Kryptoracemic Compounds Hunting and Frequency in the Cambridge Structural Database

Simon Clevers, Gérard Coquerel

CrystEngComm

Accepted Manuscript

This article can be cited before page numbers have been issued, to do this please use: S. Clevers and G. Coquerel, *CrystEngComm*, 2020, DOI: 10.1039/D0CE00303D.

ROYAL SOCIETY OF CHEMISTRY

rsc.li/crystengcomm

View Article Online
DOI: 10.1039/D0CE00303D

ARTICLE

Kryptoracemic Compounds Hunting and Frequency in the Cambridge Structural Database

Received 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

Simon Clevers[a] and Gerard Coquerel[a]

Kryptoracemic compounds (KRCs) are a rare case of racemic pairs of antipodes crystallizing in Sohncke (chiral) space groups. In order to identify KRCs in the Cambridge Crystallographic Structural Database (CSD), a Python script named ChiPi was written to automatically assign the chirality of each crystal structure. The ChiPi code is able to compare each residue contained in a crystal structure based on the chiral centres that were identified and allows discrimination between enantiomeric, diastereomeric, racemic, meso and scalemic structures. It was used to process 393012 organic entries from the CSD corresponding to almost the entire set of organic crystal structures. It is estimated that racemic compounds constitute 23.8% and 22.2% of centrosymmetric and achiral non-centrosymmetric organic structures in the CSD, respectively. The KRCs represents 0.2% of the whole database and 0.8% of the chiral space groups. The KRC occurrence represents circa 1% (724 structures) of the set of racemic compounds. The distribution of the KRCs space groups is drastically shifted toward lower symmetry space groups with a large prevalence of $P2_1$ structures. This trend is not restricted to KRCs only but can be extended to structures containing chiral molecules with an even Z' number.

Introduction

After a crystallization of a racemic solution, three main cases of phase equilibria can exist between non-racemizable enantiomers in the solid state: (i) racemic compound systems (90-95% of the cases) where the crystal contains the two enantiomers in equal amount, (ii) conglomerate systems (*i.e.* a complete chiral discrimination in the solid state, 5-10% of the cases) where both enantiomers crystallize in separate enantiopure particles and (iii) solid solution (1-2%).[1-5] These possibilities for the crystallization of racemic mixtures from solution together with the space group frequencies of crystals obtained in each case are summarized in Table 1. In conglomerate systems, each enantiomer must necessarily crystallizes in one of the 65 non-centrosymmetric chiral space groups (hereafter Sohncke SG) that do not have any inversion symmetries (the presence of these symmetry elements will generate the opposite enantiomer in the crystal structure and are thus not compatible with a single enantiomer in every particle). The frequency of spontaneous resolution is difficult to estimate because, is most cases, there is no indication in the literature telling whether an enantiopure crystal represents a conglomerate or was crystallized from an enantiopure overall composition. There is no space group (SG) restriction for solid solution or racemic compounds. Three different cases are thus possible for the crystallization of a racemic compound and statistics reveal that the majority crystallizes in (i) centrosymmetric SG, (ii) in achiral non-centrosymmetric SG, (iii) in Sohncke SG. The last case is reported as "kryptoracemate" or "false conglomerate".[6,7] In this work we will use the term kryptoracemic compounds (KRCs). The number of independent molecules in the asymmetric unit *Z'* is greater than 1. In a KRC *stricto sensu*, Z' should take an even value (to respect the racemic composition). One can extend this definition to an odd number of Z': in this case, the composition necessarily deviates from the racemic to scalemic (*e.g.* 2 enantiomers S for 1 enantiomer R). These types of scalemic compounds were referred to as "unbalanced compounds" and seems to be much rarer than the purely racemic KRCs.[6]

KRCs are considered to be rare; Fábián & Brock determined a list (manually checked) of 181 KRCs in organic structures.[8] Recently, Grothe et al published a list of 409 probable KRCs (although the list was not verified).[9] Bernal & Watkins published a review covering metal–organic compounds with a stereogenic metal atom and determined a list of 26 possible KRCs.[10] The proportion was estimated at 0.2% of the organic Cambridge Structural Database (CSD). More recently, Rekis published a list of 313 KRCs in a study based on single-component crystal structures (0.8% of his racemic compounds subset).[5] For all these surveys, the authors always mentioned the difficulties in performing an exhaustive search for this class of compounds.

In order to detect KRCs from the CSD, a thorough analysis of crystal chirality must be performed over the whole database. As highlighted by previous studies[7,8,10], there is no efficient way for searching racemic crystal structures in the CSD. The main reason is that the CSD does not store information on the stereochemistry of the entries. The only information about the chirality of a component can be found in the name, if the "rac", RS, R or S labels is indicated. But this data cannot be reasonably used to try to assign the chirality of every entry. Attempts to classify the chirality of crystal structures were already performed.

[a]*Normandie Université, Laboratoire SMS-EA3233, Université de Rouen Normandie, F76821, Mont Saint Aignan, France*

Electronic Supplementary Information (ESI) available: ChiPi Python script, Tutorial to use Chipi, information about ChiPi procedure, Lists of KRC refcodes, results file of organic teaching subset. See DOI: 10.1039/x0xx00000x

View Article Online
DOI: 10.1039/D0CE00303D

Table 1 Formation of crystalline structures from racemic solution. [a] "unbalanced compounds" are not obtained from racemic solution because they deviate from the 50:50 (R:S) composition. Nevertheless, we include this very rare compounds in an extended definition of kryptoracemic compounds. [B] scalemic compounds are not allowed in centrosymmetric or in NC achiral SG but we refer here to scalemic AU (i.e. structure having odd Z'). [c] This study. [d] These values are strongly biased toward non-Sohncke SG because of the used detection method.

		Organic Crystal Structure database (100%)		
		Achiral SGs (75%)[c]		Chiral SGs (25%)[c]
		Centrosymmetric (85.5%)[c]	NC (15.5%)[c]	Sohncke SG (100%)
Racemic Compound (90-95%)[1]	Structure	Permitted	Permitted	Permitted (KRC)
	Frequency	92.75%[c]	6.25%[c]	1%[c]
	Top SG	$P2_1/c$, C2/c, Pbca, P-1	$Pna2_1$, $Pca2_1$, Cc	$P2_1$, $P2_12_12_1$
Conglomerate (5-10%)[1]	Structure	Forbidden	Forbidden	permitted
	Frequency	0%	0%	100%
	Top SG	/	/	$P2_12_12_1$, $P2_1$ C2, P1
Solid solution (1-2%)[d]	Structure	Permitted	Permitted	Permitted
	Frequency	81%[5]	7%[5]	12%[5]
	Top SG	$P2_1/c$, $P\bar{1}$ C2/c, Pbca	$Pna2_1$, Cc, $Pca2_1$	$P2_12_12_1$, $P2_1$, P1
Scalemic compounds (unbalanced crystallization)[a] <1%	Structure	Forbidden[b]	Forbidden[b]	Permitted
	Proportion	228 entries[c]	17 entries[c]	37 entries[c]
	Top SG	$P\bar{1}$, $P2_1/c$, C2/c	Cc, $Pna2_1$	$P2_12_12_1$, $P2_1$

In 2000, the CSD contained 77986 unique organic structures (64.5% were non-centrosymmetric and 35.5% were centrosymmetric). On these data, Dalhus *et al* selected 9817 structures assuming that the distribution was the same in the whole database and they manually determined the chirality for each structure. One can notice that this subset contained 7% crystal structure redeterminations (*i.e.* duplicates: crystal structures of a same compound but resolved several times). They estimated that the frequency of centrosymmetric racemates was 23% in centrosymmetric structures. Nowadays, the strategy employed by Dalhus *et al.* could hardly be applied. [11] The exponentially growing crystallographic data (more than 1 million crystal structures in CSD in 2020) necessitates the development of tools able to automatically assign the chirality of crystals. Probably the most complete statistical survey of organic crystals on stereoisomerism in the CSD was performed by Grothe *et al*. [9] They analyzed 254354 entries and their main conclusions are summarized in Table 2. Unfortunately, their compute code used is not freely available for the scientific community. To our knowledge the only software serving to perform batch assignment of chirality on a large number of structures and that is freely available is ChiralFinder develop by Eppel *et al.* ChiralFinder[12] can sort out a list of structures according to the chirality of crystals (achiral, meso, racemic, chiral). Nevertheless, this software required the export of the structures from *Conquest* and, unfortunately, large numbers of structures are not treated (circa 7%) especially when disorder is involved in the packing. The flexibility of the software is also limited because we cannot directly extract other crystal data as SG, R-factor, density, cell parameters, etc. that could be of relevance for a statistical survey.

The main motivation for this publication is to access the chirality of organic crystals in order to assess the frequency of racemic compounds (RC) and chiral crystals over different space groups in the Cambridge Structural Database. For that purpose, we developed a Python script named ChiPi and entirely based the script on CCDC Python API.[‡] The simplicity is that we only need a refcode list to start the determination of crystal chirality. The program could easily be modified to directly work in CSD subsets without exporting files from Conquest. The program is based on functions provided by CCDC API Python solution (v 2.3.0). All functions are use in standard mode without modifying standard parameters. The ChiPi source code is also freely available in the supplementary material (ChiPi.py).

Out of the 393012 entries analyzed, ChiPi found 191936 chiral residues for 160201 chiral chemicals representing 668152 assignment of chiral centers. The carbon atom represents 98.3% (657040 atoms) of these 668152 stereocenters. The number of R and S atoms are almost identical with 50.59% (337999 hits) and 49.41% (330153 hits), respectively. The proportion of chiral atoms having hydrogen atom has one of the four constituents represents 79.3% (530149 hits) of the stereogenic centers (80.7% of the chiral carbon atoms). The missing hydrogen atoms in the crystallographic data are thus of particular importance in the determination of the stereocenter chirality. It was estimated that 5.7% of crystal structures having at least one molecular residue showing one stereocenter with hydrogen atom as one the four substituents are concerned by this problem. It represents at most 9% of the stereocenters detected by ChiPi. In the following, we use ChiPi script to investigate the frequency of racemic compounds (RCs) in the CSD focusing our study on the detection of KRCs.

Determination of subsets

ConQuest 2.03(Build 257310) [13] was used to search the CSD 5.41 database. The refcode list of our subset was exported, as well as the coordinate files in *coord* and *gcd* format. The different subsets analyses were extracted from the CSD database in gcd file format, using Conquest with the following restrictions: 3D coordinates determined, no errors, not polymeric, only organics. Crystal structure determination from powder was

allowed. This represented 415167 entries. Each entry in the Cambridge Structural Database (CSD) is referenced by a refcode that is a series of 6 letters. With time, an entry in CSD can have several structure redetermination (duplicates) that are indicated by a number just after the refcode. These duplicates contain different data collections (at different temperature and/ or pressure or determined by different research groups). They also account for polymorphs of the same compound. The number of duplicates can create bias in a statistical survey although for most of the structures the number of redeterminations is non-existent, for certain compounds or series of compounds this number is not acceptable. For instance, the well-known glycine (GLYCIN) has 100 crystal structure redeterminations in the CSD (v5.41)! In addition, the CSD database keeps all structures even those that have been "Marshed"[14-24] and that could create a statistical bias in particular for the account of polymorphism because a Marshed structure often coincided with a space group change. In this work, duplicates structures were filtered keeping those with the lowest R-factor and with different space group settings and Z' values. However, this method could remove from this dataset polymorphs having the same space group and Z'. Furthermore, our dataset was split in non-disordered (ND) and disordered (D) structures and the above procedure will keep duplicated structures if a molecule possesses structure in both subsets. Out of the 415167 structures, 22155 duplicates (5.3% of the CSD) were found. For instance, the number of duplicates was reduced to 7 for glycine. The distribution of duplicates in different subsets is summarized in the supplementary information (SI-1). This distribution is relatively homogeneous in the whole CSD and, interestingly, one can notice that it does not change the statistics of distribution of the different subsets after filtering. This means that the number of redeterminations in each subset is proportionally similar.

Determination of the crystal chirality by ChiPi

The ChiPi code was written in Python 2.7.15 with the version 2.3 of the CCDC Python API. ChiPi can analyze each crystal structure and class them in the following subsets: (a) Achiral if the structure does not any contain chiral molecules; (b) Chiral if the structure contains chiral molecules in enantiopure amount (it must crystallize in Sohncke SG); (c) Racemic if the structure contains enantiomers in racemic amounts; (d) Meso if the structure contains non-optically active stereoisomers, it means that the molecule is not chiral (despite containing an even number of stereogenic centers); (e) Diast if the structure contains at least a couple of diastereomers, (f) Scalemic if the structure contains enantiomers in scalemic proportion, (g) KRC if the structure contains enantiomers in racemic proportion and crystallized in Sohncke SG. Explanations of the general procedure used by ChiPi to determine the chirality of each crystal is available in the supplementary materials (SI-3 with an example in the SI-5) as well as results obtained for the organic teaching subset of the CSD (Teaching_results.xlsx). If a problem occurs during this determination, the structure is discarded. Generally, circa 3% (10165) of the structures were removed from the dataset because of (i) a problem during the assignment of bond types and/or missing hydrogen atoms (7126 structures) and (ii) the presence of "mixed chiral" atoms (3039 structures). Two different notions must not be confused in the following: (i) the chirality of asymmetric unit (AU) that represents the relation between the molecules in the AU and (ii) the chirality of the structure that represents the relation between molecules in the unit cell. For instance, a centrosymmetric crystal can be racemic with a chiral AU that contains two molecules of the same enantiomer (Z'=2).

Comparison with other programs and estimation of the errors

ChiPi results were essentially compared to examples given by Grothe *et al.* and to results obtained with the program Chiralfinder develop by Eppel *et al*. As mentioned by Grothe *et al.* most of the programs have problems determining the chirality of the asymmetric center in molecules with interconnected rings. Their program detects, for instance, five chiral centers in the CSD entry GIGSOE while only one is detected by *Mercury* (Figure 1a) or by PLATON[25]. Nevertheless, the reason does not lie on a problem of calculation but more on the quality of the crystallographic data. Indeed, checking "3D coordinates determined" in Conquest, does not ensure the completeness of the crystal structure. In most of cases, the hydrogen atoms are missing. Therefore, *Mercury*[26] does not correctly access the chirality of the molecule because the carbon atom is only connected to three neighbors. Hopefully, the "auto edit structure" capability provided by *Mercury* can assigned "unknown" bond types and missing hydrogen atoms. After completion of the structure, both (PLATON and *Mercury*) are able to correctly detect and assign atom chirality for this structure (see Figure 1b).

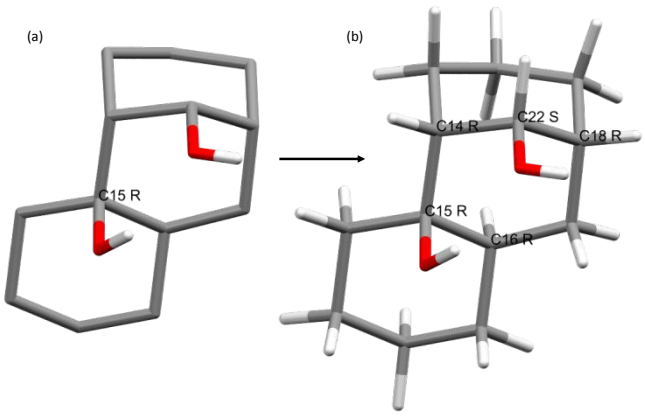


Figure 1 Molecule in GIGSOE before "auto-edit structure" feature of Mercury where only 1 chiral atom is detected (a) and after the edition (symbolized by black arrow) where 5 chiral atoms are detected (b). It highlights the importance of the completeness of crystallographic data especially for the presence of hydrogen in the determination of the chirality by computer algorithm.

View Article Online
DOI: 10.1039/D0CE00303D

Table 2 Frequency of chiral, racemic and achiral structures in centrosymmetric (C), non-centrosymmetric (NC) and Sohncke (S) space groups. N is the number of structures analyzed in each study. Statistics were performed by divided the number of structures by the total number of structures in each subset. [a]No attempt was made to estimate this proportion, [b]this study. [c] solvates, salts and co-crystal were excluded.

Ref	N	%Chiral structures in			%Racemic structures in				%Achiral structures in			
		NC	S	CSD	NC	S (KRC)	C	CSD	NC	S	C	CSD
[11]	9379	-	-		2.3%	0.07%[a]	23%	15.6%	-	-	-	-
[27]	34946 b	82%	82%	17%	-	-	35%	24%	18%	18%	65%	50%
[28]	100864	-	-	25%	-	-	-	18%	-	-	-	57%
[8]	174465	-	-	-	-	0.4%	-	-	-	-	-	-
[9]	254354	-	-	-	-	0.4%	-	-	-	-	-	-
[5]	178924	-	81% [c]	22% [c]	-	0.6% [c]	-	23% [c]	-	19% [c]	-	54% [c]
ChiralFinder[b12]	393004	62%	75%	18%	4%	0.6%	22%	17%	30%	20%	70%	56%
ChiPi[b]	393012	64%	78%	19%	4%	0.8%	24%	18.6%	30 %	20%	73%	62%

We assume that, in most of the cases, the automatic assignment of missing hydrogens, that corresponds to step 2 of ChiPi script, is correct (if a problem occurs in any steps of this procedure the structure is not treated- see the SI-3). Contrary to the algorithm developed by Grothe *et al.*, ChiPi is able to treat structures with stereogenic centers located on the same ring.

To compare our results on a large dataset, we used another program named *ChiralFinder* (CF) [12] that accepts data from the CSD (in coord format) and returns gcd lists of achiral, chiral, racemic, meso and errors structures (hereafter "not-treated"). The main results obtained both with CF and ChiPi are summarized in the supplementary information (SI-2). Globally, the results between both scripts are similar but in certain cases the differences are important especially for disordered structures (e.g. achiral structure). One can notice that the number of untreated structures by ChiralFinder is sometimes important reaching circa 30% of certain subset. It could explain differences between both algorithms. Out of the 393012 structures; the total number of non-treated entries by ChiralFinder and ChiPi is 7% and 3%, respectively.

Errors in the determination of the chirality also depends on type of atom: by analyzing the classification of different structures, it seems that a part of Boron or Phosphorus atoms was potentially more often detected as achiral by ChiPi (although it was difficult to estimate a number) and while *Mercury* correctly assigned this atom to be chiral centers. This bias (or bug in Python API) will necessitate further developments but should not drastically change the statistics of this study. In the following, we assume that the non-treated structures have the same distribution in different crystal classes (a favorable indicator is that the SG ranking of the non-treated structures is the same as that for the whole CSD). The estimation of the error by comparison with other studies is not trivial because the subset and the restrictions on the analyzed structures often differ. One can try to determine it by comparing results obtained on known structures. For instance, concerning KRCs, Grothe *et al.* published a list of 409 structures although this list needed to be carefully checked. Among these structures, ChiPi detects 98 % of these structures as KRC structures, two of them are assigned to be racemic (actually, ChiPi detected non-Sohncke space groups), one was identified as a meso and one was not treated (problem in the coordinates). Therefore, ChiPi was able to detect and correctly assign 99% of the KRCs of this list (discarding the two racemic structures).

Out of the list published by Fábián *et al*. (247 structures including the 181 confirmed structures), 232 structures (94%) are assigned to be KRCs. The others are detected as chiral (VEYBEH that could be in fact a solid solution or scalemic compound and PEMWOU that is a cis/trans enantiomerism), 1 meso (NAHZAX), 1 diast, 4 not-treated (because of presence of "mixed" chiral atoms or problems in the determination of the chirality). For comparison, in the list of Grothe *et al*., 64 structures belonging to the list of Fábián *et al* are missing. These differences essentially lie in the way of detection of the chiral atom and the chosen subset.

Table 3 Estimation of the assessment error by ChiPi for different crystal classes. ([a]for meso, this error is over estimated)

Class	Estimated error /classes
Racemic	3%
Chiral	1%
Achiral	1%
Diast	1%
Scalemic	8%
Kryptoracemate	4%
Meso[a]	35%

Even if the similarity between ChiPi and these two lists is good, it does not really assess the error of misassignment on the detected KRCs structures in the whole CSD. The main limitation of ChiPi program is probably the detection of meso structures that represents the main source of missed assignments. Grothe *et al* published a list of possible mesoisomer structures (5697 entries). Among them 92% (5224 entries) crystallize in non-Sohncke SG and 8% (474 entries) in Sohncke SG. Assuming that all structures of this list are effectively meso, ChiPi is only able to detect 61.7% of the structures as possible meso structures. The others are assigned to racemic (28.6%), chiral (3.1%), achiral (2.8%), scalemic (0.04%), diast (0.02%) and 3.62% were not treated principally due to the presence of "mixed" chiral atoms in the structures. The detection of meso compounds is almost entirely based on the determination of the molecular point-group. Unfortunately, the algorithm used by CCCD python API seems to have some difficulties for a number of molecules. For instance, the molecule in AVAYIF structure is not

determined as Cs point group contrary to the other algorithm as SYMMOL (included in PLATON). This lies in the algorithm used that do not allow a change in the distance or angle tolerances. As discussed with CCDC staff, this should be implemented in further versions of Python API. Maybe, implementation of new algorithms of molecular point group calculations (as SYVA[29] or SYMMOL[30]) could also be helpful.

Based on these results and last statistics, we can roughly estimate the error at 2% for KRC detection in the CSD although there is no easy way to estimate non-detected structures (due to wrong assignment of chirality for example). Additionally, the Marshed structures that particularly concern Sohncke SG can also generate circa 2% of wrong structures. Finally, the error on KRCs is thus estimated at 4%. The other error estimations for different classes are summarized in Table 3. Grothe *et al*. estimates the proportion of meso-compound to at 2.2% of the CSD. We found 1.9%. Accounting the error on the detection of meso compounds by ChiPi, the proportion of meso structures is probably closer to 2.5% in the CSD.

Results and discussions

Racemic and Kryptoracemic Compounds (KRCs) in CSD

Out of the 392012 analyzed structures by ChiPi, 748 are classified as KRCs. Rapid check of the newest KRC structures revealed that 16 are in fact meso compounds that represent an error of circa 2%. In addition, 21 structures have been "Marshed" and consequently were discarded. It means that errors on KRCs detection is circa 5% (a majority of them being Marshed structures), slightly above the estimated error of 4%. One can also notice that 66 structures (including "Marshed" structures) belongs to the "doubtful list "of Fábián *et al*. Out of these structures, 49 were not, at first, rejected until further redetermination and collection of better crystallographic data, there is no obvious reason to discard them.

The final list of KRCs is obtained after merging the two known previous lists of Kryptoracemate and leads to 724 structures (refcodes in the supplementary materials). It represents circa 0.18% of the CSD, 0.75% of the Sohncke SG and circa 1% of the racemic compounds. The frequencies of KRCs in the entire CSD subset and different subset are given in Table 4. It seems that the frequency of KRCs is slightly higher in disordered structures (1%) compared to non-disordered (0.6%) and that ionic associations have no influence on the formation of KRC. Nonetheless, the majority (70%) of KRCs crystallize in non-disordered non-ionic structures. It is worth mentioning that a part of detected KRCs could be solid solutions. According to Rekis[5] this part is estimated to 14 structures (2% of the KRCs). The proportion of racemic compounds in achiral and chiral and the predominant SG are given in Table 1 .

Each structure of this list is tested for additional symmetry with PLATON (ADDSYM) in batch mode. KRC candidates are classified in two main groups:

(i) A class with no alert in *PLATON* (565 structures)

(ii) B class in which *PLATON* ADDSYM alerts occurs (159 structures, for a maximum non=fit of 20%).

Among the B class, ADDSYM Exact calculations were performed in *PLATON* (*i.e.* for maximum non-fit of 0% with non-metric tolerance), only 64 structures still have a *PLATON* alert. Although, a *PLATON* alert does not necessary mean that the structure is uncorrected (the opposite is not true), these 159 structures are discarded and classified as ambiguous. One can notice that among the B class, 46% of the structures are $P2_1$ and 40% are P_1. The main change proposed by *PLATON* is an addition of a center of inversion transforming a KRC into a regular RC. The missing symmetry and the consequence on the space group change for the B class are summarized in the supplementary materials (Platon_Alert.xlsx).

For 28 (5%) structures of the A class, a local/non-crystallographic inversion center is detected by PLATON, 110 (20%) have disorder in the structure although the disorder not necessarily implies the stereogenic centers.

Table 4 KRC frequency in Non-Centrosymmetric (NC) SGs for non -disordered (ND), non-ionic (NI), Disordered (D) and ionic (I), Sohncke and the entire CSD subsets

Structure type	Sohncke SG	KRC	KRC Entries
Disordered and ionic	72.7%	1%	31
Disordered and non-ionic	82.6%	0.9%	122
Non-disordered and ionic	76.'%	0.6%	68
Non-disordered and non-ionic	83.9%	0.6%	503
Sohncke SG	100 %	0.75%	724
CSD (organics)	24.5%	0.18%	724

Comparison of chiral molecule conformations in single-component crystal structures with Z'=2

ChiPi can calculate pairwise molecular overlays as an indicator of conformation differences between pairs of the same enantiomers or a couple of antipodes in crystal structures. The root mean square deviation (rmsd) comparison can be viewed as an indicator of conformational differences. A low value means that the molecular conformations are close for both molecules while a high value should highlight the conformational differences. An example of the operation performed by ChiPi is plotted in Figure 2. The general procedure is described in the supplementary information (SI-4). The conformational comparison is performed for molecules crystallizing as pure components (without any other molecules as coformers or solvent molecules) and Z'=2. With this restriction there are 359 KRCs, 871 non-centrosymmetric RCs, 7000 centrosymmetric RCs and 11785 chiral structures. The results of rmsd comparison for each pair of enantiomers in these structures are summarized in Table 5 through five main indicators: the mean value, the standard deviation (std); the median value, the 10th percentile (P10, i.e. 10% of the structures have a lower rmsd value than P10) and the 90th percentile (P90, *i.e.* 10% of the structures have a higher rmsd value than P90).

Previous determination of rmsd comparison for enantiomeric pair in NC crystal structures (not necessarily kryptoracemic) were performed by Dalhus & Gorbitz[11] and they found an average deviation of 0.19 Å.

View Article Online
DOI: 10.1039/D0CE00303D

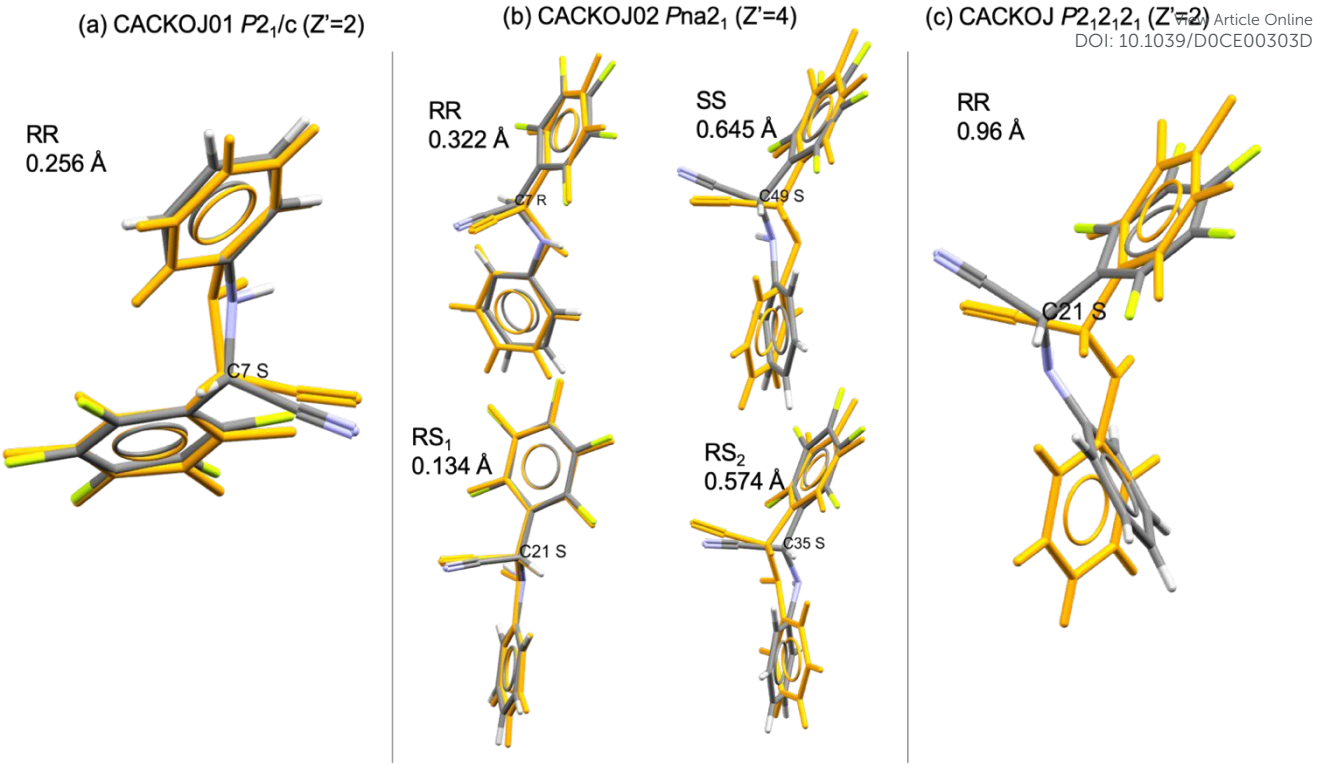


Figure 2 Overlay comparison after inversion for two antipode in the AU of CACKOJ01 structure, the rmsd =0.256 angstrom (a); overlays in CACKOJ02 (only four of the six comparisons are shown) (b) and in CACKOJ (Z'=2)

Fábián *et al*. found a similar value of 0.25 Å for the 181 kryptoracemates in their final list and a median value of 0.14 Å. We found very similar values, for the 359 KRCs with Z'=2 with an average rmsd of 0.29 Å and median value of 0.16 Å. In most cases, the conformations of the enantiomers were very similar with a 10% of the KRCs having a rmsd difference as low as 0.04 Å. This is probably due to constraints during the refinement to force both molecules to adopt the same conformation. 10% of KRCs have a rmsd higher than 0.77 Å.

Additionally, the values obtained for KRCs and centrosymmetric RCS are almost the same. For non-centrosymmetric RCs (*i.e* crystallizing in achiral SGs), all indicators have lower values compared to other RCs with, for instance, a median and P90 rmsd values of 0.10 Å, and 0.51 Å, respectively compare to 0.19 Å and 0.78 Å for centrosymetric RCs. Therefore, the difference in molecular conformation between antipodes seems to be lower for antipodes in achiral RCs.

One can also notice that the difference of molecular conformation between overlay of the same enantiomer is more important for chiral structures with a mean rmsd value almost twice higher compare to mean rmsd values of NC-RCs, C-RCs or KRCs. The conclusions are the same for other indicators (std, median, P10, P90). We confirm Dalhus et *al.* results who noticed that differences in conformations between two enantiomers are higher in chiral structures than the differences between conformations of a pair of opposite enantiomers in racemic structures (including centrosymmetric, achiral NC and KR structures). This difference could, for a part, find an explanation by instabilities induced by presence of pseudo-symmetry elements or in the constraint differences created during the structure resolution of centrosymmetric and non-centrosymmetric structures (*e.g*. the presence of inversion center in the structure will be benefit to similar conformations between antipodes).[31,32]

Table 5 Comparison of molecular conformation in single-component Z'=2 structures: Mean , standard deviation (std), median, 10th percentile (P10): 10% of the structures having a lower rmsd value, 90th percentile (P90): 90% of structures having higher value of rmsd values obtained for the comparisons of enantiomeric pairs (only for Z'=2) in Racemic (Centrosymmetric and NC) and Chiral crystals. Values are given in angstrom. N is the number of structures analyzed for each subset.

	Non-centrosymmetric			Centrosymmetric
Class	Kryptoracemic (Aclass)	Racemic (Achiral SG)	Chiral	Racemic
N	359	871	11785	7000
Mean	0.29	0.21	0.5	0.32
Std	0.33	0.27	0.52	0.37
Median	0.16	0.10	0.34	0.19
P10	0.04	0.03	0.07	0.05
P90	0.77	0.51	1.14	0.78

Space group frequency for KRC and RC

Among the NC structures, the SG frequency ranking is $P2_12_12_1$, $P2_1$; $Pna2_1$; P1, C2, $Pca2_1$ representing circa 87% of all NC structures. The SG ranking for racemic structures is summarized in Table 6. Among Sohncke structures, the most frequent space group is $P2_12_12_1$ (46.6%) followed by $P2_1$ (34.5%), *P*1 (5.3%), *C*2 (4.9%) and $P2_12_12$ (2%). We found a completely different distribution of SG for KRCs (A class) with 53.4% in $P2_1$, 27.7% in $P2_12_12_1$, 11.2% in *P*1, 2.5% in *C*2 and 1.8% in $P2_12_12$. There is a complete inversion of the population between $P2_12_12_1$ and $P2_1$ crystals although $P2_12_12_1$ is circa 35% more abundant than $P2_1$ in the entire CSD. The SG frequency for enantiopure chiral

structures with Z'=1 (47150 entries) is almost identical to the entire Sohncke SGs while for enantiopure chiral structures with Z'=2 (8365 hits, *i.e.* having two enantiopure molecules in the AU) the frequency of SGs changes similarly to the ranking observed for KRCs. All information are summarized in Table 7 together with the SG rankings for enantiopure chiral structure and KRCs with higher Z'.

In fact, the winner for the first SG rank seems to be cyclic: (i) for even Z' the $P2_1$ space group is over-represented with a frequency always around 50% while (ii) for odd Z' the trend returns to "normal" ranking. In addition, we show in Figure 3 that *P*1 seems to be also impacted cyclically with the increase of Z'.

Table 6 Frequency SG ranking for racemic compounds in the CSD

Space group (space group number)	Frequency
$P2_1/c$ (14)	49.2%
$P\bar{1}$ (2)	28.8%
C2/c (15)	7.1%
Pbca (61)	5.3%
$Pna2_1$ (33)	2.1%
Cc (9)	1.4%
$Pca2_1$ (29)	1.3%
Sohncke SGs	1%
Other	3.7%

For KRCs, the fraction crystallizing in $P2_1$ space group is also circa 50% for Z'=2, 4 and 6. For scalemic or unbalanced compounds (odd Z'), there are only structures with Z'=3 if we consider pure compounds. It seems that for this category; the distribution is closer to the global CSD ranking. Therefore, the KRC SG frequencies versus Z' seems to follow the same trend as for enantiopure chiral structures. We may infer that this SG distribution of structures versus the Z' is a general trend for structures crystallizing in Sohncke SG whatever the chirality of the structure (enantiopure, racemic or scalemic). The same study including structure where achiral molecules crystallize together with an enantiopure proportion of chiral molecule shows the same trends (statistics made for 1 to 4 chiral molecules in the AU, for more molecules the number entries of structures is too low to make statistics – not shown). Because of the prevalence of Z'=1 (almost 50% of Sohncke subset), the global SG ranking hides this alternation between $P2_12_12_1$ and $P2_1$ SGs for the first rank. We can also notice that with higher Z' number (>6) the prevalence of *P*1 space group increases progressively to reach 100% that confirms the common observation that higher Z' structure crystallizes in space group of lower symmetry. In Figure 4, we show the prevalence of $P2_1$ structures over $P2_12_12_1$ structures increases only for even Z' (for odd Z' the ratio of $P2_1$/ $P2_12_12_1$ remains constant).Observation of abnormal space group frequencies for Z'>4 have already been reported by Brock. [33] She notices that, for these structures, $P2_1$ is over-represented compared to structures with Z'<4 (24% versus 9%) and, although 40% more frequent than $P2_1$ in the CSD; the frequency of $P2_12_12_1$ falls drastically. The frequency of KRCs in her subset was also higher than for the whole CSD. This probably lies with the tendency of KRC to crystallize in $P2_1$ SG. It is also stated that "if a local/non-crystallographic inversion center (or glide plane) is combined with an n-fold modulation or a hydrogen bond n-mer (n>3), the result is a high Z' structure". Therefore, each enantiopure chiral structure (from Z'=1 to Z'=6) that represents 56738 structures and the KRC structures were analyzed using PLATON to check for a possible missed symmetry and/or the presence of local/non-crystallographic symmetries in routine mode. The comparison of the percentage of both values versus Z' together with results obtained for KRCs (Z'=2, 4 and 6) and scalemic (Z'=3) structures are plotted in Figure 5. In enantiopure chiral structures, the proportion of *PLATON* alerts and local non-crystallographic inversion (NCI) centers is always statistically higher (circa 10% of the structures having *PLATON* alerts) for even Z' compare to odd Z' numbers (2% of PLATON alerts). For Z'=5, this number is null but statistics on this subset could be erroneous because of the low number of structures in this subset (22 if we consider only enantiopure compounds, 33 for all structures). For even Z' chiral structures, in 80% of the alerts, *PLATON* proposes to add an inversion center. In 20% of the cases *PLATON* proposes to increase the symmetry of the space group (but remaining in Sohncke structures). In most of cases, alerts concern the $P2_1$ and *P*1 space groups with circa 50% and 40% of the alerts, respectively. Interestingly, for $P2_1$ alerts, and in 20% of the cases it is proposed to change the SG into $P2_12_12_1$ and in 70% of the cases to add an inversion center. For *P*1 structures, 95% of the proposed new SG possesses inversion centers or glide planes. Nevertheless, even if the structures having alerts are discarded from each Z' subset, the SG ranking is not strongly impacted.

For the KRC (Z'=2, 4 or 6), and scalemic (Z'=3) subsets, a similar trend exists between even and odd Z' (although the number of structures could bias the statistics). PLATON alerts for an even value of Z' correspond to 21%, 37% and 14% of the structure in each subset for Z' equals to 2, 4 and 6, respectively. For Z'=5; this value falls at 5%. The number of NCI centers is also statistically higher for even Z' compared to odd Z'. 99% of the PLATON alerts concern the addition of an inversion center or a glide plane. Out of these alerts, 45% concern $P2_1$ and 40% *P*1.

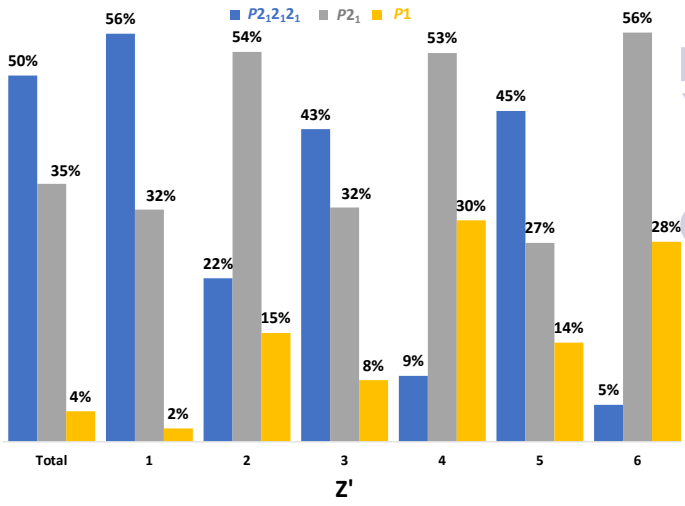


Figure 3 Frequency of $P2_12_12_1$, $P2_1$ and P1 SG versus Z' (from 1 to 6), for enantiopure Sohncke crystal structures

View Article Online
DOI: 10.1039/D0CE00303D

Table 7 SG ranking in % for Sohncke SG for all Sohncke crystals, enantiopure chiral crystals, pure KRCs and scalemic compounds versus Z'. [a]The number of enantiopure structures with Z'=5 and KRCs with Z'=6 are particularly low and could create bias. To have an acceptable number of structures for Z'>2, statistics are made on the complete list of KRCs (A class + B Class, it does not drastically change the KRC statistics trend). Grey color is a guideline to spot the most impacted SG frequencies with the Z' distribution. N is the number of structures for each subset.

	Sohncke SG	CHIRAL (enantiopure) for Z'=						KRCs for Z'=				Scalemic
Z'	All	1	2	3	4	5	6	All	2	4	6	3
$P2_12_12_1$	46.6%	55.4%	22.2%	41.9%	8.9%	45%	5%	23.1%	28.2%	3%	0.00%	35%
$P2_1$	34.5%	31.5%	53.1%	31.9%	53.5%	27%	55%	51.8%	52.4%	52%	57%	23%
$C2$	4.9%	4.2%	5.3%	6.3%	4.6%	14%	4%	2.5%	2.8%	0.00%	0.00%	6%
$P1$	5.3%	1.8%	14.8%	8.7%	29.9%	14%	27%	17.4%	12.9%	43%	43%	18%
$P2_12_12$	2%	1.7%	1.6%	1.9%	0.3%	0.00%	3%	1.9%	1.3%	2%	0.00%	6%
Other SGs	6.6%	5.3%	3%	9.1%	2.7%	0.00%	6%	3.3%	2.4%	0.00%	0.00%	12%
N	96129	47150	8365	504	697	22[a]	80	724	451	59	7[a]	20

If we compare chiral structures and KRCs (including scalemic structures) with the same Z' (Z'=1 naturally excluded), the number of alerts and NCI centers are always higher in the case of KRCs with 22% of alerts and 4.7% of NCI centers versus 9% and 1% for enantiopure chiral structures. These high values in KRCs, are probably due in part to the structures being assigned to wrong space groups. This behavior seems more pronounced than for chiral enantiopure structures with Z'>1 having also structures presenting higher values of *PLATON* alerts compared to Z'=1 enantiopure structures (one should recall that PLATON frequency alerts in enantiopure chiral Z'=1 is only 0.5% and a NCI center is detected only for 0.1% of the structures).

This alternation of the $P2_1$ and $P2_12_12_1$ for first rank in KRCs is probably a consequence of wasting inversion centers due to a mismatch between pairwise molecular interactions and possible crystal symmetries.[34] The consequence or expression of this frustration could be linked to the prevalence of lower symmetry space group ($P2_1$) compensated by higher frequency of non-crystallographic symmetry elements between molecules (Figure 5). Moreover, it seems easier to relate an even number of molecules by NCIs especially between two antipodes.

This conclusion also applies, while less obviously, for enantiopure compounds (where only one enantiomer is present in the structure). A thorough analysis of these enantiopure crystal structures with an even Z' could be interesting. These structures exhibiting a higher frequency of local symmetry (compared to odd Z' enantiopure crystal) could be easier to accommodate the presence of a counter-enantiomer in the structure and therefore could have a certain propensity to form a solid solution.

The interpretation and the reasons for the existence of high Z' structures are often discussed in the literature.[33,35-38] Some may infer that the reason lies on "bad crystallization" and that the proportion of polymorphs should be higher in these structures compared to Z'=1 structure.

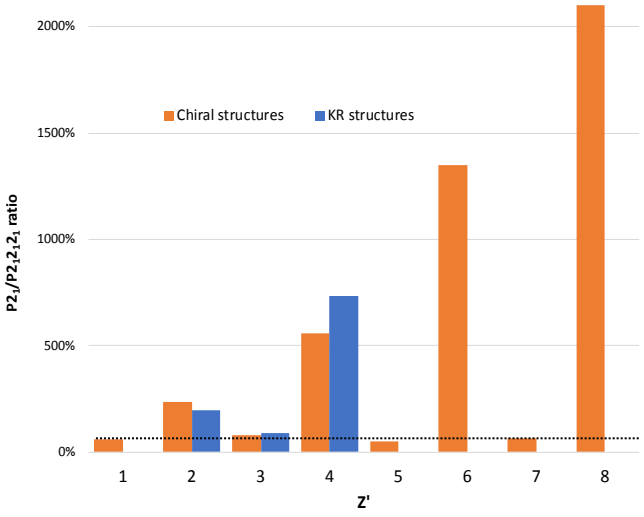


Figure 4 Ratio $P2_1/P2_12_12_1$ evolution versus Z'. Statistics made for all the KRCs and chiral structures. Dash-line is a guideline showing that the ratio is almost constant for odd Z'. The number of structures for chiral crystals are 51674, 8459, 476, 605, 24, 58,5 and 22 for Z'= 1, 2, 3, 4, 5, 6, 7 and 8, respectively. For KRCs (including scalemic compounds), the number of structures for Z'=2, 3 and 4 is 588, 19 and 76, respectively.

Polymorphism in KRCs

The frequency of occurrence of polymorphism in KRCs is estimated at circa 2.6% while it is estimated to only 1.8% in the whole CSD. Determination of polymorphism in the CSD in not a trivial task because a redetermined structure is not necessarily linked with a polymorph (it could be a Marshed structure, or an erroneous crystal structure or simply a redetermination by other research group). Moreover, the polymorph information is not always assigned or is assigned even though only one polymorph is referenced in the CSD. For example, the KRC polymorphic information is indicated for 3.6% of the structures and for 2.7% for the whole CSD (excluding KRC structures). In our study, out of the 393012 entries analyzed, the proportion of structure redeterminations using method described in section "Determination of subset" is estimated at circa 3.7% of the CSD (14782 entries) for circa 6900 unique refcode families. This leads to frequency of occurrence of polymorphism estimated at (6900/393012) 1.8% of the CSD (in fact it is over-estimated since

View Article Online
DOI: 10.1039/D0CE00303D

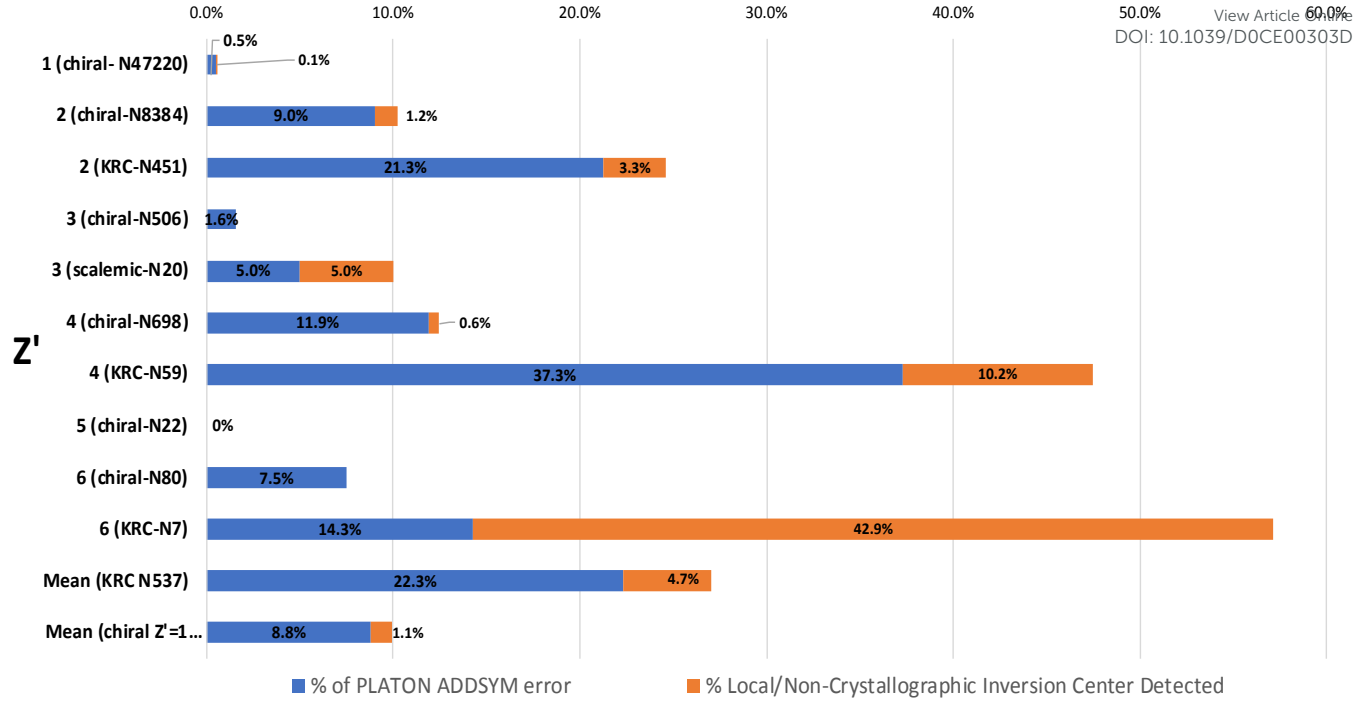


Figure 5 Percentage of PLATON ADDSYM alerts and of local/non-crystallographic inversion center detected in enantiopure crystal for Z' from 1 to 6, for KRCs (for Z'=2,4,6) and scalemic structure (Z'=3). For enantiopure, Z'=5 subset contains only 22 enantiopure structures, therefore the statistics were made including structures containing achiral molecule that increases the number to 33 structures. The number of KRC structures in the Z'=6 subset is too low to draw reliable conclusions. N is the number of structures analyzed in each category.

redetermined structures are not necessary polymorphs and could coincide with disordered/non-disordered structure resolutions). However, this value seems to be in agreement with literature and can be assessed as a good estimation of occurrence of polymorphism in or our subsets (The frequency of occurrence of polymorphism variables between subsets of the crystal types (solvate, co-crystals, salts…) but it is estimated to be circa 1.2% for single organic components in the CSD).[39]

In KRC subset, the number of unique entries having a redetermination is 22 for A class KRCs (for 26 structure redeterminations, *i.e.* certain entries are at least resolved twice in Sohncke SG) and 38 for all KRC structures (with 32 unique families) that represents (22/565) 3.9% of A class and (32/724) 4.4% of the KRCs, respectively. Out of these structure redeterminations, 19 are confirmed to really belong to a polymorphic system and are summarized in Table 8. Other structures exhibiting disorder. Therefore, the occurrence of polymorphism in KRCs is estimated at circa (19/724) 2.6% of the KRC structures. It is statistically higher than estimated polymorphism in the whole CSD (1.8%). This could be an indication that compounds that could crystallize as KRCs have a higher chance of being polymorphs. Among the 19 polymorphic systems, there are also systems having many polymorphs with 2 (74%), 3 (16%), 4 (5%) and 5 (5%) known polymorphs. In most of cases, polymorphism involves a usual racemic centrosymmetric polymorph crystallizing mainly in $P\overline{1}$ or $P2_1/c$. Interestingly, the ONODAY system exhibits three polymorphs having Z'>1 with two KRC structures crystallizing in $P2_1$ (Z'=4) and in $P2_12_12_1$ (Z'=2) and one centrosymmetric polymorph in $P2_1/c$ (Z'=2). The rmsd comparisons of each pair of molecules in the AU give a mean value of 0.185 Å for the same chirality and 0.143 Å for the opposite chirality in the $P2_1$ crystal. It is much higher than in $P2_12_12_1$ and $P\overline{1}$ polymorphs where the opposite molecule is virtually identical with 0.058 Å and 0.054 Å for rmsd values, respectively. This globally respects the rule asserting that molecular conformations between antipodes are closer than for molecule of the same chirality.

The CACKOJ system is a counter example. In this case, the rsmd value in the $P2_12_12_1$ polymorph (Z'=2) is 0.96 Å for overlay of the antipode highlighting important conformational differences The mean values are also relatively high for molecules of the same chirality (0.483 Å) and of the opposite chirality (0.376 Å) in the $Pna2_1$ structure (Z'=4) while for the $P2_1/c$ (Z'=2) the rmsd value is 0.256 Å. Nevertheless, these values hide disparities of the molecular conformations between different couples of molecules in the $Pna2_1$ structures. Indeed, each molecule in the AU exhibits different conformations and the rmsd values for the comparison of R and S molecules are comprise between 0.134 Å. and 0.574 Å (see Figure 2). One can notice that CAKKOJ crystallizes as centrosymmetric RC, non-centrosymmetric RC and KRC. Every case is specific and the low number of polymorphic systems makes it difficult to spot a clear and significant trend between high Z' and conformational differences in KRCs.

Comments about frequency of conglomerate

As previously mentioned, there is no indicator in the CSD to know if an enantiopure structure has been crystallized from racemic solution. Therefore, the frequency of occurrence of spontaneous resolution cannot be determined.

Table 8 Inventory of polymorphic systems involving KRCs. The type refers to the composition of AU in KRC crystal: (I) single-component, (II): co-crystal with achiral molecule, (III): co-crystal with chiral molecule, (IV): ionic. Symbols D, ss and NC stand for disorder in the structure, suspected solid solution and non-centrosymmetric, respectively. PN is the number of known polymorphs.

	REFCODE	SG	Z', Z	density	PN	Type
1	CACKOJ[40]	$P2_12_12_1$	2, 8	1.583	4	II
	CACKOJ01	$P2_1/c$	2, 8	1.569		racemic
	CACKOJ02	$Pna2_1$	4, 16	1.603		racemic NC
	CACKOJ03	$P2_1/c$	1, 4	1.651		racemic
2	ONODAY01[41]	$P2_1$	4, 8	1.251	3	I
	ONODAY	$P2_12_12_1$	2, 8	1.202		I
	ONODAY02	$P2_1/c$	2, 8	1.209		racemic
3	QIMBAS[42]	$P2_1$	2, 4	1.276	2	III
	QIMBAS01	$P2_12_12_1$	2,8	1.231		III
4	DLMSUC01[43]	$P2_1$	2,4	1.408	3	I
	DLMSUC	$C2/c$	1, 8	1.39		racemic
	DLMSUC02	$P\bar{1}$	2, 4	1.421		racemic
5	FOHLIY[44]	$P2_1$	2, 4	1.17	2	IV
	FOHLIY01	$Pbc2_1$	2, 8	1.177		racemic NC
6	HISRIL01[45]	I2	2, 8	0.998	2	I
	HISRI	$P\bar{1}$	2, 1	1.037		racemic
7	JIZJOR03[46]	$P2_1$	4, 8	1.229	3	I
	JIZJOR04[47]	Pc	4, 8	1.229		racemic NC
	JIZJOR02[47]	$Pbca$	1,8	1.249		racemic
8	NISMUX02[48]	$P2_12_12_1$	2, 8	1.92	2	I
	NISMUX01	$P\bar{1}$	2, 4	1.898		racemic
9	NOLFUP	$P2_1$	4, 8	1.313	2	I
	NOLFUP01	P2/c	1.5, 6	1.296		racemic
10	PDTOMS11[49]	$P1$	2, 2	1.149	2	I
	PDTOMS10	$P2_1$	2, 4	1.136		I
11	POWWUW01[50]	$P2_1$	2, 4	1.385	2	I
	POWWUW	$P2_1$	1, 2	1.247		I
12	QOVREZ01[51]	$P2_1$	2, 4	1.463	2	I
	QOVREZ	$P\bar{1}$	2, 2	1.48		racemic
13	TETBUS01[52]	$P2_1$	6, 12		5	I - D
	TETBUS02	$C2$	8, 32	1.147		I
	TETBUS	$C2/c$	1, 8	1.127		Racemic
	TETBUS03	$P2_1/c$	1, 4	1.099		Racemic
	TETBUS04	$C2/c$	1, 8	1.07		Racemic - D
13	TOJPOA01[53]	$P2_1$	2, 4	1.282	2	III
	TOJPOA	$P2_12_12_1$	1, 4	1.267		III-D
15	VUTZIT01[54]	$P4_1$	2, 8	1.144	2	I
	VUTZIT	Cc	1, 4	1.148		Racemic
16	YIXVAD[45]	$I2$	2, 8	0.992	2	I
	YIXVAD01	$P\bar{1}$	1, 4	1.012		racemic
17	GENLET01[55]	$P2_1$	4, 8	1.316	2	I/ss
	GENLET	$P\bar{1}$	1, 2	1.319		Racemic
18	IQAREY01[56]	$P2_1$	2, 4	1.382	2	I
	IQAREY	$P2_12_12_1$	1, 4	1.384		I
19	ZOCPUE[57]	$P2_12_12$	2, 8	1.219	2	I-D
	ZOCPUE01	Iba2	1, 8	1.193		Racemic

Nevertheless, one should remark that the SG frequency of achiral molecules crystallizing in Sohncke SG(*i.e.* structure with no resolvable molecules) is remarkably similar to those of chiral molecules (see Table 9). Moreover, it was demonstrated that symmetry dependencies are consistent in structures with chiral and achiral molecules or when Sohncke and non-Sohncke structures are compared.[58]

Table 9 SG frequency of achiral and chiral molecules crystallizing in Sohncke SG. N is the number of structures in each subset.

View Article Online DOI: 10.1039/D0CE00303D

		Achiral	Chiral
SG n°	SG Symbol	Frequency (N)	Frequency (N)
19	$P2_12_12_1$	50.2% (8856)	48.4% (35079)
4	$P2_1$	33.3% (5874)	36.3% (26275)
1	$P1$	5.7% (1005)	5.3% (3804)
5	$C2$	3.6% (640)	5.4% (3928)
18	$P2_12_12$	2.4% (417)	2.0% (1455)
92	$P4_12_12$	1.6% (282)	0.6% (447)
96	$P4_32_12$	1.2% (208)	0.6% (421)
20	$C222_1$	0.8% (144)	0.6% (447)
76	$P4_1$	0.7% (116)	0.4% (289)
145	$P3_2$	0.5% (87)	0.4% (304)

An estimation of the frequency of spontaneous resolution may come by assuming that the distribution of achiral molecules crystallizing in Sohncke SGs is similar to the conglomerate frequency. Among Sohncke structures, 78.5% are chiral, 19.7% are achiral, 0.8% are meso, 0.8% are racemic (KRCs) and 0.3% are diast. Out of the 393012 analyzed structures, ChiPi detects 210721 achiral structures with 18722 crystallizing in Sohncke SGs. Thus, we estimate of the probability of spontaneous resolution at circa below 8% (18722/210721). It could represent at most 6000 structures of chiral organic structures. It is worth mentioning that out of the 210721 achiral structures a part contains resolvable molecules (atropoisomer) considered as negligible. This rough estimation could also fluctuate because it does not account for molecular symmetry considerations that could force achiral molecules to crystallize in Sohncke SGs (e.g. C2 molecular symmetry). This value is consistent with recent study of Rekis (single-component crystal structures, 178924 structures) and Fábián *et al* (Z'>1 representing 174465 organic structures) estimating the frequency of spontaneous resolution to 9.5% and circa 6%, respectively. These values are also consistent with the estimation of Collet *et al* that 5-10% of resolvable molecules crystallized as conglomerate.

Conclusions

The low frequency of KRCs and RCs in non-centrosymmetric SG is once more an indication of the prevalence of inversion center in crystal packing of racemic compounds.[58,59] The number of non-centrosymmetric racemic compounds is estimated to be 6 – 6.5% of the organic structures in the CSD. This value seems to be constant over the last 10 years.

The number of enantiopure structures in Sohncke SGs is estimated at 78%, the other structures are achiral (20%), meso (1%), KRCs (0.8%), diast (0.3%). The "unbalanced compounds" (scalemic composition) are rarer than KRCs and represents less than 1/10000th of the entire CSD (37 structures). Of course, this low frequency of scalemic compounds is probably the consequence of low number of studies for crystallization from scalemic mixtures in enantiomeric systems.

A new list containing 724 structures has been documented and should deserve more attention to establish the authentic KRCs. Out of this list, 159 KRC structures were classified 'ambiguous' because of the PLATON ADDSYM alert (although, it could be an indication of the prevalence of pseudo-symmetry in this class of compounds). For 5%, (among 565 structures) *PLATON* detects a non-crystallographic inversion center.

The SG frequency ranking is abnormal in KRCs with the $P2_1$ space group over-represented (50% of KRC structures) compared to normal Sohncke SG ranking (35%). While there are in general 35% more $P2_12_12_1$ structures than $P2_1$ in the entire CSD, this number drastically falls in KRCs. When Z' is an even number, the frequencies are completely inverted with 130% more $P2_1$ than $P2_12_12_1$ structures. The prevalence of $P2_1$ space group is not only restricted to KRCs but is valid for even Z' in Sohncke SG regardless if the molecules are chiral or not. By contrast, the odd Z' structures follow the same trends as the whole CSD (globally similar to Z'=1 structures). 56738 single component crystallizing in Sohncke SGs for Z' =1 to 6 were checked by *PLATON* in batch mode. The number of alerts and non-crystallographic inversion centers detected in these structures follows the same trends than the ratio of $P2_1/P2_12_12_1$ structures. This relation could be a consequence of missing some symmetry elements in these structures for even Z' leading to a prevalence of $P2_1$ over $P2_12_12_1$ structures. However, it is worth mentioning that the omission of the structures having PLATON alerts or non-crystallographic inversion centers does not change the SG frequency among even Z' structures. A thorough investigation of the crystal structures should be performed, especially to check the presence of pseudo twofold axes or 2_1 screw axes in order to find an explanation to that abnormal SG ranking.

Circa 20000 molecular overlays have been performed in enantiopure and racemic single component crystals (for Z'=2). The principal conclusion is that the molecules are more different in enantiopure than in racemic structures (*i.e.* the molecular conformation deviates more for two of the same enantiomers than for a pair of antipodes). For a part, this deviation could be explained by the consequence of pseudo-symmetry in the structure.[60]

KRCs have a greater propensity to exhibit polymorphism (2.8%) compared to the entire CSD but, to date, there is no significant evidence of any relationship with the molecular conformations adopted by molecules in the structure.

The data and information that could be extracted from the CSD need to be refined. For instance, KRCs exhibiting disorder could actually correspond to a slight deviation of the racemic composition and thus these could be solid solutions. Future work will hopefully solve this problem. We hope that ChiPi script could be useful for the community interested in chirality in the solid state and everyone is free to use it.

Conflicts of interest

There are no conflicts of interest to declare.

Notes and references

View Article Online
DOI: 10.1039/D0CE00303D

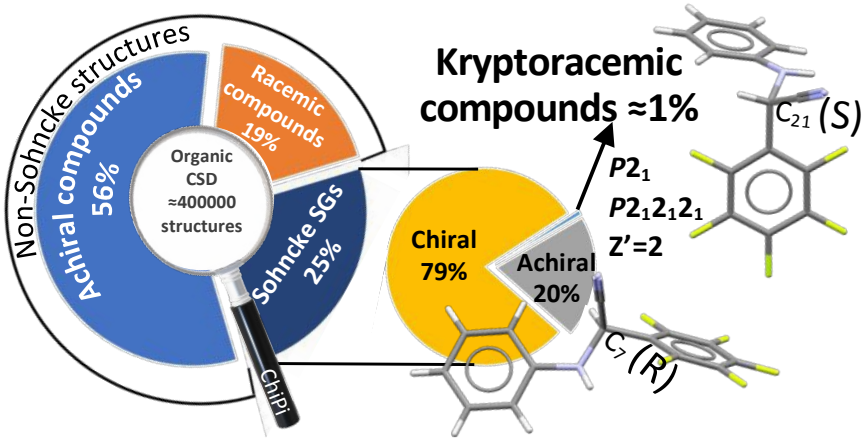
‡ ChiPi code will be updated to work with future CCDC releases. The updates will be available here: https://labsms.univ-rouen.fr/en/content/chipi

1 J. Jacques, A. Collet and S. H. Wilen, *Enantiomers, racemates, and resolutions*, 1981.
2 G. Coquerel, *Chem. Soc. Rev.*, 2014, **43**, 2286–2300.
3 T. Rekis, A. Bērziņš, L. Orola, T. Holczbauer, A. Actiņš, A. Seidel-Morgenstern and H. Lorenz, *Crystal Growth & Design*, 2017, **17**, 1411–1418.
4 C. Brandel, S. Petit, Y. Cartigny and G. Coquerel, *Curr. Pharm. Des.*, 2016, **22**, 4929–4941.
5 T. Rekis, *Acta Crystallogr B Struct Sci Cryst Eng Mater*, 2020, **76**.
6 I. Bernal and R. A. Lalancette, *Comptes Rendus Chimie*, 2015, **18**, 929–934.
7 R. Bishop and M. L. Scudder, *Crystal Growth & Design*, 2009, **9**, 2890–2894.
8 L. Fábián and C. P. Brock, *Acta Crystallogr B Struct Sci*, 2010, **66**, 94–103.
9 E. Grothe, H. Meekes and R. de Gelder, *Acta Crystallogr B Struct Sci Cryst Eng Mater*, 2017, **73**, 453–465.
10 I. Bernal and S. Watkins, *Acta Crystallogr C Struct Chem*, 2015, **71**, 216–221.
11 B. Dalhus and C. H. Görbitz, *Acta Crystallogr B Struct Sci*, 2000, **56**, 715–719.
12 S. Eppel and J. Bernstein, *Acta Crystallogr B Struct Sci*, 2008, **64**, 50–56.
13 I. J. Bruno, J. C. Cole, P. R. Edgington, M. Kessler, C. F. Macrae, P. McCabe, J. Pearson and R. Taylor, *Acta Crystallogr B Struct Sci*, 2002, **58**, 389–397.
14 D. A. Clemente and A. Marzotto, *Acta Crystallogr B Struct Sci*, 2003, **59**, 43–50.
15 D. A. Clemente, *Tetrahedron*, 2003, **59**, 8445–8455.
16 D. A. Clemente and A. Marzotto, *Acta Crystallogr B Struct Sci*, 2004, **60**, 287–292.
17 D. A. Clemente, *Inorganica Chimica Acta*, 2005, **358**, 1725–1748.
18 R. E. Marsh and D. A. Clemente, *Inorganica Chimica Acta*, 2007, **360**, 4017–4024.
19 R. E. Marsh, V. Schomaker and F. H. Herbstein, *Acta Crystallogr B Struct Sci*, 1998, **54**, 921–924.
20 R. E. Marsh and I. Bernal, *Acta Crystallogr B Struct Sci*, 1995, **51**, 300–307.
21 R. E. Marsh and F. H. Herbstein, *Acta Crystallogr B Struct Sci*, 1988, **44**, 77–88.
22 F. H. Herbstein and R. E. Marsh, *Acta Crystallographica Section B*, 1998, **54**, 677–686.
23 R. E. Marsh, *Acta Crystallogr B Struct Sci*, 1999, **55**, 931–936.
24 R. E. Marsh, *Acta Crystallogr B Struct Sci*, 2000, **56**, 744–744.
25 A. L. Spek, *Acta Crystallogr D Biol Crystallogr*, 2009, **65**, 148–155.
26 C. F. Macrae, I. J. Bruno, J. A. Chisholm, P. R. Edgington, P. McCabe, E. Pidcock, L. Rodriguez-Monge, R. Taylor, J. van de Streek and P. A. Wood, *J Appl Crystallogr*, 2008, **41**, 466–470.
27 E. Pidcock, W. D. S. Motherwell and J. C. Cole, *Acta Crystallogr B Struct Sci*, 2003, **59**, 634–640.
28 J. van de Streek and S. Motherwell, *CrystEngComm*, 2007, **9**, 55–64.
29 L. Gyevi-Nagy and G. Tasi, *Computer Physics Communications*, 2017, **215**, 156–164.

30 T. Pilati and A. Forni, *J Appl Crystallogr*, 2000, **33**, 417–417.
31 D. Watkin, *J Appl Crystallogr*, 2008, **41**, 491–522.
32 H. Flack and G. Bernardinelli, *Inorganica Chimica Acta*, 2006, **359**, 383–387.
33 C. P. Brock, *Acta Crystallogr B Struct Sci Cryst Eng Mater*, 2016, **72**, 807–821.
34 A. D. Bond, *CrystEngComm*, 2010, **12**, 2492–2500.
35 R. Taylor, J. C. Cole and C. R. Groom, *Crystal Growth & Design*, 2016, **16**, 2988–3001.
36 G. R. Desiraju, *CrystEngComm*, 2007, **9**, 91–92.
37 K. M. Steed and J. W. Steed, *Chem. Rev.*, 2015, **115**, 2895–2933.
38 M. Hoquante, M. Sanselme, I. B. Rietveld and G. Coquerel, *Crystal Growth & Design*, 2019, **19**, 7396–7401.
39 K. Kersten, R. Kaur and A. Matzger, *IUCrJ*, 2018, **5**, 124–129.
40 R. Laubenstein, M. D. Şerb, U. Englert, G. Raabe, T. Braun and B. Braun, *Chem. Commun. (Camb.)*, 2016, **52**, 1214–1217.
41 U. B. R. Khandavilli, M. Lusi, B. R. Bhogala, A. R. Maguire, M. Stein and S. E. Lawrence, *Chem. Commun.*, 2016, **52**, 8309–8312.
42 N. Tumanova, N. Tumanov, F. Fischer, F. Morelle, V. Ban, K. Robeyns, Y. Filinchuk, J. Wouters, F. Emmerling and T. Leyssens, *CrystEngComm*, 2018, **20**, 7308–7321.
43 Y. Schouwstra, *Acta Crystallogr B Struct Crystallogr Cryst Chem*, 1973, **29**, 1636–1641.
44 A. Hempel, N. Camerman, A. Camerman and D. Mastropaolo, *Acta Crystallogr Sect E Struct Rep Online*, 2005, **61**, o1595–o1597.
45 J. B. van Mechelen, R. Peschar and H. Schenk, *Acta Crystallogr B Struct Sci*, 2008, **64**, 249–259.
46 P. R. Sahoo and S. Kumar, *Sensors and Actuators B: Chemical*, 2016, **226**, 548–552.
47 V. Seiler, N. Tumanov, K. Robeyns, J. Wouters, B. Champagne and T. Leyssens, *Crystals*, 2017, **7**, 84.
48 O. A. Lodochnikova, R. M. Khakimov, L. Z. Latypova, A. R. Kurbangalieva and I. A. Litvinov, *Russ Chem Bull*, 2016, **64**, 2444–2453.
49 W. Wong-Ng, P. T. Cheng and S. C. Nyburg, *Acta Crystallogr B Struct Sci*, 1984, **40**, 151–158.
50 A. Turza, A. Pop, M. Muresan-Pop, L. Zarbo and G. Borodi, *Journal of Molecular Structure*, 2020, **1199**, 126973.
51 S. Krishnaswamy, R. G. Gonnade, M. M. Bhadbhade and M. S. Shashidhar, *Acta Crystallogr C Cryst Struct Commun*, 2009, **65**, o54–o57.
52 M. M. H. Smets, M. B. Pitak, J. Cadden, V. R. Kip, G. A. de Wijs, E. R. H. van Eck, P. Tinnemans, H. Meekes, E. Vlieg, S. J. Coles and H. M. Cuppen, *Crystal Growth & Design*, 2017, **18**, 242–252.
53 N. Tumanova, V. Seiler, N. Tumanov, K. Robeyns, Y. Filinchuk, J. Wouters and T. Leyssens, *Crystal Growth & Design*, 2019, **19**, 3652–3659.
54 H. Quast, J. Carlsen, H. Röschert, E. M. Peters, K. Peters and H. G. V. Schnering, *Chem. Ber.*, 1992, **125**, 2591–2611.
55 O. A. Lodochnikova, L. S. Kosolapova, A. F. Saifina, A. T. Gubaidullin, R. R. Fayzullin, A. R. Khamatgalimov, I. A. Litvinov and A. R. Kurbangalieva, *CrystEngComm*, 2017, **19**, 7277–7286.
56 D. S. Giera, L. Hennig, T. Gelbrich and C. Schneider, *Zeitschrift für Naturforschung B*, 2011, **66b**, 419–424.
57 A. T. Gubaidullin, A. I. Samigullina, Z. A. Bredikhina and A. A. Bredikhin, *CrystEngComm*, 2014, **16**, 6716.
58 R. Taylor, F. H. Allen and J. C. Cole, *CrystEngComm*, 2015, **17**, 2651–2666.
59 A. Kitaigorodsky, *Molecular crystals and molecules*, Academic Press, 1973.
60 D. Watkin, *J Appl Crystallogr*, 2008, **41**, 491–522.

View Article Online DOI: 10.1039/D0CE00303D

View Article Online
DOI: 10.1039/D0CE00303D



Determination of the kryptoracemic compounds frequency in the Cambridge Structural Database using CCDC Python API script.