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Crystal Engineering and Chloro-Methyl Interchange – a CSD Analysis

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A search method for investigating the extent to which chloro-methyl interchange is exhibited by crystal structures deposited with the Cambridge Crystallographic Database is presented. Using the October 1998 release with 190,307 data entries, 105 pairs were identified for which there was a common molecular framework, differing only in the presence of a chloro or methyl group. Approximately 30% appear to demonstrate isotructural packing arrangements. Two examples within the database that were found not to show Cl-Me interchange were subsequently examined from the viewpoint of structural mimicry and the formation of mixed crystals.

Keywords: chloro-methyl interchange; isostructural; co-crystallisation; structural mimicry; polymorphism

INTRODUCTION

There is increasing interest in the prediction of organic crystal structures based solely on molecular information. As things currently

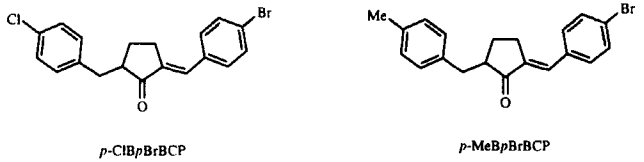
stand, however, there is no reliable method for predicting which of the large number of low energy crystal arrangements will be the actual one adopted. Whilst significant progress has been made in the development of computational methods for structure prediction[1,2] solid state organic chemists still depend heavily upon identifying, and subsequently using, systematic packing features within crystals.[3]

Kitaigorodskii,[4] for example, proposed that under appropriate circumstances, interchanging single functional groups of comparable volume on a molecule, such as the chlorine atom (20 $Å^3$) for a methyl group (24 $Å^3$) (so-called chloro-methyl interchange) might not result in significant changes in crystal packing. Whilst various examples are documented[5] where similar packing arrangements exist after such interchange, as yet no detailed systematic assessment of this crystal engineering principle has been reported.

An aim of the work reported here was to test the validity of chloro-methyl interchange using the extensive amount of crystallographic information contained within the Cambridge Structural Database (CSD).[6] The approach was to develop suitable computer programs to search for, and extract, details of molecular fragments which exhibited appropriate chloro-methyl exchange. The resulting "hits" were then assessed as to whether isostructural interchange had indeed occurred.

Closely related to this topic is the idea of structural mimicry where non-isostructural molecules co-crystallise to yield mixed crystals where one component is forced to adopt a packing arrangement different from that which it adopts in the pure crystal. For example, the chlorinated and methylated derivatives of the fragment 2-benzyl-5-bromobenzylidine-cyclopentanone analysed by Jones *et al.* (*p*-

ClB*p*BrBCP and *p*-MeB*p*BrBCP (Figure 1)), are non-isostructural.[7] The chlorinated fragment (photoinert in the solid state) adopts a bent conformation in the solid state whilst the methylated fragment (photoreactive in the solid state) adopts a planar conformation. A reactive mixed crystal of the chloro and methyl form can be prepared, however, in which the chloro derivative takes on a planar conformation.



p-ClB*p*BrBCP *p*-MeB*p*BrBCP

FIGURE 1 Non-isostructural chloro-methyl interchanged molecules.

To examine this idea of structural mimicry, four examples of chloro-methyl interchanged fragments retrieved from the CSD search that did not show isostructural arrangements were chosen: 4-methylbenzamide (**I**),[8] 4-chlorobenzamide (**II**),[9-11] 2-methylbenzamide (**III**)[12] and 2-chlorobenzamide (**IV**)[13] (Figure 2). Mixed crystals of **I+II** and of **III+IV** were therefore examined from the viewpoint of structural mimicry.

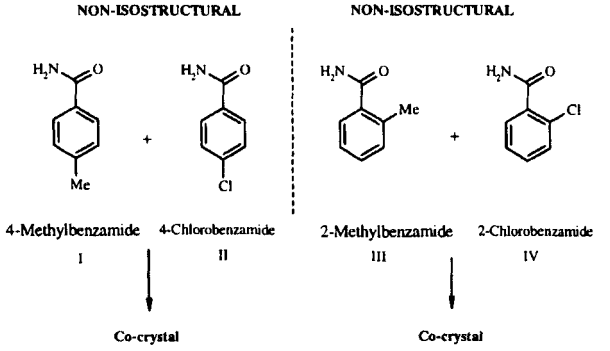


FIGURE 2 Non-isostructural molecules used for structural mimicry studies.

One structure is known for both **I** and **III**. Four polymorphic forms of compound **II** are reported in the literature: two room temperature polymorphs (α and β) and higher temperature γ(50°C) and δ(80°C) polymorphs.[9-11] Two room temperature polymorphs (α and β) are described by Kato *et al.* for **IV**.[13] Interestingly, two additional disordered forms were obtained for **IV**, the γ and δ forms, but further attempts by the same authors to obtain these two forms failed. Only the α forms of **II** and **IV** have been observed from the crystallisation experiments we have carried out, however, and so the following discussion of the hydrogen bonding networks in **II** and **IV** is limited to these polymorphs (Table 1).

TABLE 1 Unit cell parameters and CSD codes for **I**, **II**, **III** and **IV**.

Compound	Unit Cell Parameters / Å		
I DABVAD01[8]	$a = 9.858$ $b = 7.526$ $c = 10.764$	$\beta = 111.3°$	$P2_1/a$
II PCBZAM01[9] α form	$a = 15.027$ $b = 5.481$ $c = 14.486$	$\alpha = 97.84°$ $\beta = 111.99°$ $\gamma = 95.17°$	 $Z = 6$
III NABQEM[12]	$a = 12.184$ $b = 6.077$ $c = 4.992$	$\alpha = 89.82°$ $\beta = 97.09°$ $\gamma = 95.82°$	$P\text{-}1$ $Z = 2$
IV CLBZAM10[13] α form	$a = 14.127$ $b = 10.683$ $c = 5.051$	$\beta = 90.2°$	$P2_1/n$ $Z = 4$

Common features are observed in the hydrogen bonded networks of compounds **I**, **II**, **III** and **IV**. The hydrogen bond array displayed in each structure is produced from the well established motifs **a** and **b** illustrated in Figure 3.

TABLE 2 Torsion angle measured for compounds **I**, **II**, **III** and **IV**.

Compound	Torsion Angle / °
I	24.6
II	33.2, 29.3, 17.8 (three molecules form the asymmetric unit)
III	41.2
IV	48.3

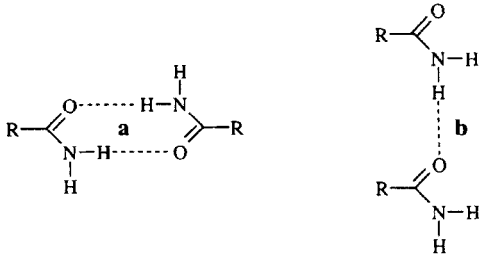
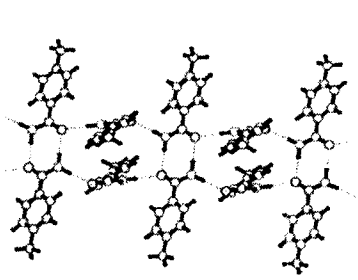
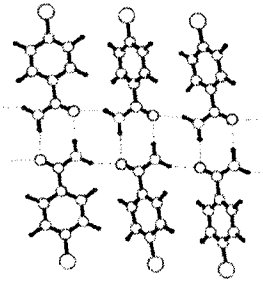


FIGURE 3 Robust hydrogen bonding motifs created by an amide group.

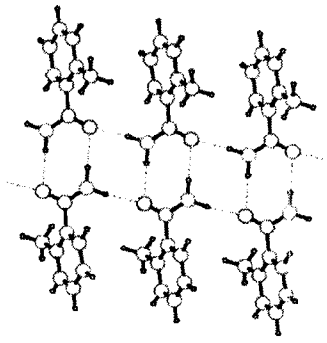
The 'broken-ladder' network in **I** distinguishes the ribbon from those in **II**-**IV** and also results in the generation of a 2-D sheet (Figure 4). No inter-ribbon hydrogen bonds are observed for **II**, **III** and **IV**. Close packing of the four types of ribbons is achieved by rotating the phenyl groups relative to the amide portions so as to reduce steric interactions along the length of each ribbon (Figure 5 and Table 2).



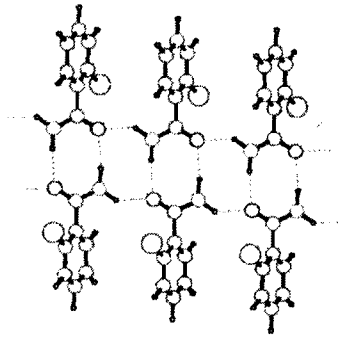
Ribbon arrangement in **I**



Ribbon arrangement in **II**

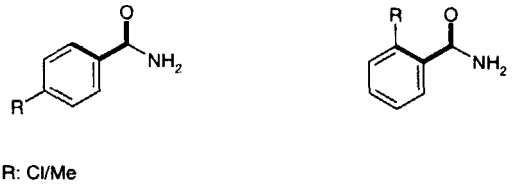


Ribbon arrangement in **III**



Ribbon arrangement in **IV**

FIGURE 4 Comparison of the hydrogen bond arrangements in **I, II, III** and **IV**.



R: Cl/Me

FIGURE 5 Torsion angle highlighted for **I-IV**.

Although compounds **III** and **IV** display the same 'ladder' hydrogen bond array, their crystal structures are not isostructural. Adjacent dimers within ribbons of **III** are related by an inversion centre, whereas in **IV** adjacent dimers are related by a mirror plane. Additionally, the mode of packing of ribbons are different for each compound.

RESULTS

2.1 CSD search procedure

The October 1998 release version of the CSD was searched using QUEST. This version contains 190,307 data entries. Searching began by retrieving those compounds containing either a chlorine atom or a methyl group to create two files; one for molecules containing a chlorine atom and the other for molecules containing a methyl group. Scheme 1 summarises the overall methodology.

The two separate QUEST files were then opened, and each string was stored into three different arrays containing the REFCODE, element identity and their associated stoichiometry. In the next step methyl and chloro pairs were identified by the presence/absence of an extra carbon atom and three hydrogen atoms and one less chlorine atom. The chloro-methyl-interchanged fragments were then written into a single output file. Duplicate entries were excluded.

The definition of a chloro-methyl-interchanged fragment by simple numerical comparison of numbers of atoms is clearly limited. An example is shown in Figure 6.

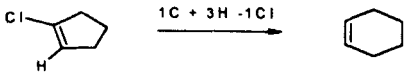
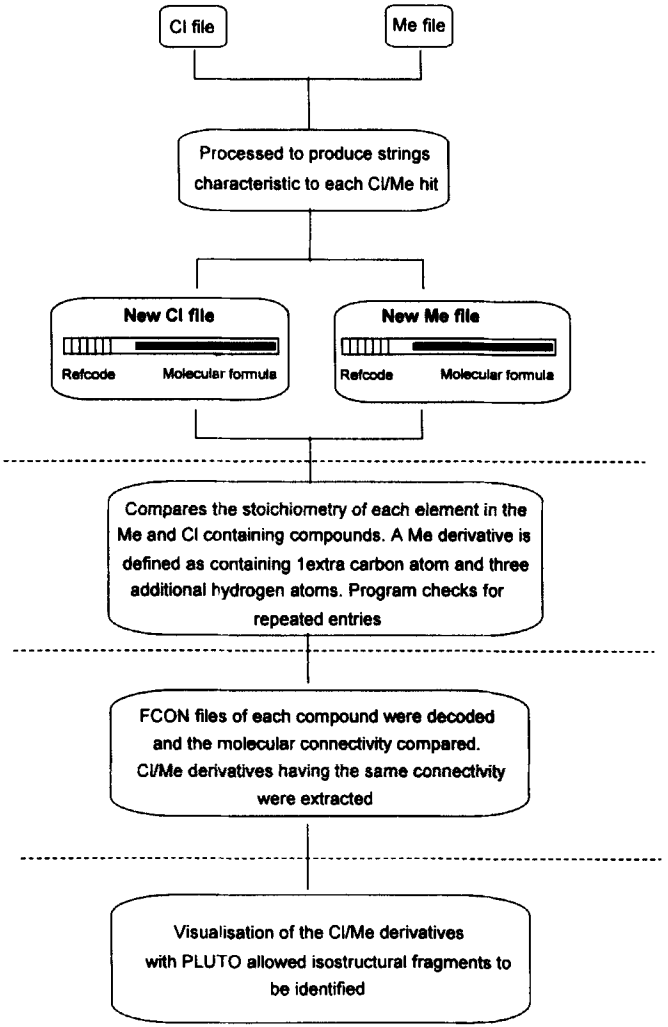


FIGURE 6 An example of the limitation of simple stoichiometric comparison for identifying suitable molecular fragments.



SCHEME 1.

To overcome this problem a separate program was used to compare the molecular connectivity of chloro-methyl interchanged fragments. This comparison resulted in a list of 105 molecular fragments for which crystallographic data existed for chloro and methyl interchanged fragments.

Graphical comparison of these fragments, using PLUTO, revealed 29 isostructural arrangements i.e. approximately 30% of the possible instances. The REFCODES for these are shown in Table 3. The last five entries (25-29)[14-17] represent an interesting sub-group in which repeated chloro-methyl interchange occurs (Table 4).

TABLE 3 REFCODES for isostructural Cl-Me interchanged molecules obtained from the CSD.

REFCODE	REFCODE	REFCODE	REFCODE	REFCODE	REFCODE
1 BDIXNA	6 MTCYME	11 CUXDII10	16 ZUGPOG	21 WEPZUM	27 LEJYUU
1 BDIXNC	6 CTCYME	11 KADMOR	16 ZUGPOH	21 WIKKUW	28 CORCUH
2 ROHZUJ	7 MTPHOS	12 KOTGOP	17 TOEFIM10	22 YOWVUF	29 KIDBUU
2 ROHZIK	7 CTPHOS	12 KOTGUV	17 CPEFIM	22 ZOHNUF	
3 CINWEB	8 VEVBUT	13 NOFXON	18 NOFWAG	23 TEMYUF	
3 CINWAX	8 JENHIV	13 NOFXIP	18 RIWRUK	23 TEMZAM	
4 CISFEP	9 FIXGAU	14 TEHKOG	19 DEMPIU	24 LEKPEW	
4 CISFAL	9 JIGGAH	14 TEHKUH	19 HAXTOP	24 PABZEX	
5 COFTAS10	10 SEDCIN	15 JILXAD	20 FAKKEH	25 CORDES	
5 COFSUL10	10 KIKCEM	15 YUFNVI	20 JORGIG	26 PABZAT	

TABLE 4 Repeatedly interchanged fragments.

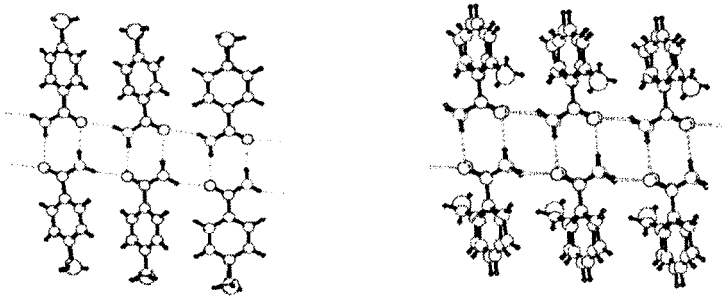
Molecular Structure	Unit Cell Parameters	Space Group and Cell Formula Units
 CORDES[14]	*a*:8.533 *b*:10.187 *β*: 97.970 *c*:13.526	$P2_1/c$ Z = 4
 CORCUH[14]	*a*:8.410 *b*:10.194 *β*: 98.040 *c*:13.329	$P2_1/c$ Z = 4
 PABZAT[15]	*a*:8.480 *b*:9.998 *β*: 97.930 *c*:13.221	$P2_1/c$ Z = 4
 LEJYUU[16]	*a*:8.464 *b*:10.020 *β*: 98.660 *c*:13.296	$P2_1/c$ Z = 4
 KIDBUU[17]	*a*:8.485 *b*:9.010 *β*: 98.410 *c*:13.378	$P2_1/c$ Z = 4

2.2 Structural mimicry studies

Re-crystallisation of **I**, **II**, **III** and **IV** from ethanol, ethyl acetate or toluene showed no evidence for polymorphism (by powder X-ray diffraction) for either the pure materials or the co-crystals. This is to be compared with the literature reports of polymorphs found for **II** and **IV**. There were, however, pronounced changes in morphology and samples were, therefore, gently ground before powder diffraction patterns were recorded to avoid preferred orientation effects. Indexing the powder patterns of re-crystallised **I**, **II**, **III** and **IV** showed the calculated values of the unit cell parameters of **I** and **III** to match the values reported in the literature, and the calculated unit cell values of **II** and **IV** corresponded to the α-polymorphs in each case.

Given the similar ribbon arrangement within **III** and **IV** it was expected that mixing within the ribbon will readily occur. Indeed single crystals corresponding to a 1:1 mixture did show mixing within the ribbons, although the overall structure adopted (Figure 7) was that of **IV** – see cell parameters in Table 5. In the case of **I** and **II** the 1:1 co-crystal adopted the packing of **II** within a disordered chain arrangement.

Other compositions were grown from ethanol solutions of **I** + **II** and of **III** + **IV**, in 2 dram sample vials. The vials were covered with perforated wax film and the solvent allowed to evaporate slowly at room temperature over 2-3 days. All crystals were stored in sealed sample bottles below 0 °C. Powder X-ray patterns were recorded at room temperature using a STOE diffractometer with Cu Kα radiation.



Ribbon arrangement in **I+II** Ribbon arrangement in **III+IV**

FIGURE 7 Comparison of the hydrogen bond arrangements in co-crystals of **I+II** and **III+IV** respectively.

TABLE 5 Single crystal diffraction data obtained for mixed crystals.

Mixed Crystal	**Unit Cell Parameters**		**Space Group and Cell Formula Units**
I+II	$a = 5.400$	$\alpha = 111.62°$	$P\text{-}1$
	$b = 14.424$	$\beta = 95.08°$	
	$c = 14.987$	$\gamma = 97.73°$	$Z = 6$
III+IV	$a = 5.048$		$P2_1/n$
	$b = 10.832$	$\beta = 93.07°$	
	$c = 13.922$		$Z = 4$

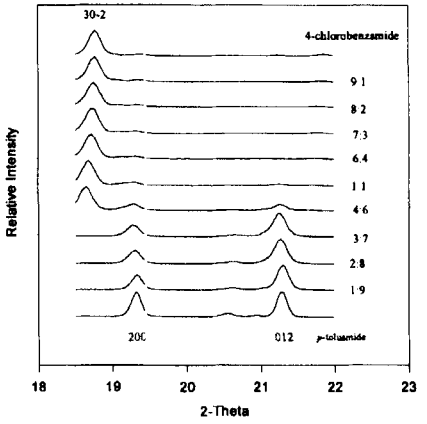


FIGURE 8 PXRD patterns for co-crystals of **I** and the triclinic α form of **II** with differing stoichiometry.

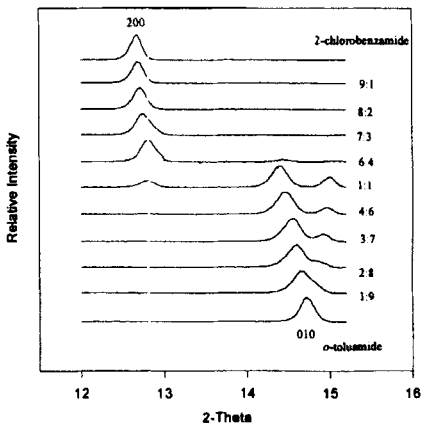


FIGURE 9 PXRD patterns of co-crystals of **III** and the monoclinic α form of **IV** with differing stoichiometry.

Figures 8 and 9 show the PXRD patterns obtained for the various compositions. There is, for both systems, a sharp transition between structure types, although in both cases the systematic shift of the reflections would appear to confirm co-crystal formation at the different stoichiometries. Habit modification effects are likely to follow the trends established for benzamide and benzoic acid.[18]

The data confirms the role that co-crystallisation can play in controlling, via structural mimicry, the three-dimensional packing arrangement adopted during crystallisation.

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