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Are Racemic Crystals Favored over Homochiral Crystals by Higher Stability or by Kinetics? Insights from Comparative Studies of Crystalline Stereoisomers

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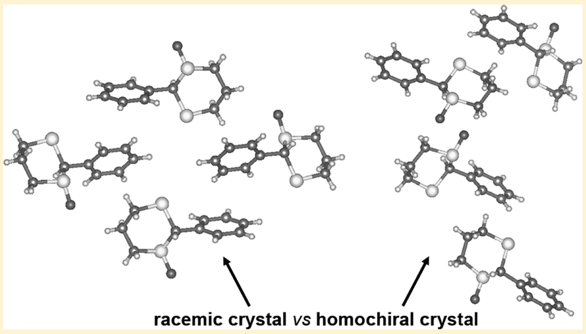
Supporting Information

ABSTRACT: The crystal and molecular structures of 134 pairs of diastereoisomers and of 279 racemic−homochiral pairs were retrieved from the Cambridge Structural Database. Lattice and intramolecular energies are calculated. Density differences between crystals of stereoisomers of all kind are mostly within 5%, as observed also for crystal polymorphs. Racemic crystals are predominantly, but not exclusively, more stable and more dense. Denser crystals are predominantly more stable, but there is no quantitative correlation between density and energy differences between partners in the chosen pairs. Second-order symmetry operators are neither ubiquitous in the racemic nor patently superior to first-order operators in promoting crystal cohesion. Thermodynamic, energetic factors in the final crystalline products are not enough to explain the (largely) predominant occurrence of racemic crystallization from racemic solution. At least for homogeneous nucleation, a probabilistic factor, from kinetics or from statistical predominance of mixed versus enantiopure aggregates, must be in action during the early separation of liquid-like particles, which are thought to be the precursors of crystal nucleation.



INTRODUCTION

The predominance of racemic crystallization over formation of a conglomerate of homochiral crystals from a liquid of nonequilibrating enantiomers is an outstanding, unexplained fact in organic solid-state chemistry. A ratio of 9:1 in favor of racemic crystals is often quoted,[1] presumably without a proper quantitative statistical basis; besides, this ratio may well be variable for different classes of compounds. An understanding and possible control of this phenomenon is highly desirable for the advancement of academic knowledge but obviously also for progress in industrial process design.[2] One step upstream, a deeper understanding of the organization of molecular materials requires command of the relationships among molecular constitution, molecular conformation, chirality, and crystal packing.

In a seminal paper,[3] pairs of molecules having identical composition and chemical connectivity but different arrangement of atoms in tridimensional space—that is, stereoisomers—were classified by Mislow in two categories: *enantiomers*, when they are nonsuperimposable mirror images, or *diastereisomers*, when they are not related by an isometry (a symmetry operation). An extension of these definitions to large and complex organic molecules, where several conformational (i.e., torsional) degrees of freedom may coexist, depends on the analysis of the position of the minima of energy profiles and of their curvatures and requires a quantitative estimation of the energy barriers to interconversion and of the energy separation between isomers. On the other hand, pairs of molecules of identical chemical composition but with different connectivity are called *constitutional* isomers, the modern version of the old-fashioned name of *valence* isomers. Interconversion in this case is not allowed at room conditions, as it would require the breaking of a chemical bond at a very large energy expense.

In search of an answer to the title question, the main purpose of this work is the comparison of crystallographic, physicochemical, and energetic properties of pairs of stereoisomers in the crystalline state. We compare experimental properties (space group symmetry, density, etc.) and calculated properties (molecular and lattice energies) of these pairs, looking for any relationship between molecular stereochemistry and crystal "stereochemistries", or spatial assembling modes and properties, and in search of correlations between chirality and relative stability. Crystal and molecular structural data are extracted from searches over the Cambridge Structural Database[4] (CSD). To assess the sensitivity and reliability of our methods, a calibration test is carried out, comparing different independent determinations of the same crystal structure, where properties should be identical. We then compare pairs of crystals of diastereoisomeric molecules, and, finally, pairs consisting of racemic and homochiral crystals of the same compound.

As can easily be guessed, several interesting trends are eventually highlighted, but such investigations provide suggestions rather than conclusive correlations. In some cases,

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however, even the exclusion of a correlation may provide valuable information or may dismiss wrong assumptions. Our comparisons show that racemic crystals are not necessarily denser than homochiral ones and that denser crystals are often, but not necessarily, more stable, contrary to some conventional wisdom. Some advantages in lattice energy or in pairwise molecular interactions appear in racemic crystals, but they are neither ubiquitous nor sufficient to explain the preponderance of racemic crystallization. This leaves the way open for suggesting a major influence of kinetic factors during the crucial events that take place at the first stages of crystal formation, when diffusion control and/or aggregation into liquid-like micelles play a decisive role. These are discussed, together with some simulations of the liquid−solid transition, in terms of current theories of nucleation.

■ METHODS

Definitions and Data Retrieval. Pairs of molecules to be compared must have (a) the same chemical composition, (b) the same number of atoms of each type (e.g., hydrogen: acetylenic, aromatic, aliphatic, alcohol, acid; carbon: sp^2, sp^3, aromatic; etc.), and (c) the same number of bonds between each pair of atom types. When chemical connectivity is different, the classification is "*constitutional isomers*", for example, 1,2- and 1,3-disubstituted benzenes or propanes; these systems are different crystals of different compounds. When chemical connectivity is identical, the molecules are "*conformational isomers*". We consider here as stereoisomers those pairs of molecules where at least one conformational barrier (at the stereoisomeric moiety) is substantial ($\gg RT$) and the two isomers are locked into different tridimensional structures which are carried over to the crystalline state. There is no simple way of establishing a priori the actual value of energy barriers; besides, crystal constraints may add to the purely intramolecular barriers. For all search purposes, we accept the classification present in the Cambridge Structural Database[4] (see below) when it explicitly labels pairs as stereoisomers on the basis of their extensive experience on the subject. To these stereoisomers, the Mislow classification of either *enantiomers* or *diastereoisomers* applies, depending on the presence and/or nature of the symmetry relationship, already evident on consideration of the space group symmetry. A detailed description of all our assumptions and definitions, including a discussion of the relationship between isomerism and conformational barrier heights, is found in Appendix A (Supporting Information). The issues of stereoisomery, along with conformational polymorphism in crystals, have been discussed in an extensive review paper.[5]

In the following, "*rac*" denotes the crystal of a 1:1 enantiomer mixture, while "*hom*" denotes the corresponding homochiral crystal. *Hom* and *rac* are different crystals; crystals of diastereoisomers are also different, while *hom* crystals of each of the two enantiomers are identical, except with respect to polarized light. Details of the enantiomeric status of the liquid from which the crystals in our sample were grown cannot be traced back because this kind of information is not in the CSD and is only (but not always) present in the original publications, whose survey would be prohibitive for so many compounds. It is, however, likely that most of our homochiral crystals have been produced from a solution of homochiral molecules. Crystal structures of *rac*−*hom* pairs have been retrieved from the CSD by searching for the text string "for racemate, see" for organics only: this search identifies homochiral crystal structures for which the CSD also contains the crystal structure of the racemate. For each of them the corresponding racemate crystal structure was also retrieved. Amino acids and peptides were excluded having already been the subject of a similar work.[6] After screening out of disordered structures, hydrates or solvates, and a few unexplained errors detected by our retrieval software, the final sample consisted of 279 pairs, which we call *rac*−*hom* set *A*. A further screen-out was based on quality of the crystal structure and feasibility of ab initio calculations (i.e., smaller molecules) for a subset of 97 *rac*−*hom* pairs for which the electron density and PIXEL calculations could be comfortably carried out (see below). This was called *rac*−*hom* set *B*. The final lists of CSD refcodes are available as Supporting Information (Table S1). Homochiral/racemic (*hom*−*rac*) crystal pairs were studied a long time ago for general organics[7] on a reduced data set and without energy calculations and more recently for proteogenic amino acids.[6]

The same procedure was carried out by automatically searching the CSD for the text string "for stereoisomer, see". The maximum number of atoms was set to 30, with chlorine as the heaviest allowed element. A matching software was then prepared to automatically recognize identical chemical composition and/or identical number of bonds between atomic species. The software identified 134 pairs of diastereoisomers (the DIAST set). The final list of CSD crystal structure refcodes is also available as Supporting Information (Table S2).

Energies and Densities. Intermolecular energies are evaluated in a first approximation by the atom−atom (AA) CLP force field.[8] For a better approximation, for data sets *rac*−*hom* B and DIAST, intermolecular energies are also calculated by the PIXEL method,[9] in which each molecule is represented by a large number (up to 20000) of negative charge points together with the appropriate positive nuclear charges. For the PIXEL calculation, electron densities for the molecules considered are calculated at the MP2/6-31G** level using the geometry of each molecule "frozen" as extracted from the crystal structure. The same calculation also yields the energy of formation of each molecule in the crystal conformation. The lattice sublimation energy is calculated in the usual[8] approximation as $U(\text{lattice}) = -E(\text{lattice}) - 2RT$, while the atomization energy is the negative of the energy of formation calculated by the ab initio program, or $U(\text{mol}) = -E(\text{MP2/6-31G**})$. For *rac*−*hom* pairs, differences are then taken as $\Delta U(\text{lattice}) = \text{U}(\text{lattice, rac}) - U(\text{lattice,hom})$, and $\Delta U(\text{mol}) = U(\text{mol,rac}) - U(\text{mol,hom})$, so that a positive ΔU in both cases identifies the racemate as the more stable system. The total difference between crystal pairs is then given by $\Delta U(\text{tot}) = \Delta U(\text{lattice}) + \Delta U(\text{mol})$. Densities are renormalized for differences in temperature of the X-ray determination using the relationship $\text{d}(295) = \text{d}(T) \exp[\alpha(T - 295)]$, with $\alpha = 0.0001\ \text{K}^{-1}$, typical of organic materials.[10a] Corrections are small and scarcely influential. Density differences are evaluated as $\Delta d = d(rac) - d(hom)$. For pairs in the DIAST data set all the above procedures hold, except that the reference within the pair is taken as the more dense isomer, so that density differences are always positive.

All calculations were carried out with the CLP program package,[11] including Fortran source modules and full documentation with examples, to allow reproducibility of the present results.

Molecular Similarity. Two simple empirical indices of the similarity or difference in overall shape for a pair of isomer molecules can be constructed using the molecular moments of inertia. The moments are larger for conformers whose distribution of atomic masses is more distant from the center of mass. Calling $\text{d}S_t$ the percent difference in the t-th moment (along the x, y, or z inertial axes), for an A−B pair the sum of the three components, $\Sigma(\text{d}S_t)$, is positive when the A molecule is more diffuse in space while the B molecule is more globular. The sum of the absolute values, $\Sigma(|\text{d}S|)$, is an approximate indicator of the overall shape difference between conformers.

■ RESULTS AND DISCUSSION

Tests on Multiple Determinations. For a test of the sensitivity of our approach to random variations in experimental conditions, a preliminary analysis was conducted on 74 pairs of high quality, independent determinations of the same crystal and molecular structure at the same (room) temperature. The list of structure identifiers, called CSD refcodes, and the data for the comparison are given as Supporting Information, Table S3. Figure S1, Supporting Information, shows graphically the results. In about 90% of the pairs the density difference is below 1% and the lattice energy difference is below 2 kJ mol^{-1}. These are the limits of discrimination in our treatment, and anything within these limits may be ascribed to random factors related to an almost infinite variety of conditions in the X-ray structure determination.

Diastereoisomers. Figure 1 shows a scatter-plot of energy differences versus density differences in the DIAST data set.

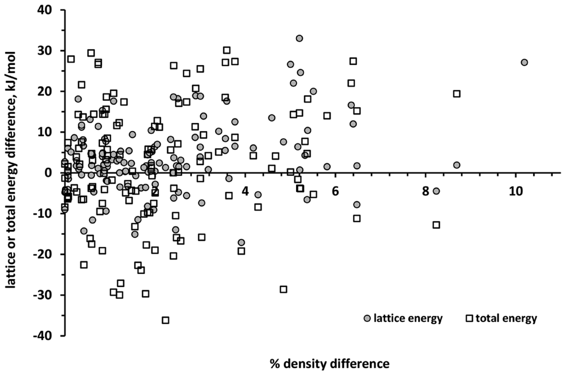


Figure 1. Scatter-plot of differences in PIXEL lattice energy against difference in density (more dense minus less dense) in the 134 isomers of the DIAST data set. A positive number indicates that the crystal is more dense and more stable. A few outliers with Δd > 7% are structures determined at largely different temperature, where the empirical density correction may be less accurate.

The data (84%) are clustered within a density difference of less than 5%, but PIXEL lattice energy differences are as high as 25 kJ mol^{-1}. The denser crystal has a more cohesive lattice energy in 65% of the pairs, but one can hardly speak of a correlation: one sees at most a crude tendency of more stabilizing lattice energy with higher packing coefficient, as seen more clearly in Figure S2 (Supporting Information). This tendency can be ascribed to the influence of dispersive forces, ubiquitous even in harder, hydrogen-bonded crystals. When total (lattice + intramolecular) energies are considered, the denser crystal is more stable in only 57% of the cases.

Figure S3 (Supporting Information) shows the components of relative stability in diastereoisomer crystal pairs. For 52% of the cases there is compensation between intra- and intermolecular energies (less stable crystal with more stable molecule), while the remaining 48% corresponds to a more stable crystal comprising the more stable molecule. This almost perfect balance shows there is no general tendency to trade-off, and molecules and crystals can adjust with little effort to intra- and intermolecular energy differences of 5−10 kJ mol^{-1}. A special case is the pair EZOJUZ−MACLAE,[12] where one partner forms an intramolecular hydrogen bond, gaining stability in intramolecular energy but losing in intermolecular energy (64 and 68 kJ mol^{-1}, respectively). Other examples of trade-off are cis−trans isomers, e.g., DOKXUW−DOKYAD or MOHCES−MOLHIF[13] (structural drawings and a Hirshfeld surface analysis[14] for these cases are given in the Supporting Information, Figure S4). Finally, Figure S5 (Supporting Information) shows that the above conclusions are broadly the same when the much less expensive atom−atom lattice energies are used instead of the more accurate PIXEL energies. Significant differences in absolute numbers may appear, but trends in differences are the same.

The case of a cluster of isomeric trichlorohexane diols,[15] including both diastereoisomers and valence isomers, better illustrates all the aspects of our interpretations, the limits of accuracy of the inherent calculations, as well as the richness of detail that a parallel geometric and energetic analysis provides in crystal packing studies. Table 1 shows the relevant data, while Figure S6 (Supporting Information) shows the actual conformations of all the isomers in Table 1. All these crystals either of diastereoisomers or of constitutional isomers are comprised within a density range of 7.5% with a moderate correlation between lattice energy and density. In this particular case there is almost exact compensation between conformational energy gain and lattice energy loss; eventually, total crystal energies are almost identical within the limits of the calculation, irrespective of the compounds being diastereoisomers or valence isomers. Exceptions to the trends are for wrong or inaccurate structures (high *R* factor). The calculation not only explains the crystal packing of these isomers but also points out possible shortcomings of the X-ray experiment.

Table 1. Energies and Densities of the Isomeric Trichlorohexane Diols, Relative to the Crystal with Highest Density[a]

		differences				
refcode[15]	trichloro diol	% density	lattice *E*	intram. *E*	total *E*	*R* factor[b]
CUGQIF	2,4,5−1,3	0	0	0	0	3.72
HOYCUU	3,4,5−1,2	−0.3	+13	−9	+4	2.55
HOYCOO	2,4,5−1,3	−2.8	+16	−7	+9	3.46
CUGPEA	2,4,5−1,3	−1.8	+18	−20	−2	3.13
CUGPIE	2,4,5−1,3	−2.4	+24	−29	−5	3.89
CUGQEB	2,4,5−1,3	−7.6	+32	−32	0	3.96
CUGQAX	2,4,5−1,3	−2.0	+24	−29	−5	6.41
CUGNUO	3,4,5−1,2	+1.0	0	+31	+31	5.48
CUGPAW	3,4,5−1,2	−6.5	+26	+3	+29	7.09

[a] Energies in kJ mol^{-1}. See the Supporting Information, Figure S6, for pictures of the isomers. Pairs of 2,4,5−1,3 compounds or of 3,4,5−1,2 compounds are diastereoisomers, pairs made of one 2,4,5−1,3 and one 3,4,5−1,2 compound are constitutional isomers. [b] Values higher than 5% indicate some difficulties in the refinement of the structure.

Homochiral and Racemic Crystal Partners. The distribution of space groups follows the general trend in organic crystal structures: *hom* crystals are mostly $P2_1$ or $P2_12_12_1$, while *rac* crystals are mostly $P1$- or $P2_1/c$, but some examples of the polar, noncentrosymmetric space group $Pna2_1$ appear, where a glide plane is the operator of inversion of handedness. Within the limits of the many biases present in the CSD collection, it appears that *rac* and *hom* crystal structures are often determined together (52% of the sample), but if not, the crystal structure of the racemic partner is more frequently (34%) determined first. The *R* factor of the racemic crystals is higher than that of the homochiral partner in 62% of the samples. The number of molecules in the asymmetric unit is the same (Z' = 1) in 71% of the sample, and in 19% it is higher in the *hom* partner. Especially for small molecules, often the two structures are quite similar, with the homochiral partner using two molecules in the asymmetric unit to substitute for the centrosymmetric pair of the *rac* partner. Whether there is a message on crystal stability in this fact remains to be seen. Figure S7 (Supporting Information) contains some graphic representations of these results.

In the *rac*−*hom* pairs, the similarity index $\Sigma(|dS|)$ is below 10 in 90% of the cases, indicating that the conformations of the

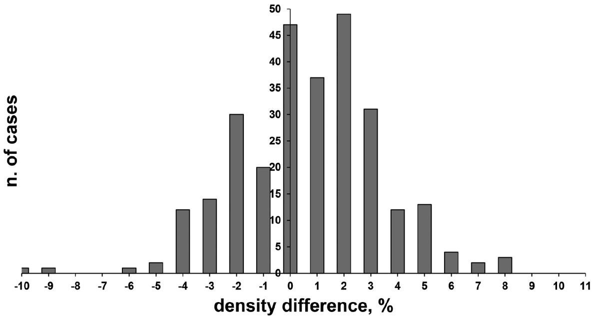


Figure 2. Histogram of *rac*–*hom* density differences (right side, *rac* more dense). 279 pairs.

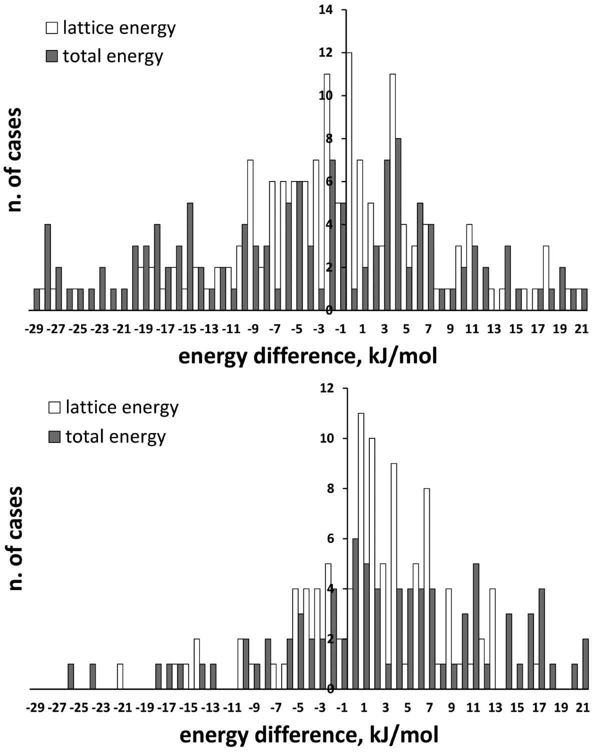


Figure 3. Histograms of energy differences between diastereoisomers (top; right–left equally populated) and for *rac*–*hom* pairs (right side, *rac* more stable).

two molecules are nearly identical in the majority of occurrences. There are nevertheless some cases of extreme diversity in the molecular conformation, as shown in Figure S8a (Supporting Information). These large shape differences do not influence either density or stability, as shown in Figure S8b (Supporting Information). Molecular shape, whatever is meant by that, is not a valid parameter in matters of crystal constitution or stability.

Figure 2 shows the histogram of density differences between *rac* and *hom* crystals. Figure 3 shows the histogram of energy differences, in comparison with the corresponding histogram for diastereoisomers. Table 2 collects some numerical results taken out of these figures.

Ninety-seven percent of the density differences are within ±5%. A similar result was found for crystals of diastereoisomers (Figure 1) and also for polymorphic pairs.[10b] This further confirms that the bulk of crystal density is determined by atomic composition and that the effect of chemical structure and of its adaptation into the symmetry constraints of a crystalline environment is much subtler and acts for just a few percent points. This is in agreement with the well-known difficulty of crystal structure prediction for organic compounds. The distribution of energy differences is wider in the diastereoisomer pairs, where the molecules are different, than in the enantiomer pairs, where the chemical component is the same.

Density differences between *rac* and *hom* crystals are smaller than the discrimination limit of 1% for 37% of the data. Outside that noise interval, *rac* crystals are more dense in 42% of the sample against 21% of the opposite occurrence. The higher density of *rac* crystals is then predominant but far from exclusive. Lattice energy differences are smaller than 2 kJ mol^{-1} for 22 (PIXEL) or 17% (atom–atom) of the data. Outside that noise interval, *rac* crystals are more stable by a 2:1 (PIXEL) or 3:2 (atom–atom) ratio. *Rac* crystals are then more stable in general—the more accurate methods better supports this conclusion—but not more stable systematically. The above conclusions apply also when total (lattice + intramolecular) energies are considered. The absolute values of energy differences seldom exceed 10 kJ mol^{-1}, the same order of magnitude as in the energy differences calculated for pairs of polymorph crystals.[10b]

Figure 4 shows the density–stability plot where the upper right quadrant is densely populated, broadly indicative of more

Table 2. Analysis of the Population of Racemic–Homochiral Pairs of Crystal Structures[a]

	97 pairs, *rac-hom* set B		279 pairs *rac-hom* set A	
density[b]			all data	Δ > 1%
same density			17%	
rac more dense			54%	41%
hom more dense			29%	22%
lattice energy	all data	Δ > 2 kJ mol^{-1}	all data	Δ > 2 kJ mol^{-1}
rac more stable	69%	54%	57	49
hom more stable	31%	24%	43	34
Etot, lattice+intram. energy	all data	Δ > 2 kJ mol^{-1}		
rac more stable	70%	59%		
hom more stable	30%	24%		
more dense (>1%) and	rac	33%		
more stable (>2 kJ mol^{-1})	hom	11%		

[a] See graphic form of the distributions in Figures 2–4. [b] Bins of 1% have been prepared so that $\Delta d = x$ has all data within $x - 0.5$ and $x + 0.5\%$, so, e.g., "same density" means $-0.5 < \Delta d < +0.5\%$.

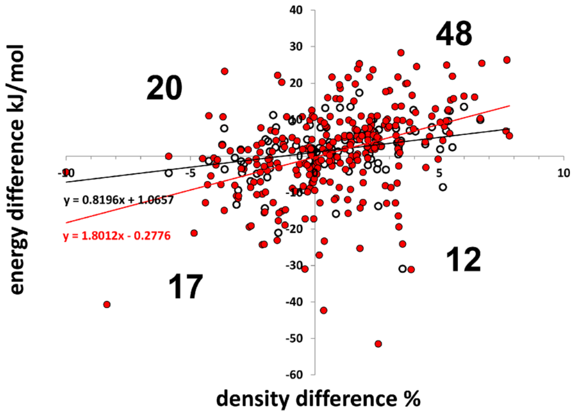


Figure 4. Black circles: *rac*—*hom* lattice energy difference versus percent density difference for the 97 pairs in the B data set (accurate PIXEL lattice energies). The large numbers are the populations of the four quadrants: 48 for *rac* more dense and more stable, 17 *rac* less dense and less stable, only 12 cases *rac* more dense and less stable. The small dots are for the 279 pairs in the *rac*—*hom*-A data set (atom—atom, less accurate lattice energies).

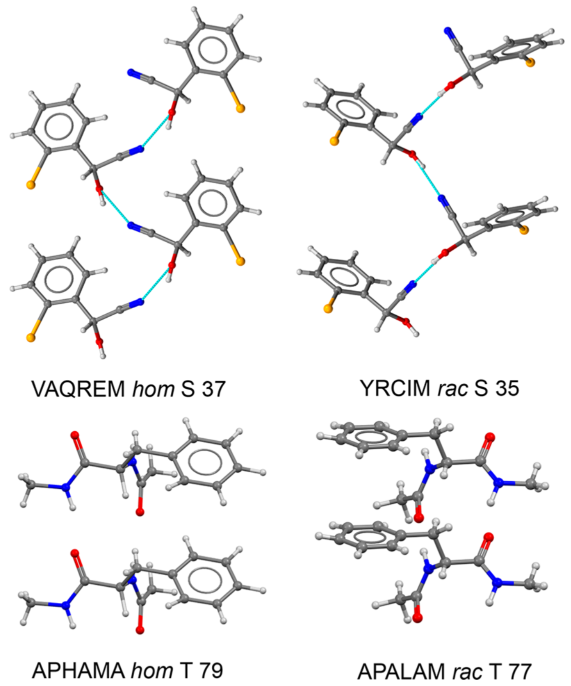


Figure 5. Top determinants in *hom* (left) and *rac* (right) pairs: examples of same energy and same operator: T, translation; S, screw axis. Numbers are pairing energies in kJ mol^{-1}. APHAMA, APALAM;[18] VAQREM, YIRCIM.[19]

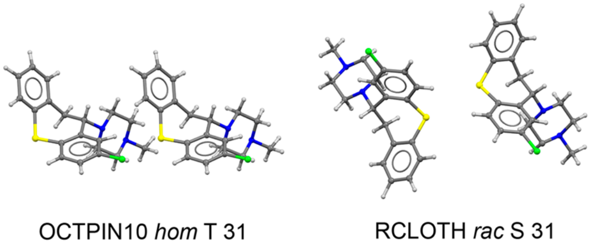


Figure 6. Crystal pairs[20] with top determinant of same energy but different operator: T, translation; S, screw axis.

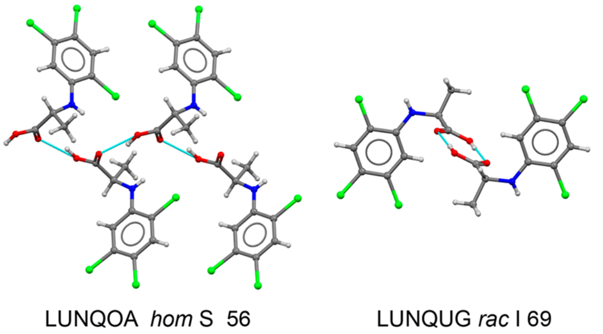


Figure 7. Crystal pairs[21] with top determinant with cyclic H-bonded dimer vs catemer.

stability with closer packing, but again (compare with Figure 1), one can hardly speak of a real correlation between energy and density differences. Of the other possibilities, less dense/less stable is rare, and compensation takes another third of the cases. Remarkably Figure S9, Supporting Information, shows that there are very few serious discrepancies in ΔE's between the atom—atom inexpensive method and the PIXEL method. The less accurate method magnifies the absolute value of the differences, but the changes of sign are relatively rare. Figure S10, Supporting Information, shows the scatter-plot for differences in intramolecular energy and differences in lattice energy for the *rac*—*hom-B* database. The quadrant where racemic crystals are more stable on both counts is the most populated, comprising, however, just some 50% of the data. The quadrant for racemic less stable on both counts is almost empty.

First- vs Second-Order Symmetry Pairing. The alternative to a thermodynamic argument invoking relative stabilities in favor of racemic crystals is a kinetic argument: Is primary molecular association somehow faster and/or more persistent for a pair of enantiomers that are related by second-order symmetry operators than for a pair of homochiral molecules?

Ideally, a computational answer to this question would require a dynamic simulation of supersaturated solutions, since the effects of transport, diffusion, solute—solvent interaction, and even mechanical treatment[16] are important or may be even decisive. For a preliminary analysis, again based on extant structures, that is, the final outcome of the process, a simple but revealing indicator is the nature of the top structure determinant in the crystal, that is, the symmetry operator and pairing energy of the most stabilizing first-neighbor molecular couple in each crystal structure. This is estimated by calculating all molecule—molecule cohesive energies in the crystal by PIXEL and ranking them in order of importance.[17] One sees a wide variety of pictures: some *rac*—*hom* pairs have nearly identical top determinants (Figure 5), with nearly identical energy; others (Figure 6) identical energies with different operators. A common occurrence (Figure 7) is the cyclic hydrogen-bonded pair in the racemic crystal over a center of symmetry, against the catemer ribbon in the homochiral crystal, along a screw axis. In such cases, the single hydrogen bond in the screw-related pair provides about one-half of the coupling energy of the cyclic dimer. In one exotic example (Figure 8), the molecules form associations with nearly identical structures using a 3-fold screw axis or a center of symmetry—operators that could not be more different. Note that in Figures 5 and 6 the top determinant in the *rac* crystal is not over a second-order

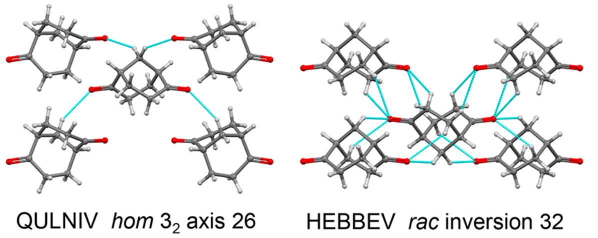


Figure 8. Crystal structures[22] with top determinants of same energy and same structure but quite different symmetry operators.

symmetry operation. Figure S11 (Supporting Information) shows some more examples.

The structures in Figures 5−8 and Figure S11 (Supporting Information) are spot checks but are representative of the wide variety of possibilities. The top determinant in *rac* crystals is second-order in about 60% of the cases, suggesting that chirality-inverting symmetry has no exclusive advantage over chirality-preserving symmetry in fostering stability in the final crystalline structure.

Racemic vs Homochiral Crystals and Liquids: Case Studies. The structure and properties of the respective liquid precursor states could be another source of thermodynamic or kinetic imbalance between racemic and homochiral systems. To probe this hypothesis, Monte Carlo simulations were carried out on liquid droplets, homochiral (that is, composed of 100% of one enantiomer) or racemic (50% of each enantiomer).[23] The simulation uses the approximate atom−atom potential energy field to calculate equilibrium cohesive energies, equilibrium densities, and internal structure of the phases. The latter is here represented by the radial distribution functions of the centers of mass, that is, a plot of the number of molecule−molecule distances present, as a function of distance, split into contributions from homochiral pairs and from pairs made of opposite enantiomers.

Numerical results are collected in Table S4 (Supporting Information), and the main points can be summarized as follows. For compound **1** (Chart 1), bicyclo[3.3.0]octa-3,7-diene-2,6-dione,[24] the cohesive energies and densities of the *hom* and *rac* liquids are identical, but in the racemic liquid there is a minor predominance of dimers made of pairs of opposite enantiomers (Figure 9a). For compound **2**, malic acid,[25] the cohesive energy and density of the racemic and resolved liquids are very similar, the homochiral liquid being actually slightly more cohesive and more dense (by 1−2%, that is, within the uncertainty limits of the method). The analysis of the internal structure of the racemic liquid reveals that the coupling of opposite enantiomers is predominant (Figure 9b). There is thus a drive to pairing of opposite chirality in racemic liquids, stronger with stronger intermolecular forces. *hom*-**1** crystals come from asymmetric synthesis, and *hom*-**2** crystals are available in nature.

A further example of the complexity of the issue is provided by the two (hydroxymethyl)-2-oxazolidinones **3** and **4**. Compound **3** is reported to be a spontaneously formed conglomerate of homochiral crystals, while its constitutional isomer **4** forms racemic crystals.[26] The explanation of this very puzzling fact seems beyond the capabilities of our analysis: crystals and liquids of both isomers have the same cohesive energies within our uncertainty limits (Table S4, Supporting Information), and coupling of opposite enantiomers predominates in the liquid also for the isomer forming a conglomerate under spontaneous resolution (Figure S12, Supporting Information).

Within the limits of our simulation methods, such results show that condensation of racemic liquids is not energetically favored over condensation of enantiopure liquids and strongly suggest that once a racemic liquid or micelle is formed, the association of pairs of opposite enantiomers is more frequent than the association of pairs of same enantiomers, so that the demixing of separate enantiomers becomes more and more unlikely as the intermolecular binding forces become stronger.

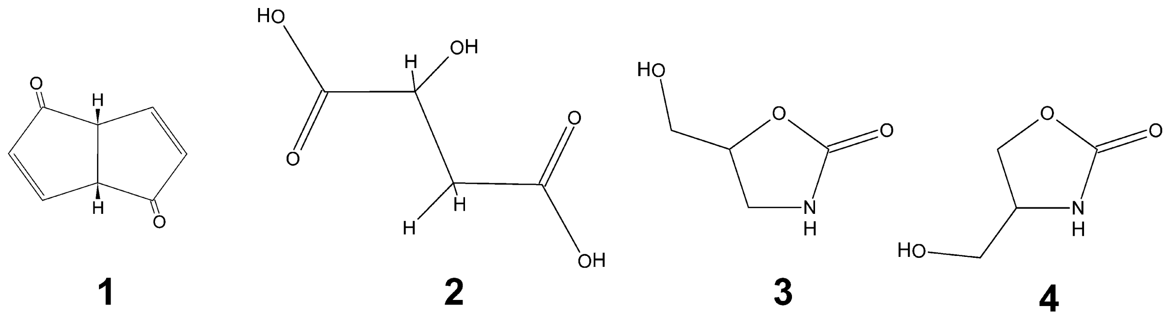
■ CONCLUSION

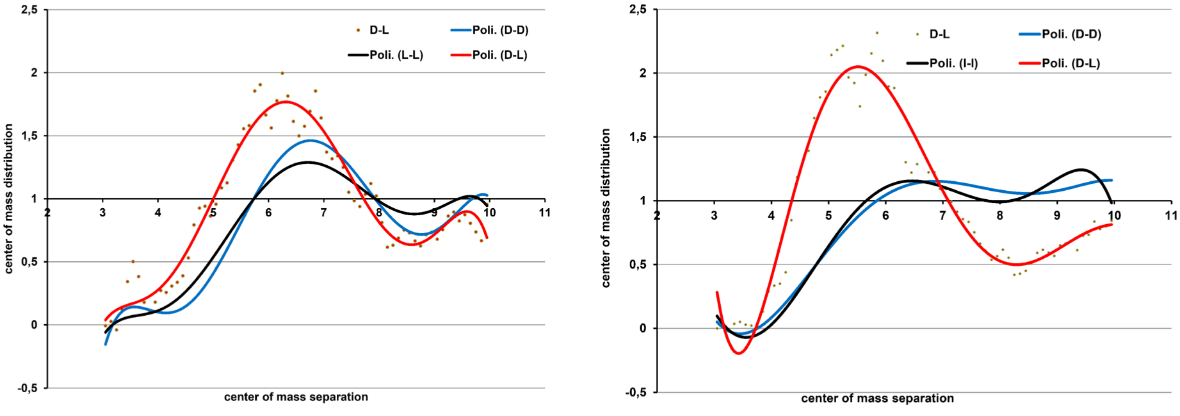
(1) Density differences between pairs of crystals of diastereoisomers, or pairs of racemic and homochiral crystals, or even of constitutional isomers, very seldom exceed 5% and never exceed 8%. This finding is consistent with what is found for crystal polymorphs. In organic molecules conformational flexibility is often high, and the intermolecular potential of organic molecules is very versatile. Therefore, an organic molecule of a given chemical composition can always find ways of reaching a limiting ratio of occupied to free space in the crystal or that organic crystals can easily survive small variations of this ratio, so that small density differences can hardly be seen as proof of relative stabilities. Thus, crystal density is mainly determined by chemical composition and intramolecular structure, and only to a minor extent by the structural features of the crystalline assembly.

Seeing the matter from the other side, for all kinds of isomers crystallization occurs only if density reaches a prescribed value, with a tolerance of ±5%. A theory or even just a method to predict this threshold density would be very useful, but it is not presently available.

(2) Racemic crystals tend to be denser than their homochiral partners, in terms of relative populations (Figure 2). The distribution goes from 50−50 to 2:1, depending on how the

Chart 1





a)

b)

Figure 9. Radial distribution functions of the centers of mass in the racemic liquids of (a) dihydropentalene dione, 1, and (b) malic acid. D−L coupling, red lines, is slightly more frequent for 1 and largely more frequent for 2.

result in Table 2 is interpreted. In any case, our results do not supporting the "common wisdom" rule according to which racemic crystals must be systematically denser than homochiral crystals.

(3) Denser crystals are also more stable in most cases, roughly by a 2:1 ratio, but without any valid statistical correlation (see the scatterplots in Figures 1 and 4). In fact, *rac* crystals are more dense and more stable only in 33% of the pairs. This result shows that racemic crystals are not systematically more stable than their homochiral counterparts. Of course, all energy-dependent conclusions are as reliable as the method for the energy calculations. The noise level of our methods is of the order of 2−3 kJ mol^{-1}, either from the intrinsic accuracy of the computations or from the random variances in structural data. It is, however, to be hoped (or trusted) that the importance of any systematic errors in the energy calculations may be less dramatic when considering energy differences between very similar systems. In this respect, it is encouraging that the same conclusions may be reached by two computational methods of different accuracy level, atom−atom and PIXEL.

(4) A kinetic argument in favor of the *rac* structure might surmise that the preference arises from longer persistency and/or faster propagation of the primitive cohesive motifs in determining the eventual growth of the racemic crystal. This argument seems plausible in the case of catemer vs cyclic dimer aggregation, Figure 7, when comparing the growth along a single-bonded string against growth in doubly bonded dimers, but seems much more problematic when the main drive is to stacking in both phases, as, e.g., in Figure 5a. A detailed study of the correlation between these elementary structures and the ease of spontaneous resolution is indeed very trying, but there is little doubt that a molecular level understanding of this phenomenon cannot dispense with energy calculations of the kind described in this paper. The complexity of the problem makes so that qualitative views based on the identification of special contacts or synthons[27] have no chances of being of any assistance.

(5) Our general results demonstrate that the energetic advantage of racemic crystal structures is not pervasive, neither in total crystal energies nor in the association energies of predominant molecular pairs in the crystal. Therefore, the thermodynamics of the final crystal products cannot alone explain the large preference for racemic crystallization from racemic solutions.

(6) Even admitting that racemic crystals may have a minor energetic advantage, as seems to be implied by some of our results in Table 2, it is difficult to imagine how this difference in a property of the macroscopic crystal could be effective in preventing the concomitant formation of homochiral crystal nuclei, unless these nuclei already have a prominent crystalline character. Recent views[28] on crystal formation invoke a two-step mechanism by which molecules first condense into liquid-like aggregates and then evolve into a crystalline embryo. Molecular dynamics simulation confirms the two-step mechanism for $CaCO_3$[29] and for larger organic molecules.[30]

(7) Our simulations strongly suggest that *hom* and *rac* liquids are isoenergetic. The explanation of the predominance of *rac* crystallization cannot go through a thermodynamic (stability) argument concerning the liquid precursors. Moreover, as soon as primary condensed micelles of 50:50 enantiomeric composition are formed, our results demonstrate that within these liquid-like entities there is a significant preference for coupling of opposite enantiomers, perhaps just because of higher encounter frequency.

(8) We are thus led to formulate the hypothesis that the key event in the preference for racemic crystallization is of a statistical nature. In a homogeneous, 50:50 racemic, supersaturated solution, and in the assumption of ideally homogeneous nucleation, segregation of micelles made of a single enantiomer in the diffusive regime of a liquid state where molecules travel distances of 10−20 Å in times of the order of nanoseconds would be highly unlikely for kinetic reasons. Otherwise, in terms of entropy, such a segregation would require a sort of Maxwell's demon to overcome the constraints of the Second Principle. So the theory of two-step nucleation mechanism and the experiment of relative rarity of racemic crystallization complement and support each other.

(9) Nevertheless, spontaneous resolution, or spontaneous ripening of enantiomeric excess, does occur in a small but not negligible number of cases. In view of the points made previously in this discussion, a legitimate hypothesis is that such occurrences must require some deviation from ideal homogeneous conditions, possibly in terms of a hidden imbalance in the distribution of enantiomers, or because of the unknown presence of some kind of chiral steering entity. Such seeding

boundary conditions are usually predetermined in "guided" enrichment of homochiral crystals.[2]

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Appendix A, Tables S1−S4, and Figures S1−S11. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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