**, *A39*, 737–740. (b) Donohue, J. *Acta Crystallogr.* **1985**, *A41*, 203–204. (c) Wilson, A. J. C. *Acta Crystallogr.* **1988**, *A44*, 715–724.

(37) Most of these chiral structures are in space group $P2_12_12_1$ (11.9%) or space group $P2_1$ (6.6%).

(38) While the members of a pair of enantiomorphous space groups (e.g., $P3_1$ and $P3_2$) are nonequivalent for homochiral substrates, they lead to essentially equivalent, isometric structures for an enantiomeric pair of substrates. Thus when crystals are grown from a racemic solution or melt, the number of chiral space groups available is effectively reduced from 65 to 54.

(39) Kitaigorodskii, A. I. *Organic Chemical Crystallography*; Consultants Bureau: New York, 1961; pp 65–112.

(40) The commonly held idea (e.g., Nicoud, J. F.; Twieg, R. J. In *Non-Linear Optical Properties of Organic Molecules and Crystals*; Chemla, D. S., Zyss, J., Eds.; Academic Press: New York, 1987; Vol. I, p 253) that large dipole moments are an important factor leading to centrosymmetry in molecular crystals is refuted by a recent study based on data from the CSD (Whitesell, J. K.; Davis, R. E.; Saunders, L. L.; Wilson, R. J.; Feagins, J. P. *J. Am. Chem. Soc.* **1991**, *113*, 3267–3270) and is in any case contrary to elementary physics. When the potential or the electric field at distance r from a molecule is expressed as a series in r^{-1}, r^{-2}, r^{-3}, etc., the series expansion is only valid when r is large compared with the distances within the molecule. This is not the case for interactions between neighboring molecules in crystals.

(41) Addadi, L.; Berkovitch-Yellin, Z.; Weissbuch, I.; Lahav, M.; Leiserowitz, L. *Top. Stereochem.* **1986**, *16*, 1–85.

(42) And certainly the oldest! See Pasteur, L. *Ann. Chim. Phys.* **1848**, *24*, 442–459. For a detailed description of Pasteur's achievement with instructions for repeating his crystallization experiments with sodium ammonium tartrate, see: Kauffman, G. B.; Myers, R. D. *J. Chem. Educ.* **1975**, *52*, 777–781.

(43) A useful survey of methods of optical resolution by direct crystallization is found in Chapter 4 of ref 2. The method of resolution by entrainment is discussed in detail.

(44) The most common chiral space group, $P2_12_12_1$, is unambiguously determined by Laue symmetry and systematic absences; the same is almost true of the second most common group, $P2_1$, because $P2_1/m$ is relatively rare as long as the molecules do not contain a mirror plane. The main problem concerns the members of the space group pair $P1/P\bar{1}$, which are not distinguishable by systematic absences alone. The presence of only a single (noncentrosymmetric) molecule in the unit cell would, however, strongly suggest $P1$.

(45) The individual crystals of a conglomerate, although formally in a chiral space group, are not necessarily chirally pure (see: Davey, R. J.; Black, S. N.; Williams, L. J.; McEwan, D.; Sadler, D. E. *J. Cryst. Growth* **1990**, *102*, 97–102). The crystals may contain the wrong enantiomer in solid solution, or they may be twinned at the macroscopic or microscopic level.

(46) For example, see: Eliel, E. L. *Stereochemistry of Carbon Compounds*; McGraw-Hill: New York, 1962; p 46.

been identified as being chiral, it can be used to seed a second crystallization of the racemic solution. This well-known procedure, termed resolution by entrainment, can lead to a complete or partial separation of enantiomers.[43,47]

Conclusion

A comparison of densities of 65 chiral/racemic pairs culled from the Cambridge Structural Database has shown that the racemic crystals are, on average, ca. 1% more tightly packed than their chiral counterparts (although for many individual pairs the racemic crystal has the lower density). A corresponding comparison of densities for 64 polymorphic pairs (i.e., pairs of structures containing molecules or ions that are achiral or enantiomers that interconvert rapidly in solution) shows no significant difference in packing density between the racemic and chiral members. Wallach's 1895 rule seems to be substantiated, but only for resolvable enantiomers.

The key to this difference is the recognition that any such comparison of chiral/racemic pairs will be affected by bias if the enantiomers are resolvable. Pairs for which the racemic crystal is more stable than its chiral counterpart will be included in the comparison, but pairs for which the racemic crystal is markedly less stable will be excluded, the racemic crystal being then unobtainable. Because of this bias, *any* comparison of corresponding chiral/racemic pairs will suggest that racemic crystals are the more stable. This is the case, for example, for the 36 pairs of racemic and chiral crystals for which thermodynamic data concerning melting behavior were collected by Jacques, Collet, and Wilen.[7] A theoretical argument has been advanced by these authors for the greater stability of racemic crystals in general.[28] This argument, however, is invalid since it rests on an erroneous assumption, namely that the entropy of a racemic crystal is systematically larger than that of a chiral crystal by $R \ln 2$ because of the mixing of the enantiomers. This assumption contradicts the third law of thermodynamics, which states that all ordered crystals have zero entropy at 0 K.

In estimating the relative thermodynamic stabilities, the direct comparison of the melting points of the chiral and racemic crystals can be misleading because the two solids are not in equilibrium with the same liquid phase. It is more informative to compare the melting point of the racemic crystal with the melting point of the 1:1 conglomerate, i.e., the eutectic temperature of the mixture of enantiomeric chiral crystals. If one of the enantiomers is not available, the eutectic temperature can be estimated from the melting point and heat of fusion of the other.

Although much of the evidence for the apparent greater density and thermodynamic stability of racemic crystals relative to their chiral counterparts is undermined by the presence of the aforementioned bias, there is probably also a genuine intrinsic difference in their relative stabilities. About 90% of the compounds that can crystallize in either racemic or chiral space groups prefer the former. This preference need not be a result of special kinds of interactions between opposite enantiomers; rather, it can be attributed to the additional possibilities for favorable packing arrangements available in racemic space groups.

The evidence collected here adds some support to the general correlation between the densities and packing energies of polymorphic crystals.

There is also a kinetic factor that could be important during crystallization from a racemic solution or melt. The presence of the "wrong" enantiomer is likely to inhibit the formation of viable nuclei of the chiral crystal but not of the racemic one and might also act as a "tailor-made" impurity in the subsequent growth phase of the chiral crystal.

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Supplementary Material Available: Line drawings and literature references for structures included in the final tabulation (37 pages). Ordering information is given on any current masthead page.

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(47) Collet, A.; Brienne, M.-J.; Jacques, J. *Chem. Rev.* **1980**, *80*, 215-230.

Stealth Stereocontrol: Stereochemical Reversal of a Michael Addition Reaction

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Abstract: The nitroalkene, methyl 5,6-dideoxy-2,3-*O*-isopropylidene-6-nitro-6-(phenylthio)-β-D-ribo-hex-5(*Z*)-enofuranoside (**1**), was found to react with nucleophiles to give, on ozonolysis, the corresponding phenyl thiolesters **3**, **5**, **6a–c**, and **7** bearing the nucleophilic residue α to the carbonyl group. The nucleophiles Me$_3$SiOK, NaOMe, NaOCH$_2$Ph, and TsNHK all stereoselectively (7:1–50:1) reacted to give products with the *allo*-thiouronate configuration. In contrast, potassium succinimide and phthalimide, nucleophiles with aerofoil bulk, gave substituted *talo*-thiouronates (>15:1).

The addition reactions of nucleophiles to 1-nitro-1-(phenylthio)alkenes, followed by ozonolysis of the intermediate nitronates, represent a convenient method for the synthesis of α-substituted phenyl thiolesters.[1] This chemistry is useful for the preparation of acyclic systems,[2] bicyclic β-lactams,[3] and tetrahydrofuran and tetrahydropyran derivatives.[4] Recently we had occasion to employ this methodology in the total synthesis of polyoxin C and related

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(1) Barrett, A. G. M. *Chem. Soc. Rev.* **1991**, *20*, 95. Barrett, A. G. M.; Graboski, G. G. *Chem. Rev.* **1986**, *86*, 751.

(2) Banks, B. J.; Barrett, A. G. M.; Russell, M. A. *J. Chem. Soc., Chem. Commun.* **1984**, 670. Barrett, A. G. M.; Graboski, G. G.; Russell, M. A. *J. Org. Chem.* **1986**, *51*, 1012.

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