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Reevaluating the Stability and Prevalence of Conglomerates: Implications for Preferential Crystallization

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Abstract

Chiral resolution by preferential crystallization from a racemic or scalemic solution occurs by selective crystallization of a single enantiomer as a homochiral solid phase, known as a conglomerate. However, there is a prevailing perception that stable homochiral crystals are quite rare and are estimated to form in only 5–10% of all chiral compounds. In this work, the prevalence rate of stable conglomerates is reexamined using dispersion-corrected density-functional theory calculations for a collection of homochiral and heterochiral crystal pairs. The homochiral crystal is found to be the thermodynamically stable phase for 19% of the examined compounds. This value represents a lower bound of the prevalence rate since our sample is necessarily biased because the comparison is limited to cases where a stable heterochiral phase exists and does not include molecules with no reported heterochiral phase. Even so, this lower bound is two to four times higher than the often-quoted conglomerate prevalence rate, a value that is also based on (experimental) thermodynamic quantities. In addition,

our results are used to reexamine Wallach’s rule and the close-packing principle. It is concluded that the prevalence of stable conglomerates has been underestimated and, provided thermodynamic equilibrium drives the crystallization process, preferential crystallization has a much wider scope of applicability than previously assumed.

Introduction

Preferential crystallization offers one of the most scalable and attractive methods for production of chiral fine chemicals in enantiopure form.^{1–3} Due to the high degree of reproducibility once the process is vetted and also to its potential for high mass throughput in production, preferential crystallization remains the method of choice for the resolution of racemic mixtures on the industrial scale. A critical requirement to the application of a preferential crystallization campaign is the ability of the racemic mixture to crystallize in a phase composed of two homochiral enantiopure crystals (a conglomerate) rather than as a 1:1 heterochiral co-crystal of the two enantiomers (a racemate). Molecules that do not form stable conglomerates can not be resolved effectively by classical preferential crystallization.

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It is widely believed that compounds with a stable conglomerate phase are rare, with an often-quoted estimate of 5–10% of molecules forming stable conglomerates.^{4,5} Due to the perceived rarity of conglomerate-forming crystalline samples, preferential crystallization is not usually considered as a means of obtaining enantiopure material until the latter phases of process development, rather than at the outset of research.

The high prevalence rate of heterochiral crystals has been justified in the past using Wallach’s rule,⁶ which states that heterochiral crystals pack more densely than their homochiral counterparts, coupled with an assumed correlation between density and stability.^{7,8} However, previous investigations of the validity of Wallach’s rule found mixed results,^{4,8–14} and the claim that density and stability are directly related has also come under scrutiny in the literature.^{8,14,15} In this work, the validity of Wallach’s rule and the relationship between density and stability are re-examined.

The estimate of the conglomerate prevalence rate originates from Jacques et al.’s seminal monograph,⁴ where the fusion temperatures of 1308 compounds reported in the Beilstein handbook were examined. A subset of 126 of these compounds, for which the fusion temperature of the enantiopure crystal is 20°C higher than the heterochiral form, were selected as likely forming stable conglomerates. From this subset, 32 compounds were prepared and 21 of these were found to crystallize as conglomerates, leading to the conclusion that the frequency of conglomerates is in the range of 5–10%. As expressed by the authors,⁴ this is a very qualitative estimate, and is also at odds with our personal (unsystematic) experience regarding the crystallization of racemic mixtures. It is also interesting to note that Jacques et al. did observe that the frequency of conglomerate formation was higher (2–3 times greater) for organic salts. It is unclear whether this discrepancy suggests a differential probability of conglomerate formation for ionic crystals or is simply due to a biased set of structures. The key question is whether this estimate reflects the average frequency of stable conglomerates for all chemical

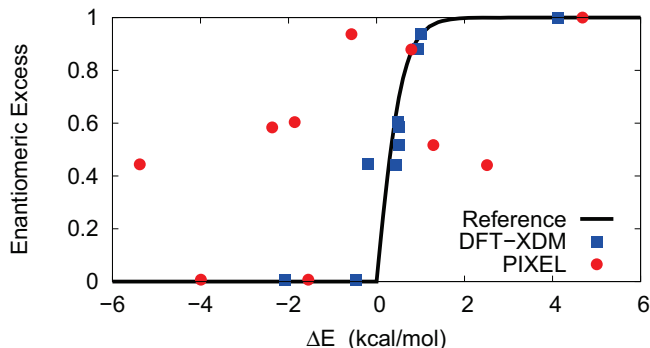
space.

Thermodynamics is not the only factor controlling crystallization. Kinetic effects, as well as the potential formation of twinned crystals, solvates, and competing polymorphs, also play very important roles^{1,5,16} and complicate first-principles prediction of the resulting crystal phase. However, the presence of a thermodynamically more stable heterochiral crystal phase usually precludes any attempt to develop a chiral resolution by crystallization. Thus, the existence of a stable enantiopure phase is a necessary (but not sufficient) condition for the application of a preferential crystallization strategy.

The aim of the present work is to examine the prevalence rate of chiral compounds forming thermodynamically-stable conglomerates using modern computational techniques. The prevalence rate is calculated by comparing the computed lattice energies for a set of homochiral/heterochiral crystal pairs obtained from the Cambridge Structural Database (CSD).²² This sample set is necessarily biased in detriment of stable conglomerates,⁸ which is a limitation of our study. The bias occurs because only crystals for which the heterochiral form can be crystallized with enough quality to undergo single-crystal diffraction are included in the data set; cases where only the homochiral form is stable enough to be isolated could not be considered. Hence, this allows us to estimate a lower limit to the general applicability of the preferential crystallization technique.

This study is made possible by the evolution of dispersion-corrected density-functional theory (DFT) methods to the point where they are able to reliably model intermolecular interactions in molecular crystals.^{17–19} The relative stabilities of the homochiral and heterochiral crystal phases can be experimentally determined from measurements of the enantiomeric excess (e.e.) of a solution in contact with both crystal forms. In addition, the solution-phase e.e. at the eutectic is strictly under thermodynamic control. Hence, this quantity is a sensitive and pertinent benchmark for the prediction of differences in molecular crystal lattice energies using computational techniques.²⁰ Figure 1

Figure 1: Dependence of the enantiomeric excess (e.e.) at the chiral eutectic point²⁰ on the relative energy difference (ΔE in kcal/mol per molecule) between the homochiral and heterochiral crystal forms. The black line shows the result from our previously proposed thermodynamic model,²⁰ while the points correspond to experimental e.e. measurements as a function of either DFT-XDM (blue) or PIXEL⁹ (red) energies.



shows that e.e. predictions from dispersion-corrected DFT are in good agreement with the experimental measurements, yielding an average error of 10%.

In comparison, the e.e. calculated using force-field-like methods in the literature, like PIXEL,²¹ are clearly unreliable. PIXEL has been the method of choice in previous studies of relative homochiral and heterochiral crystal stabilities and of the validity of Wallach’s rule.^{9,14,15} Figure 1 suggests that these analyses could benefit from reexamination with a method capable of higher accuracy, like dispersion-corrected DFT.

In this article we show, based on dispersion-corrected DFT results, that stable homochiral phases are more common than previously assumed. The predicted lower bound to prevalence rate of stable conglomerates from DFT calculations is 19%, which is significantly higher than the often-quoted but qualitative 5 to 10% estimate.⁴ This leads to the conclusion that the utility of preferential crystallization for isolating enantiopure chiral compounds should be much more broad than previously assumed.

Methods

A search of the CSD²² was performed for all homochiral and heterochiral crystal pairs. Database entries with disorder, low quality data, or only powder diffraction measurements were disregarded. The reported unit-cell volumes of these crystals were used to count the number of cases in which the heterochiral form is more dense.

Density-functional calculations were performed to determine the relative densities and stabilities for a subset of the homochiral and heterochiral crystal pairs. This subset of crystals was chosen to include the same amino acids as in our previous study of chiral equilibrium using dispersion-corrected DFT.²⁰ Also included were pairs of crystals from both the study of Brock *et al.*,⁸ and from our database search, with unit-cell volumes of less than 1200\AA^3 and without transition-metal atoms. Structures in which the hydrogen atomic positions were ill-defined were omitted. The CSD refcodes for the crystals used in this study can be found in the Supporting Information (SI).

For all crystals, unit cell geometries and atomic positions were optimized using version 5 of the Quantum ESPRESSO program²³ with the projector augmented wave (PAW) method²⁴ and the plane-waves/pseudopotentials approach. The cut-off energy was 60 Ry and a $4 \times 4 \times 4$ \mathbf{k} -point grid was used in all cases. Calculations used the B86bPBE functional^{25,26} with the exchange-hole dipole moment (XDM) dispersion correction,^{27–29} as in our previous work.²⁰ XDM is a post-SCF correction, added to the energy from the base density functional. The dispersion energy is evaluated as a sum over all atomic pairs and includes the terms dependent on the C_6 , C_8 , and C_{10} dispersion coefficients. The values of the two parameters in the XDM damping function³⁰ were set to $a_1 = 0.6512$ and $a_2 = 1.4633$.

As in previous works,^{9,20} it is assumed that the difference in free energies will be determined solely by the electronic energies and that the thermal contributions are negligible.¹⁵ This assumption was validated by our work on the

amino acids mentioned above.²⁰ Additionally, a more recent, comprehensive study by Nyman and Day³¹ on 1061 crystals showed that thermal effects typically alter the order of polymorph stability for only about 9% of the compounds considered.

Results and Discussion

Is Wallach’s rule obeyed?

The calculated equilibrium volumes, lattice energies, and the dispersion contributions to the latter can be found in the SI. For the compounds considered in the present study, Table 1 presents the number of instances for which the heterochiral crystal is denser than the enantiopure form. Results are shown for all the structures found in our CSD search (“large” set), and for the subset for which we ran the DFT relaxations (“small” set), using both the experimental crystal volumes (“CSD”) and the calculated minimum-energy volumes (“DFT”). In the latter, thermal effects and experimental uncertainties are not present.

Our results show that the percentage of denser enantiomers for the large set of 724 crystal pairs and the small subset of 95 compounds used for the subsequent DFT calculations are in good agreement, suggesting the set of crystals used in the DFT calculations is representative. Heterochiral crystals are denser than their enantiopure counterparts in 65% of the cases considered when DFT geometry relaxation is employed. This fraction is somewhat higher than that obtained using the experimental volumes (57–58%), probably because of the mentioned thermal effects and experimental uncertainties. The present calculations confirm the results of Dunitz *et al.*⁸ and of Gavezzotti and Rizzato,¹⁴ (which were obtained using the less-accurate PIXEL method). We stress the conclusion that Wallach’s rule is not a good predictor of the entire population of chiral crystalline compounds, and there are many exceptions where the homochiral form is very much more dense.

Table 1: The total numbers of crystals in our “large” (all homochiral/heterochiral pairs from the CSD) and “small” (crystals subjected to DFT relaxation) sets. “Count” indicates the number of those pairs for which the heterochiral crystal is denser, and “percent” is the corresponding percentage. For the small set, the experimental (CSD) or calculated (DFT) volumes were used.

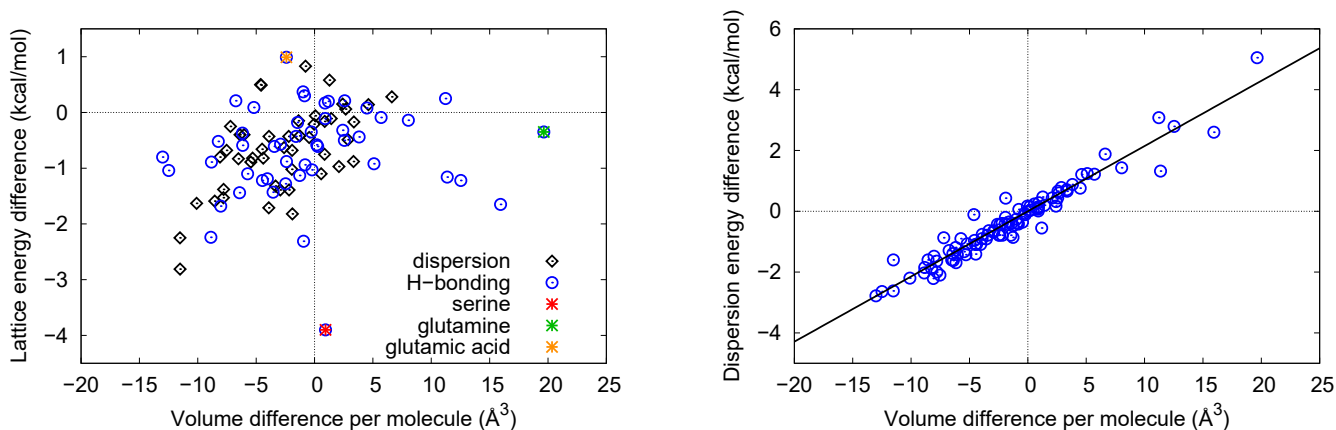
Data set	Source	Total	Count	Percent
Large	CSD	724	410	57
Small	CSD	95	55	58
Small	DFT	95	62	65

What is the relationship between energy and density?

Another long-standing question in the crystallographic literature is whether there is a correlation between packing density and stability in molecular crystals.^{7,9,14,15} Two similar studies have been conducted by Gavezzotti and co-workers,^{9,14} in which the relative energies of sets of homochiral and heterochiral crystal pairs were computed using the PIXEL force field.²¹ These works found either a weak¹⁴ or negative⁹ correlation between density and stability, contradicting the principle of close packing.⁷ For the case of the amino acids, the authors made analogy⁹ to the structure of ice, where co-operative hydrogen bonding leads to greater stability of less dense phases.

Plots of the DFT energy difference between heterochiral and homochiral crystals against volume differences are shown in Figure 2. Negative values indicate that the heterochiral crystal is more dense (x-axis) or more stable (y-axis), while positive values indicate that the homochiral form is more dense (x-axis) or more stable (y-axis). Our results show that there is a very small correlation between volume differences and lattice energy differences for the pairs considered, with a slope of 0.06384 (kcal/mol) \AA^{-3} and a correlation coefficient of $r = 0.3649$. This result agrees with the studies of Brock *et al.*⁸ and of Gavezzotti and Rizzato,¹⁴ although it contradicts the observation of a negative correlation by Dunitz and Gavezzotti.⁹ The dis-

Figure 2: Calculated lattice energy differences (left) and dispersion contribution to the lattice energy differences (right) against volume differences in the considered homochiral/heterochiral pairs. All energies and volumes are reported per molecule. In the dispersion contribution plot, the molecules are divided into two classes depending on the percentage of the lattice energy due to dispersion binding (more or less than 80% of the total lattice energy).



agreement with the latter can also be explained by the plots in Figure 2, since all the major outliers are amino acids, which were the only crystals considered in that work. This behaviour is likely specific to the exceptionally strong hydrogen bonds between the NH_3^+ and COO^- moieties present in these crystals.⁹

The results of our DFT calculations can also be used to offer insight into the reasons for the lack of correlation between density and stability. Three outliers—the amino acids serine, glutamine, and glutamic acid—stand out for having density and lattice energy differences of opposite signs, and far from the trend line. The calculated electron densities in these crystals can be used to examine the intermolecular interactions by means of the NCI plot technique^{30,32,33} and these results are included in the Supporting Information. In all three cases, the homochiral and heterochiral crystals have very different packing and hydrogen-bonding arrangements and the hydrogen bonds in the less-dense form are stronger, accounting for their greater stabilities.

Figure 2 also shows that the differences in dispersion stabilization between homochiral and heterochiral crystals correlate strongly with the differences in density, as observed before for the amino acid crystals.⁹ This is reasonable, since dispersion stabilization arises from close intermolecular contacts (i.e. dense packing) regard-

less of the identity and orientation of the particular moieties involved. The slope between the two differences is $0.2144 \text{ (kcal/mol)\AA}^{-3}$, with a correlation coefficient of $r = 0.9690$. However, the dispersion energy is only one contribution to the total lattice energy and directional interactions, such as hydrogen bonding, spoil the correlation between volume and total lattice energy differences.

Even in crystals where no hydrogen bonds are present and the dispersion contribution to the lattice energies is dominant (greater than 80%, black points in Figure 2), there is only a weak correlation between the total lattice energy and the volume differences. In this subset, the slope is $0.1428 \text{ (kcal/mol)\AA}^{-3}$, with a correlation coefficient of $r = 0.7194$. In consequence, it is not generally true that the denser crystal of a given homochiral/heterochiral pair is more stable, particularly if dispersion is not the dominant binding effect.

Prevalence of conglomerates

Finally, we examine the stability of the homochiral phase based on our calculated lattice energies. In our set, the heterochiral form is more stable than the homochiral form for 77 out of the 95 crystals (81%), as can be seen in Figure 2 (the lines above the x-axis) or in the SI. For comparison, an analogous study of

97 crystal pairs using the PIXEL force field found that the heterochiral form was more stable for 69% compounds considered.¹⁴ Based on the DFT results, 19% of chiral compounds form a stable conglomerate, and are therefore good candidates for preferential crystallization. This prevalence rate of stable conglomerates is from two to four times higher than the habitually-quoted value of 5-10%,⁴ and both are based on thermodynamic grounds.

In addition, as noted previously by Brock *et al.*⁸ any sample set of homochiral/heterochiral pairs taken from a crystallographic database is necessarily biased, since it includes only those cases where both the homochiral and heterochiral forms have been crystallized successfully. The homochiral crystal can, in principle, be crystallized from an enantiomerically pure solution. The heterochiral crystal however, has to be obtained from a racemic solution and, if the molecule shows strong preference towards conglomerates, the heterochiral structure would be inaccessible. The bias favouring heterochiral forms is reflected by our calculations, as evidenced in Figure 2. When the homochiral form is more stable, it is only slightly lower in energy than the heterochiral crystal. Therefore, we conclude that the fraction of compounds that show an energetic preference for homochiral crystals should actually be significantly larger than our 19% value. On thermodynamic grounds, conglomerates should be more common than implied by that value, and certainly more common than the widely accepted 5–10% figure.

Summary and Outlook

In this work, we reexamine the notion, common in the literature, that chiral molecules for which the homochiral crystal is more stable than the heterochiral form are rare. Dispersion-corrected DFT calculations were performed for a set of 95 homochiral and heterochiral crystal pairs from crystallographic databases to determine their relative energies and volumes. The often quoted 5 to 10% prevalence rate of conglomerates, which is also based on thermody-

amic data, is shown to be underestimated since there is only a weak energetic preference for heterochiral crystals. Our predicted value for the prevalence rate of stable conglomerates is two to four times higher (19%), and is likely to be significantly underestimated since our set is inherently biased towards cases where the heterochiral crystal is more stable and can be experimentally obtained with sufficient quality to undergo single-crystal diffraction.

In addition, using our calculated densities and lattice energies, we examined two other common arguments in the crystallographic literature: a direct correlation between density and stability, and Wallach’s rule. Although we found that dispersion contributions to the lattice energy correlate strongly with crystal density, the total lattice energies did not. Even when considering the subset of crystals whose binding is dominated by dispersion, the correlation between lattice energy and density is very modest. Regarding Wallach’s rule, we confirm previous conclusions^{8,14} that the widely-held opinion that heterochiral crystals are more dense than their homochiral counterparts is not generally valid.

Our findings have implications regarding the applicability of preferential crystallization for the resolution of scalemic mixtures. In particular, molecules that form stable conglomerates can be potentially separated by preferential crystallization, while heterochiral crystals cannot. Our results show that preferential crystallization methods should be much more widely applicable than previously assumed.

Finally, our calculations do not address the prevalence of stable conglomerates in compounds belonging to a particular family. The question of whether there are trends in the relative stabilities of the homochiral and heterochiral phases for different compound classes, such as organic salts,⁴ would be an interesting topic for future work.

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Supporting Information Available: Crystallographic data codes and predicted enantiomeric excess values for the chiral crystal pairs; the unit-cell volumes, total lattice energies, and the dispersion contributions for the homochiral and heterochiral crystals. Also shown are NCI plots for the homochiral and heterochiral forms of serine, glutamine, and glutamic acid. This material is available free of charge via the Internet at <http://pubs.acs.org/>.

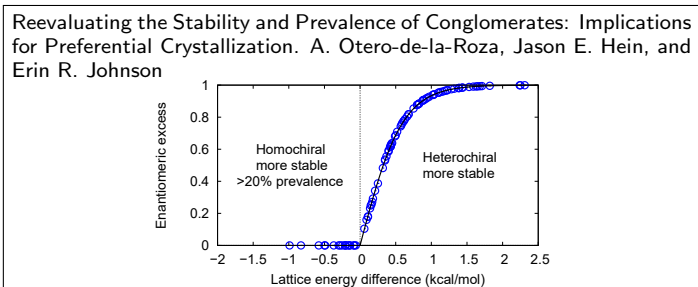
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Graphical TOC Entry

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