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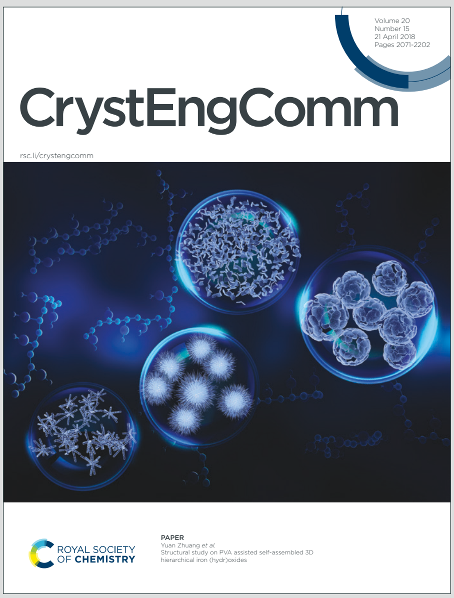

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ARTICLE

Methods for easy recognition of isostructurality - Lab Jack-like crystal structures of halogenated 2-phenylbenzimidazoles

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Tools to describe isostructurality are important in the understanding of close packing principles and in the fine-tuning of crystal properties. In order to present how different methods work in practice a series of 2-phenylbenzimidazole derivatives substituted on the phenyl ring in *ortho*, *meta* and *para* positions or simultaneously in two different positions by F, Cl and Br was selected. The flexibility of the phenylbenzimidazole frame permits a gradual isostructural change of the structures with step-by-step alteration of the internal arrangement as well as of the lengths of the unit cells perpendicular to the determining N-H...N hydrogen bonded chains. The exchange of the different halogen substituents alters the angle between the neighbouring benzimidazole moieties and the system of the secondary interactions, and finally the isostructurality terminates. The series of the isostructural crystals look like a lab Jack lifted to different heights. Although the neighbouring members of the series are highly similar, the extremes of the list vary deliberately keeping the space group and Z. It raises the question what the extents of structural differences are what we still consider being isostructural. The preference of certain intermolecular interactions divides the investigated isostructural *Pbca* crystals into two subgroups like a switch. The definition of isostructurality does not consider supramolecular similarity, although it may have a determining role as shown. It is presented how isostructurality can be described by numerical descriptors. Cell similarity (π), isostructurality (I_s), as well as molecular isometricity indices are calculated. Correlations of the molecular conformation, secondary interactions and the crystallographic parameters are revealed by statistical methods. With the use of these methods we provide an easy way to recognise and to characterize isostructurality. We show that the prerequisites of isostructurality are the similar composition and conformation of the compounds, their analogous molecular and supramolecular arrangement in the crystals having the same space group and Z. Exploitation of the Cambridge Structural Database for systematical investigations to complete the isostructural series is essential.

Introduction

More and more new substances with tailor-made properties are produced by crystal engineering[1-3]. It can come true based on the knowledge of the molecular and supramolecular properties[4-5], and crystallographic and non-crystallographic symmetries[6]. Mastering the supramolecular packing architecture, in effect synthon engineering[7-8], can be achieved through fine chemical changes. Firm transformation of crystal packing arrangement can be accomplished by influencing electrostatic and steric properties by application of substituents, changing its placement and/or chemical composition; or by the use of compounds with similar chemical composition in multi-component structures. Molecular placement and molecular conformation of flexible molecules may adjust to the chemical and supramolecular features, thus isostructural crystals can be achieved[9-10]. This way we may succeed to produce series of crystal structures with firmly gradual transition in crystal packing arrangements through chemical change. Isostructural crystals are highly similar in their packing arrangement, but may differ to a less or more extent in chemical properties, like seeding and crystal growth, recognition processes, stability, and biological activity. The balance of spatial requirements and electrostatic effects ultimately determines the crystal packing arrangement.

There is a slight structural difference between the neighbouring members in the series of fine-tuned isostructural crystals, but structural variations can already be sever among the different members of the series. The question is how large the extent of difference can be among crystal structures that we may still consider as isostructural crystals[6].

Investigation of isostructurality is a tool of understanding of the close packing principles. Recognition of isostructurality is not necessarily straightforward. Isostructurality calculations and statistical analyses are efficient tools for discovery of isostructural crystals as presented in this paper.

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Crystal structures of halogenated 2-phenylbenzimidazole (PBI) derivatives were analysed to investigate the effect of substitution on isostructurality. The molecules are substituted on the phenyl ring in *ortho*, *meta* and *para* positions or simultaneously in two different positions with fluorine, chlorine and bromine. Eight structures were retrieved from the Cambridge Structural Database[11] for the comparison. To complete the series four new compounds were synthesised, and their single crystal structures determined. Exploitation of the Cambridge Structural Database is essential in order to have complete isostructural series for the systematic investigations.

The moderate rotational freedom around the single bond between the aromatic rings of the substituted PBI chain-forming molecules generates flexible structures with variable unit cell dimensions depending on derivatisation. Owing to the presence of the determinative N-H...N hydrogen bonded chains in all crystal structures, the halogenated PBI structures will be similar to different extents. Halogen interactions are more diversified than hydrogen bonding regarding both interaction strength and directionality and are therefore applicable for more sophisticated crystal engineering purposes[12-16]. With the presence of the different halogen substituents at different positions, we have received a series of structures to test the limits of isostructurality.

Correlations of the halogen atomic positions, secondary interactions and crystallographic parameters have been revealed by statistical methods. Likeness of the structures is quantified by different kind of similarity and isostructurality calculations. The arrangement of the molecules recalls a laboratory Jack of which the height is determined by the halogen substitution.

Experimental

Synthesis and single crystal growth of OFPBI, OBRPBI, MCLPBI and MBRPBI

Synthesis of the new substituted benzimidazole compounds was performed by a slightly modified process described by Secci[17]. The corresponding halogenated benzaldehyde or benzoic acid (1 mmol), 1,2-diaminobenzene (1 equiv.) and sodium metabisulfite ($Na_2S_2O_5$, 1 equiv.) was dissolved in 4 ml DMF in a 10 ml vial suitable for an automatic single-mode microwave reactor (2.45 GHz high-frequency microwaves, power range 0–300 W). The mixture was stirred for 30 s and then heated by microwave irradiation for 40 min at 100°C. The internal vial temperature was controlled by an IR sensor. After cooling with pressurized air, the reaction mixture was poured onto ice, filtered, and dried on air. For further purification, products were recrystallized from diethyl ether (*ortho*-substituted compounds), or ethanol (*meta*-substituted compounds).

OFPBI: off-white solid, yield: 55 %; 1H-NMR is identical with previously reported[18]. 1H NMR (300 MHz, DMSO-d6) δ 12.56 (s, 1H), 8.25 (t, J = 7.3 Hz, 1H), 7.74 – 7.51 (m, 3H), 7.51 – 7.32 (m, 2H), 7.25-7.22 (m, 2H). Colourless single crystals of OFPBI were grown from tetrahydrofuran and methanol solvent mixture by slow evaporation.

OBRPBI: off-white solid, yield: 44 %; 1H-NMR is identical with previously reported[19]. 1H NMR (500 MHz, DMSO-d6) 7.81 (d, J = 8.2 Hz, 1H), 7.75 (d, J = 7.7 Hz, 1H), 7.63-7.59 (m, 2H), 7.55 (t, J = 7.5 Hz, 1H), 7.46 (t, J = 7.7 Hz, 1H), 7.24 (s, 2H). Colourless single crystals of OBRPBI were grown from methanol by slow evaporation.

MCLPBI: white-solid, yield 58 %; 1H-NMR is identical with previously reported[18]. 1H NMR (500 MHz, DMSO-d6) δ 12.99 (br s, 1H), 8.21 (t, 1H, J = 1.5 Hz), 8.13 (dt, 1H, J = 7.4 Hz, 1.5 Hz), 7.65 (d, 1H, J = 7.5 Hz), 7.59-7.53 (m, 3H), 7.30-7.22 (m, 2H); Colourless single crystals of MCLPBI were grown from ethanol by slow evaporation.

MBRPBI: yellow solid, yield: 32 %; 1H-NMR is identical with previously reported[20]. 1H NMR (500 MHz, DMSO-d6) δ 13.00 (s, 1H), 8.35 (s, 1H), 8.16 (d, J = 7.8 Hz, 1H), 7.67 (dd, J = 8.0, 1.0 Hz, 1H), 7.60 (bs, 2H), 7.50 (t, J = 7.9 Hz, 1H), 7.21 (dd, J = 6.0, 3.1 Hz, 2H). Colourless single crystals of MBRPBI were grown from ethanol by slow evaporation.

Single crystal X-ray diffraction data of OFPBI, OBRPBI, MCLPBI and MBRPBI

X-ray diffraction data were collected on a Rigaku RAXIS-RAPID II diffractometer using CuKα (OBRPBI, OFPBI) or MoKα (MCLPBI, MBRPBI) radiation with graphite monochromator. Numerical absorption correction was applied to the data. The structures were solved by direct methods (and subsequent difference syntheses). Sir2014[21] and SHELXT[22] under WinGX[23] software were used for structure solution and refinement, respectively. Anisotropic full-matrix least-squares refinements on F^2 for all non-hydrogen atoms were performed.

Hydrogen atomic positions were calculated from assumed geometries except the H_2N amine hydrogens that were located in difference maps. Hydrogen atoms were included in structure factor calculations, but they were not refined. The isotropic displacement parameters of the hydrogen atoms were approximated from the U(eq) value of the atom they were bonded to.

Statistical analysis

Multivariate data analysis was performed on the crystallographic data of the twelve investigated substituted benzimidazoles to reveal correlations and similarities between crystal parameters, molecular structures and supramolecular interactions[24-25]. Cluster analysis[24] was performed on the standardized dataset (collected in Table 1 and 2), where samples are grouped based on similarities without taking into account the information about the group membership, e.g. substitution and space groups. This technique is based on the idea that the similarity is inversely related to the distance (differences between parameters) between samples. Cluster analysis calculates the distances (or correlation) between all samples using a defined metric which is Euclidean distance in our case. Grouping of the samples was performed by Ward's method clustering algorithm. Principal component analysis (or

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factor analysis, PCA) was applied as well on the data in order to reduce the data dimensionality[25]. PCA transforms the original measured variables into new uncorrelated variables called principal components which are the linear combination of the original measured variables. All statistical evaluations were accomplished with the software Statistica[26].

Cell similarity, isostructurality and molecular isometricity calculations[27-30]

The prerequisite of isostructurality is the similarity of the unit cells. The cell similarity index (π) describes the dissimilarity of the unit cell dimensions of the compared crystals:

$$\pi = \left|\frac{a+b+c}{a'+b'+c'} - 1\right|$$

where a, b, c and a', b', c' are the orthogonalized lattice parameters of the two related crystals. In the event of a great similarity of the two unit cells, π is close to zero.

Isostructurality implies equal Z' and a similar internal arrangement in the related crystal lattices. In contrast to polymorphism, isostructurality can be characterized by numerical descriptor.

The isostructurality index (I_s) of two related crystal structures can be calculated as follows:

$$I_s(n) = \left|\left[\frac{\Sigma(\Delta R_i)^2}{n}\right]^{1/2} - 1\right| \times 100\%,$$

where *n* is the number of related non-hydrogen atoms, and *ΔRi* are the distance differences between their atomic coordinates. The compared molecules have to be selected in a way to be within the same section of the related structures, and they have to be in the closest possible selection to the origins. Crystal symmetries should be considered at the transformations. The isostructurality index takes into account both the differences of the molecular geometries and the molecular positional differences caused by rotations or translations. In the event of high structural similarity, the I_s is getting close to 100%.

The cell similarity and isostructurality calculations for the pairs of similar crystal structures were performed by software ISOS[30].

The isometricities of the related molecular moieties in different crystal structures were determined by the software Mercury[31] of CSD[11] superimposing them and calculating the root mean square of distance differences of the related atoms (rmsD), giving also the largest distance difference (maxD) between them.

Kitaigorodskii packing index (KPI) was calculated by software Platon[32].

Discussion

Structural analysis of the lab Jack crystals

Eight halogenated 2-phenylbenzimidazole crystal structures from the CSD[11] (JEYTUD[33], MINHOI[34], TUDXIB[35], LUJWIW01[36], DETKIX[37], GOLNOM[38], QERTIR[39], SEZNUH[40]) and 4 new systematically synthesised halogenated 2-phenylbenz-imidazole structures (*ortho*-fluoro- (OFPBI), *meta*-chloro- (MCLPBI), *ortho*-bromo- (OBRPBI) and *meta*-bromo- (MBRPBI) phenylbenzimidazole (PBI)) (**Table S1**) have been analysed and compared to reveal the structural similarities and differences in their fine-tuned series (**Fig 1**). The studied PBIs have been substituted on the phenyl ring in *ortho*, *meta* and *para* positions or they are substituted simultaneously at two different positions with F, Cl and Br. Our aim is to understand the close packing principles and the role of molecular conformation, supramolecular interactions and symmetries in order to be able to perform directed manipulation of molecular packing arrangements, as well as the investigation of the possible application of halogen interactions for the fine-tuning of hydrogen bonded structures, while keeping isostructurality.

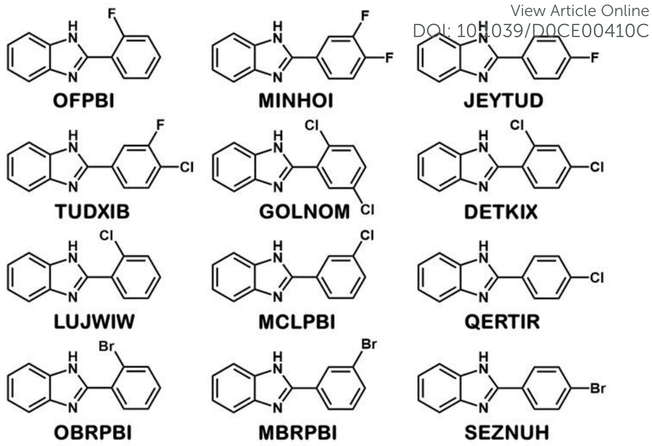

Figure 1 Formulae diagrams of the studied halogenated 2-phenylbenzimidazoles.

PBI has a rather rigid molecular structure that can be twisted around the benzimidazole-phenyl axis. The arrangement of the molecules in the crystal lattices of the halogenated PBI derivatives are determined by only one intermolecular interaction, that is significantly stronger than any other secondary interaction in the crystals. This most characteristic

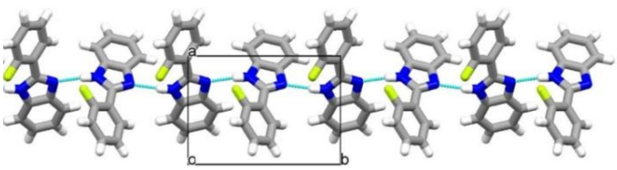

Figure 2 The N-H...N hydrogen bonds of the substituted phenylbenzimidazoles (PBIs) in the crystal structure of OFPBI as a typical example

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secondary interaction is the N-H...N type hydrogen bond in the crystals, which incorporates the amino groups of the imidazole moieties (**Fig 2**). It threads the halogenated PBIs into chains, which organize primarily the packing arrangements and only few different supramolecular interactions are possible among the hydrogen bonded molecular chains.

However, the phenylbenzimidazole derivative structures are flexible to some extent, and this flexibility permits the considerable alteration of the lattice parameters. The relative tilt of the hydrogen bonded molecules within the chain is determined by the substituents of the 2-phenylbenzimidazole skeleton. The investigated question is how and to what extent the type and the position of a halogen substituent(s) may affect and fine-tune the crystal structures, while the other influencing factors are reduced as far as possible.

Ten of the twelve 2-phenylbenzimidazole molecules crystallize in the *Pbca* space group (Z=8) and the packing arrangements of the *Pbca* structures are all similar. The single *meta*-substituted compounds (namely MCLPBI and MBRPBI) crystallize in the $P2_1/c$ space group (Z=4) and are on their part isostructural (**Fig S1**).

All PBI derivatives are organized into hydrogen bonded chains by the determining N-H...N type intermolecular interactions between the imidazole moieties. In the *Pbca* structures these molecular chains are arranged in the crystallographic *b* direction (**Fig 2)**. The length of the *b* axes is basically governed by this hydrogen bonded chains and therefore are similar for all compounds within 0.5 Å (**Table 1**). The molecules can tilt around the hydrogen bonds and the degree of the tilt determines the lengths of the crystallographic *a* and *c* axes. The length of the *a* unit cell axes is increased by 67 % and the length of the *c* unit cell axis is shrunk by 43 % within the series (**Fig S1**). There is a linear correlation between the opening angle of the benzimidazole moieties (**Fig 3, Table 2**) and the lengths of the *a* and *c* unit cell axis. In the $P2_1/c$ structures the N-H...N hydrogen bonded chains are found in the crystallographic *c* direction, and its lengths are in the range of the length of the *b* axes of the *Pbca* structures.

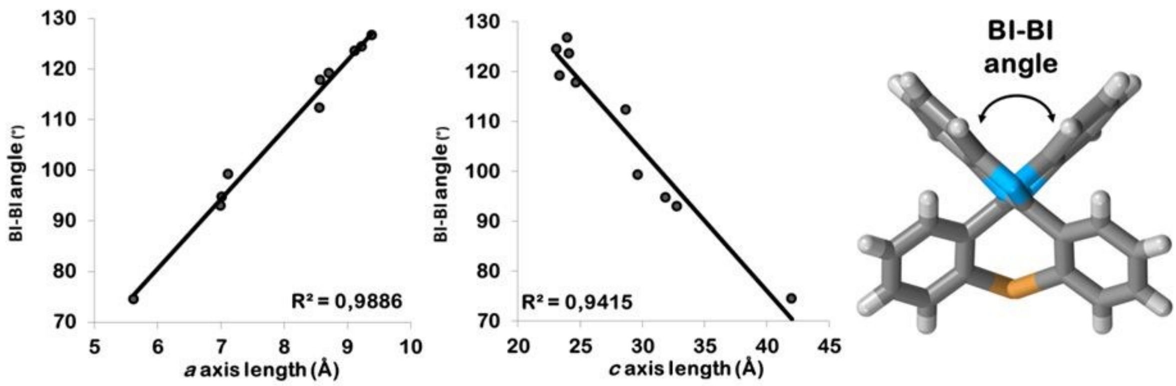

Figure 3 Correlation between the BI-BI tilt angles and the *a* as well as the *c* axes lengths in the *Pbca* structures

Table 1 Comparison of the crystal data of all investigated PBI derivatives (*Pbca* structures are listed in the order of increasing *a* axis length)

Code	Substit-uent	SG	V	a	b	c	β	Z	KPI	Dens-ity	Pack-ing
MCLPBI	mCl	$P2_1/c$	1082.2(2)	12.589(1)	9.5051(8)	9.7495(7)	111.933(8)	4	68.0	1.400	H-T
MBRPBI	mBr	$P2_1/c$	1110.9(3)	12.676(2)	9.656(2)	9.765(2)	111.638(9)	4	58.0	1.625	H-T
GOLNOM	oClmCl	*Pbca*	2301.73(6)	5.6259(8)	9.739(1)	42.007(6)	90	8	69.7	1.519	H-H
OBRPBI	oBr	*Pbca*	2279.8(2)	7.007(3)	9.936(3)	32.745(3)	90	8	66.1	1.592	H-H
LUJWIW	oCl	*Pbca*	2220.55(5)	7.0197(1)	9.9261(1)	31.8686(4)	90	8	66.9	1.368	H-H
OFPBI	oF	*Pbca*	2117.9(2)	7.1246(3)	10.0327(4)	29.629(1)	90	8	66.1	1.331	H-H
DETKIX	oClpCl	*Pbca*	2435.0(9)	8.563(2)	9.910(2)	28.694(6)	90	8	65.6	1.436	H-H
JEYTUD	pF	*Pbca*	2080(1)	8.574(2)	9.830(3)	24.680(7)	90	8	67.4	1.355	H-H
MINHOI	mFpF	*Pbca*	2028.3(7)	8.7195(17)	9.9454(19)	23.389(4)	90	8	71.9	1.508	H-H
QERTIR	pCl	*Pbca*	2157.2(8)	9.1284(18)	9.783(2)	24.156(5)	90	8	68.3	1.408	H-H
TUDXIB	mFpCl	*Pbca*	2103.35(15)	9.2302(4)	9.8500(4)	23.1247(9)	90	8	72.5	1.558	H-H
SEZNUH	pBr	*Pbca*	2205.7(7)	9.3969(17)	9.7876(18)	23.982(4)	90	8	68.5	1.645	H-H

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Table 2 Comparison of conformational data and secondary interactions for all the twelve compounds in the fine-tuned PBI series.

Code	Angle BI-BI	Dist. N-H...N	Angle N-H...N	Angle BI-Ph	oH(BI) ...oH(BI)	oH(BI) ...oH(Ph)	Dist. X...π	Dist. C-H...X	Dist. N-H...X	Dist. X...X	Dist. π...π
MCLPBI	67.83°	2.868(3)	164(3)°	26.8(1)°	2.854	3.921	4.058	3.132	-	-	3.799(2) 3.912(2)
MBRPBI	68.53°	2.867(7)	154(3)°	28.4(3)°	2.900	3.931	4.073	3.130	-	-	3.872(4) 3.972(4)
GOLNOM	74.49°	2.824	148°	27.70°	2.934	3.710	3.3077 3.5551 3.6125	3.020 3.082 3.139	2.64	-	-
OBRPBI	92.88°	2.801(6)	162(4)°	42.4(2)°	4.033	2.641	4.186	3.060 3.221	2.91(4)	-	-
LUJWIW	94.72°	2.801	163°	39.60°	4.023	2.696	4.341	2.901 3.095	2.77	-	-
OFPBI	99.21°	2.863(4)	159(3)°	35.2(2)°	4.048	2.868	4.738	2.498	2.46(3)	-	-
DETKIX	112.33°	2.866	155°	42.00°	4.911	2.429	4.295 4.698	2.945	2.79	3.506	-
JEYTUD	117.76°	2.875	163°	29.23°	5.066	2.391	-	2.703 2.844	-	3.45	3.7341
MINHOI	119.17°	2.874	158°	30.00°	5.030	2.308	-	2.508 2.746	3.04	2.849 3.387	3.5892
QERTIR	123.57°	2.905	167°	27.00°	5.365	2.322	-	3.096 3.135	-	3.346	3.8442
TUDXIB	124.40°	2.924	166°	26.90°	5.416	2.286	-	2.896 2.899 3.069	-	2.691 3.017 3.370	3.6839
SEZNUH	126.66°	2.925	168°	26.77°	5.476	2.307	-	3.212 3.217	-	3.433	3.9360

Angle BI-BI: angle between the plains of the neighbouring benzimidazole moieties [°], **Dist. N-H...N:** distance between the hydrogen bonded nitrogens [Å], **Angle N-H...N:** N-H...N angle of the hydrogen bond [°], **Angle BI-Ph:** angle between the plains of the benzimidazole and the phenyl moieties of the same molecule [°], **oH(BI)...oH(BI):** distance of the *ortho* hydrogens of the hydrogen bonded benzimidazole moieties [Å], **oH(BI)...oH(Ph):** distance of the *ortho* hydrogens of the phenyl and benzimidazole moieties of the hydrogen bonded molecules [Å], **X...π:** intra chain halogen...π interaction length of the hydrogen bonded molecules [Å], **Dist. C-H...X:** hydrogen bonds to halogen atoms [Å], **Dist. N-H...X** distance of the amine hydrogen and the halogen [Å], **Dist. X...X:** inter chain X...X halogen bond lengths [Å], **Dist. π...π** presence of π... π stacked aromatic interactions in the structures [Å], **a**: missing interactions indicated by '-'

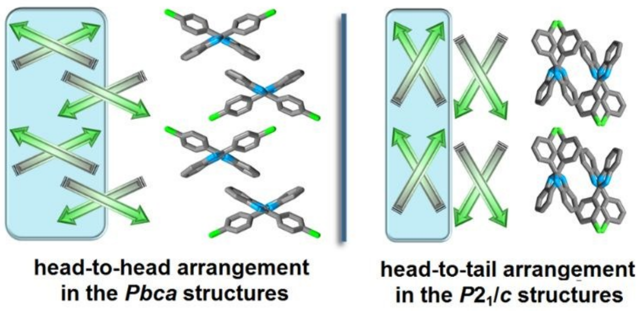

Figure 4 Schematic structural patterns in the halogenated 2-phenylbenzimidazole structures. Comparison of the packing arrangement in the *Pbca* (QERTIR) and *P*2$_1$/*c* (MCLPBI) crystals

The halogenated non-single-*meta* substituted 2-phenylbenzimidazole molecules crystallize in the *Pbca* space group, and are oriented in a head-to-head (H-H) arrangement (**Fig 4**). With this sort of organisation the similar molecular moieties get close to each other and the formation of halogen-halogen interactions is promoted. The halogenated phenyl rings form either X...X, X...H or X...π weak interactions and the benzimidazole moieties form aromatic H...π or π...π interactions. On the contrary, the *meta*-halogenated compounds, crystallized in the *P*2$_1$/*c* space group, are oriented in a head-to-tail (H-T) arrangement and the *meta*-halogens form intra-chain X...π interactions.

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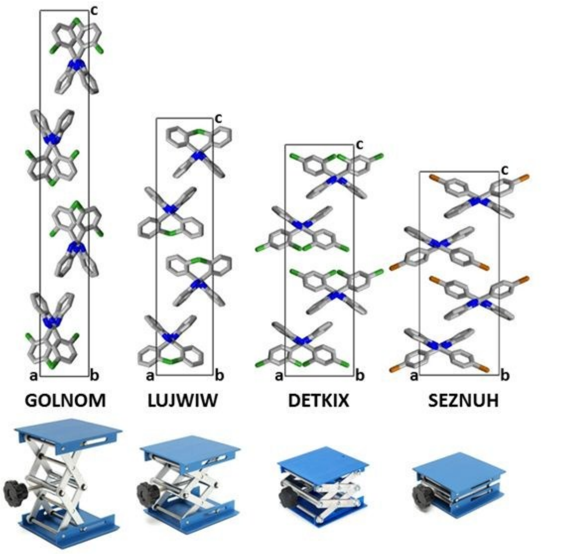

Figure 5 The lab Jack in pulled (GOLNOM), medium (LUJWIW and DETKIX) and pushed (SEZNUH) positions as an effect of the placement of the halogen substituents. Crystallographic c and a axes are proportional to the real values

In the presence of an *ortho* halogen substituent, the *a* unit cell axis is elongated (5.63-8.56 Å) and the *c* axis is shortened (28.69-42.01 Å), the tilt angle between the benzimidazole moieties (BI-BI angle) is in a smaller range (75-112°) compared to the other *Pbca* isomers – "the lab Jack is pulled to reach the high shelves" (**Fig 5, Table 2**). The gradual changes can be observed from GOLNOM (oClMCl) via OBRPBI (oBr), LUJWIW (oCl) and OFBPI (oF) to DETKIX (oClpCl). In the *ortho* derivatives an intramolecular N-H...X hydrogen bond is formed, which hampers the free rotation of the halogenated phenyl ring on the benzimidazole moiety.

Further gradual increase of the length of the a axis (8.57-9.40 Å), shrink of the *c* axis (23.98-24.68 Å), and the opening of the benzimidazoles' tilt angle (118-127°) can be observed within the group of the *para*-halogen substituted derivatives – "the lab Jack is now pushed in lower positions" (**Figure 5**). The BI-BI angle increases together with the order of the polarizability of the halogen substituents JEYTUD (pF), MINHOI (mFpF), QERTIR (pCl), TUDXIB (mFpCl) and SEZNUH (pBr).

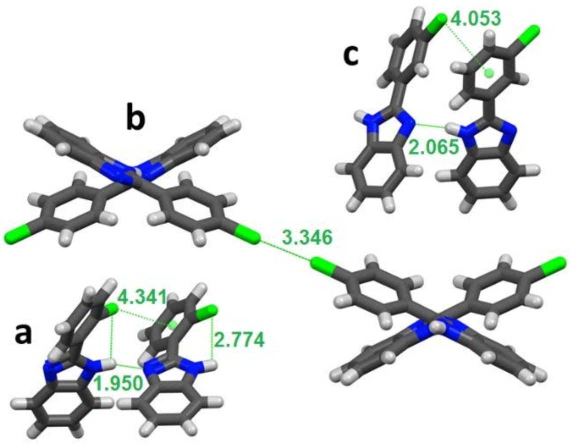

Figure 6 Secondary interactions in a: *ortho*-substituted LUJWIW, b: *para*-substituted QERTIR, and c: *meta*-substituted MCLPBI

In order to reveal what is behind the isostructural gradual change the supramolecular interactions, the synthons were analysed. C-H...X interactions are common in all studied structures. The detected BI-BI angle is mainly affected by the intermolecular X...π and X...X interactions (**Fig 6**) depending on the placement, type and number of substitutions. They make possible the fine-tuned alteration of the crystal properties (**Fig S2**).

The *ortho* position of the halogen atoms inhibit the formation of X...X interactions, because the halogens cannot get into the close proximity of each other. The most favourable intermolecular interaction in the *ortho* halogen substituent containing structures are the intra-chain X...π interactions with the phenyl ring of a neighbouring molecule (**Fig 6a**). The tilt angle decreases with increasing polarizability of the halogens in the F, Cl, Br order. This interaction fixes the PBI molecules in a relatively small tilt angle.

In the case of *para*-halogen substitution of the BPI, X...X halogen bonds can be formed between the hydrogen bonded chains. It results in an open position: the angles between the benzimidazole moieties become higher compared to the *ortho* isomers. The stronger interchain X...X interaction results in higher BI-BI angle, the angle increases in the F, Cl, Br order among the *para*-halogen derivatives (**Table 2 and Fig 6b**), the BI-BI angle is the largest in the case of the *para*-bromo-phenybenzimidazole (SEZNUH). The halogen-halogen interactions can only be formed if the phenyl- benzimidazole compounds contain a *para* halogenato substituent on the phenyl ring, otherwise it will not be present because of steric reasons. An additional *ortho* substituent lowers the BI-BI angle, while the additional *meta* substituent slightly increases the BI-BI angle.

In the isostructural series the presence of the X...π (low BI-BI angle) or the X...X (high BI-BI angle) interaction divides the crystals into two distinct subgroups (**Table 2**). Both X... π and X...X interactions are present in the crystal structure of the simultaneously *ortho* and *para* chlorinated DETKIX molecule.

In case of *ortho* substitution the BI-BI angle is in the range of 92-112°. Additional *meta* substituent lowers the BI-BI angle, it is 75° in GOLNOM. Single *meta* substitution (MCLPBI and MBRPBI) further decreases the BI-BI angle to 68°, where the benzimidazole rings of the neighbouring hydrogen bonded chains have not enough space to get in a parallel position to form π...π interactions with each other. Therefore, the packing changes from H-H to H-T and thus, the space group transforms from *Pbca* to $P2_1/c$, *the isostructurality terminates*. The space group change means the loss of a twofold screw axis symmetry, as $P2_1/c$ is a maximal non-isomorphic subgroup of *Pbca*.

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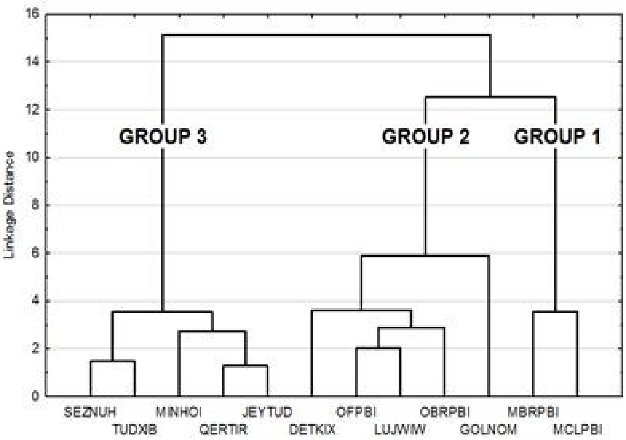

Figure 7 Cluster analysis of the crystal data, molecular conformation data and supramolecular interaction data (**Table 1** and **2, Table S2, S3 and S4**) in the fine-tuned series of halogen substituted PBI

In summary, in the fine-tuned isostructural *Pbca* series of the halogenated phenylbenzimidazole molecules the supramolecular interactions and the tilt angle of the neighbouring BPIs depends highly on the placement of the substituents: the *meta* substitution resulted in the lowest, the *ortho* substitution in medium, while *para* substitution in the highest values of BI-BI angles. The length of the most dependent crystallographic c axes changes just the opposite way. The presence of two different kinds of substituents in different positions results in an average of the structural parameters as a consequence of different cumulative effects. In the simultaneously *ortho* and *meta* chloro substituted GOLNOM the BI-BI angle is lowered, the *c* axis is elongated in an extreme extent, while the *Pbca* space group is retained.

Multivariate data analysis of the structural data

Statistical tools were used for the analysis of the crystal structures in order to apply them in the recognition of isostructurality. Multivariate data analysis was performed to reveal correlations and similarities among the members of the series of structures of systematically halogenated 2-phenylbenzimidazole derivatives. The data of crystal parameters, molecular conformations and secondary interactions involved in the analysis are summarized in **Table 1** and **2** (all data except β, Z, space group and H-H/H-T packing arrangement). The missing interactions indicated by '-' in the Tables were taken into account with a value of 7 in the statistical calculations (**Table S2**). Significant correlations among the values of the lattice parameters, the molecular conformations and the secondary interactions of the investigated crystals were found by the software Statistica[25] (**Fig S3**, **Table S3**). Cluster analysis was performed on the standardized dataset, where samples are grouped based on similarities without considering the information about the class membership.

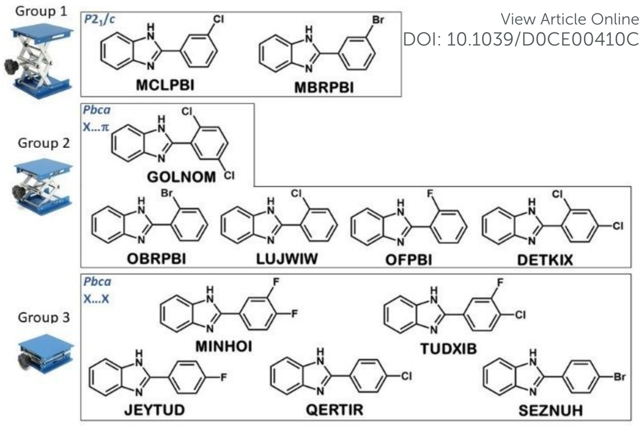

Figure 8 Grouping of the structures in the series of halogen substituted phenylbenzimidazoles based on the result of the cluster analysis

It has to be highlighted, that substitution and space group information were not taken into consideration in the cluster analysis merely based on the crystal data (a, b, c, V, KPI, density) the molecular conformation (BI-BI angle and BI-Ph angle) and the secondary interaction data (N-H...N length and angle, oH(Bi)...oH(BI), oH(Bi)...oH(Ph), X...π and X...X distances).

The tree diagram obtained by cluster analysis indicates that the structures can be divided into three distinct similarity groups (**Fig 7**) taking into account the linkage distances between their parameters. Group 1 contains the single-*meta* substituted MBRPBI and MCLPBI. They are the $P2_1/c$ structures. GOLNOM is a sort of outlier, the crystal of the *ortho*- and *meta*-substituted molecule is rather different from all other structures but more similar to the Group 2 and 3 structures, which belong to the *Pbca* structures. OBRPBI, LUJWIW, OFPBI and DETKIX belong to Group 2, they are the *ortho*-substituted derivatives. Finally, JEYTUD, MINHOI, QERTIR, TUDXIB and SEZNUH belong to Group 3, they are the PBIs with *para*-substituents (**Fig 8**). Principal component analysis has been performed for the same datasets and the same grouping of the elements could be identified as with cluster analysis (**Fig S4**, **Table S4, S5**). This grouping is in a thorough agreement with our previous crystallographic analyses (check the very same order of structures in **Table 1** and **2**) based only on mathematical data analysis without any prior knowledge of substitutions, space groups and structural analysis.

The multivariate data analysis was repeated by reduced number of parameters choosing 5 instead of 14 to investigate the chance of simplification and the limits of the methods in the isostructurality studies. The parameters were selected to represent crystallographic data (a, b and c cell lengths), molecular conformation (BI-Ph angle) and supramolecular interaction (BI-BI angle) which is an indirect information about the placement of the molecules in the unit cell. The same grouping was received by the data analysis presented on a tree

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diagram (**Fig S5**), while orders within the groups are occasionally interchanged.

The presented multivariate data analysis proves that the cluster analysis is a quick and easy-to-use tool to discover isostructurality before performing a thorough structure analysis to filter isostructural crystals out from the abundance of structures with similar cell parameters or even similar internal arrangements.

Cell similarity, isostructurality and molecular isometricity indices

In view of the similar cell dimensions, identical space groups and analogous molecular arrangements, the *Pbca* crystals of the halogenated 2-phenylbenzimidazoles are considered isostructural. However, the tilt between the molecules increases by 70 % and the length of the *a* and *c* unit cell axes varies by *ca.* 70 % within this group (**Fig 9**).

Cell similarity (π) and isostructurality (I_s) indices were calculated (**Fig 10a**) for the halogenated PBI derivatives in the *Pbca* space group. In the case of high similarity, π is close to zero. For more than half of the pairs of the structures (23 out of 45), π is less than 0.1. For the 84.4 % of the structures, π is less than 0.2. Higher π values (between 0.2 and 0.4) are calculated only in the case of GOLNOM (GOLNOM *vs.* DETKIX, OFPBI, MINHOI, SEZNUH, JEYTUD, QERTIR, TUDXIB in ascending order) which is in accordance with the observation that this is the most outlier structure from the other *Pbca* structures. This result was also received from the multivariate data analysis on the cell parameters.

The isostructurality index (I_s) takes into account both the differences in the geometry of the molecules and the positional differences caused by rotation and translation. The higher the similarity between two structures the value of I_s gets closer to 100%. The cell similarity and isostructurality indices form a well-structured pattern in function of the BI-BI angle which is in good agreement with the above detailed structure analysis and the cluster analysis as well (**Fig10a**).

Both π and I_s indices show high similarity in the group of JEYTUD, MINHOI, QERTIR, TUDXIB and SEZNUH compounds which corresponds to the cluster analysis Group 3 (**Fig 10a**, yellow highlight). These are the *para* substituted derivatives eventually with an additional *meta*-fluoro substituent. Based on the pattern of the cell similarity indices considering the entries with $\pi<0.08$, another group of compounds can be selected at lower BI-BI angles including OBRPBI, LUJWIW, OFPBI and DETKIX (top left) corresponding to the cluster analysis Group 2 (**Fig 10a**, green highlight). The variation of the *a* unit cell axis lengths is 18-22 % within this group.

It can be deduced from the data indicated in **Fig 10a** that the isostructurality index gives a strict criterion for the structural

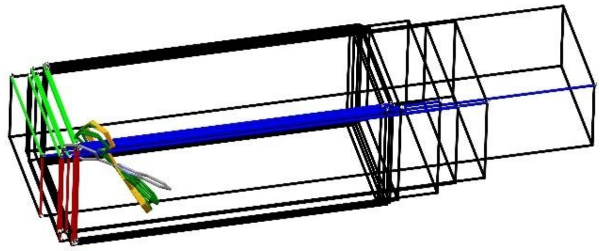

Fig 9 Superimposed *Pbca* unit cells of the halogenated 2-PBI structures indicating the arrangement of the molecules in their asymmetric unit. GOLNOM is coloured by elements, Group 2 molecules are coloured green, Group 3 molecules are yellow

similarity and decreases rapidly to zero. While the two isostructural subgroups (Group 2 having X…π interactions and Group 3 containing X…X interactions) are seemingly separated by I_s calculation, the cell similarity change within the series is rather continuous.

The molecular conformation of flexible molecules may adjust to the supramolecular features. Molecular Isometricity is a direct measure of the degree of approximate isomorphism of the compared molecules. It gives information about the molecular conformation only, it is space group independent. The superimposed molecules are characterized by the root mean square of distance differences of the corresponding atoms (rmsD) and by the largest distance difference of the compared atoms (maxD)[31]. Molecular conformation of the PBI frames irrespective to their substitution are compared (**Fig 10b**). Because of the presence of the aromatic rings in the PBI molecule the flexibility of the molecules is provided by the single bond. The Groups 2 and 3 of the *Pbca* compounds can be recognised based on their small calculated rmsD and maxD values. The BI-Ph angles vary in rather narrow ranges in the two groups, they are between 35.2-42.1° in Group 2 compounds (except GOLNOM), while these angles are between 26.7-30.0° in Group 3. Group 1 compounds can also be included in the molecular isometricity calculations and it seems that their molecular geometry is closer to Group 3 compounds than Group 2 compounds in the different $P2_1/c$ space group (Ang BI-Ph is 26.8 and 28.2°).

Packing coefficient, density, powder diffraction and isostructurality

Kitaigorodskii packing coefficients (KPI)[32] were calculated for the crystals of the 2-phenylbenzimidazoles derivatives. The KPI values correspond with the supramolecular interaction patterns, e.g. Group 2 and 3 structures separate well (**Table 1**).

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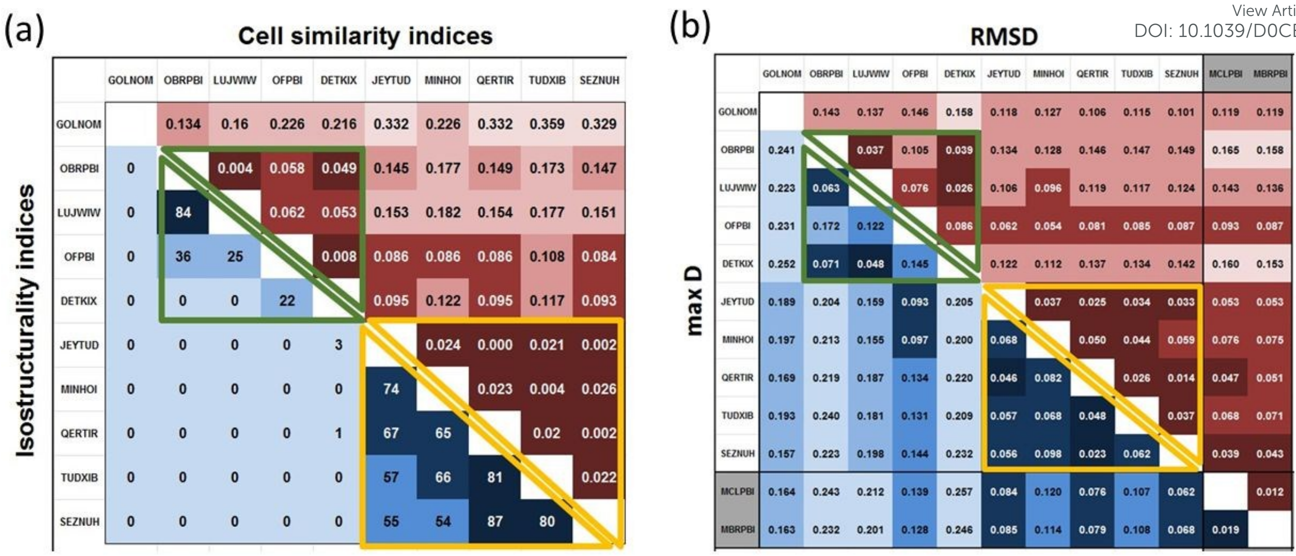

Figure 10 a., Cell similarity (π) and isostructurality (I_s) indices calculated for the halogenated 2-phenylbenzimidazoles structures

crystallize in the *Pbca* space group. b., Molecular isometricity calculations[31]: rmsD and maxD values for all the halogenated 2-phenylbenzimidazoles structures. Header of the $P2_1/c$ structures are highlighted by grey. Calculated values belong to Group 2 structures are framed with green line, values belong to Group 3 structures are framed with yellow line.

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KPI is also sensitive to the number of substituents within the Group. Calculating the density of the crystals it can be seen that the atomic weight of the substituents has higher influence on density than close packing. Notwithstanding, tendencies in the correspondence of the KPI, type and number of the substituents and the density can be observed.

Powder diffractograms are unique fingerprints of the solid compounds. The PXRD is suitable for identification of individual crystals within the isostructural series (**Fig S6**). Comparing the calculated powder patterns of the isostructural materials, they are distinctive, although sometimes some similarities can be observed. Research on match between PXRD patterns of isomorphic crystals has just commenced[42].

Isostructurality in the PBI series

The placement of the molecules in all halogen substituted 2-phenylbenzimidazole *Pbca* crystals are similar and are systematically changing in the presented fine-tuned series, listed by the increasing angle of the neighbouring benzimidazole molecules. In general, *para* substitution (Group 3) increases the tilt angle of the neighbouring benzimidazole molecules, we may say that the scissors are more open, or the lab Jack is in its lower positions. In case of *ortho* substituents (Group 2) the tilt angle of the neighbouring benzimidazole molecules is shrinking, the scissors are less open, or the lab Jack is in its higher positions. A further decrease in the tilt angle of the neighbouring benzimidazole molecules achieved by *meta* substitution (Group 1) terminates isostructurality and results in a change of the space group to $P2_1/c$.

The flexibility of the structures permits a gradual change of the lengths of the unit cells. In the presented examples it is the most pronounced (nearly twofold) in the crystallographic c direction, with unchanged space group and Z, perpendicular to the common, determining N-H...N hydrogen bonded chains.

There is a switch in the intra- and intermolecular interactions (DETKIX) which divides the investigated isostructural *Pbca* structures into two subgroups: there are X…π intermolecular interactions in Group 2 (lab Jack upper positions) and there are X…X interactions in Group 3 subgroup (lab Jack lower positions).

It is presented in the exemplary series of the substituted 2-phenylbenzimidazole structures how isostructural similarities of *Pbca* crystals can be described by numerical descriptors and how the relationship between molecular and supramolecular properties with the structural features can be revealed and characterized. Cell similarity and isostructurality indices, molecular isometricity calculations are congruent with multivariate data analysis and made possible the identification and description of the structural similarities of the PBI compounds. The types of structural information used in the different kind of structural comparisons are summarized in **Table 3**.

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Table 3 Data used in different structural analyses during the isostructurality investigations

	F	S	SG	Z	UC	V	Co	Pl	SI
CA1	-	-	-	-	✓	✓	$✓_2$	-	$✓_6$
CA2	-	-	-	-	✓	-	$✓_1$	-	$✓_1$
π	-	-	-	-	✓	-	-	-	-
$\mathbf{I_s}$	✓	✓	✓	✓	-	-	✓	✓	-
$\mathbf{I_m}$	✓	✓	-	-	-	-	✓	-	-
KPI	✓	-	-	-	-	✓	-	-	-

CA1: cluster analysis on 14 parameters, CA**2**: cluster analysis on 5 parameters, π cell similarity index, $\mathbf{I_s}$ isostructurality index, $\mathbf{I_m}$ molecular isometricity, **KPI**: Kitaigorodskii packing coefficient and calculated density; **F**: formula, **S**: substitution, **SG**: space group, **Z**: Z value, **UC**: unit cell lengths, **V**: unit cell volume, **Co**: molecular conformation, **Pl**: placement of the molecule in the cell, **SI**: secondary interactions

Conclusions

Property engineering, the fine tuning of structural properties, can be achieved by application of substituents, changing their placement and/or chemical composition influencing electrostatic and sterical properties. Both placement of the molecules in the crystal lattice and molecular conformation of flexible molecules may adjust to the supramolecular features. A given packing motif may tolerate small molecular changes, and the structures remain isostructural despite the chemical changes within a limit.

The packing arrangements of the neighbouring structures in the fine-tuned series – like during the move of the lab Jack up or down - are highly similar. The structures from the two ends of the ordered list – like the open and the closed lab Jack positions - have low similarity. It is a question whether we recognise and consider the two opposite terminal members of the structure series being isostructural? It is necessary to work out a method in consensus to determine and define the criteria for the limits of isostructurality: what the extent of differences is we can still consider similar.

There are crystals, whose cell parameters are similar, the space groups are the same, the arrangements of the molecules are analogous in all structures, the only difference is in the preference of intermolecular interactions – like Group 2 and 3 in the example series above. By the IUCr definition[41] "Two crystals are said to be *isostructural* if they have the same structure, but not necessarily the same cell dimensions nor the same chemical composition, and with a 'comparable' variability in the atomic coordinates to that of the cell dimensions and chemical composition." This definition does speak about the need to "have the same structure", but it does not say anything about the probable necessity of similarity of the supramolecular interactions as a criterium of isostructurality of crystals.

Unit cells of different compounds with different internal arrangement may be occasionally similar. Notwithstanding, cells of chemically similar compounds with analogous internal arrangement are necessarily similar. Anyhow, recognition of isostructurality is not necessarily straightforward, see the case of the two termini of the presented series of 2-phenylbenzimidazoles in the *Pbca* space group.

Here is a recommendation for a technique, how to recognise and numerically describe isostructurality step by step:

1. Isostructurality analysis of crystals of similar composition should start with the calculation of the cell similarity index (π).
2. Conformation of molecules in the isostructural crystals are alike. Their similarity can be compared by molecular isometricity calculations.
3. Multivariate data analysis (cluster analysis or principal component analysis) of the structural data, especially in case of higher number of crystals, can assist grouping the structures into subclasses.
4. The prerequisite of isostructurality is the similar molecular geometry and the analogous placement of molecules in the crystal lattice, it is described numerically by the isostructurality index (I_s).
5. Isostructurality investigations have to be completed with the similarity check of the synthons, the supramolecular interactions among the compared crystals.

Calculation of cell similarity (π) and isostructurality (I_s), as well as molecular isometricity indices, completed with a prior multivariate data analysis of the structural data contribute to the easy recognition and characterization of isostructural crystals. Tools to describe isostructurality are important in fine-tuning of crystal properties with the final aim to prepare new materials with desired properties.

Conflicts of interest

There are no conflicts to declare.

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Notes and references

1 G. R. Desiraju, *Acc. Chem. Res.*, 2002, **35**, 565-573
2 G. R. Desiraju, *Nature*, 2001, **412**, 397–400
3 V. A. Russell and M. D. Ward, *Chem. Mater.*, 1996, **8**, 1654-1666
4 G. Resnati, E. Boldyreva, P. Bombicz and M. Kawano, *IUCrJ*, 2015, **2**, 675–690
5 R. Taylor, J. C. Cole, C. R. Groom, *Cryst. Growth Des.*, 2016, **16**, 2988–3001
6 P. Bombicz, *Crystallography Reviews*, 2017, **23**, 118–151

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DOI: 10.1039/D0CE00410C

7 P. Bombicz, T. Gruber and C. Fischer, *CrystEngComm*, 2014, **16**, 3646–3654
8 E. J. C. de Vries, S. Kantengwa, A. Ayamin and, N. Báthori, *CrystEngComm*, 2016, **18**, 7573-7579.
9 C. Fischer, P. Bombicz and G. Lin, *Cryst. Growth Des.*, 2012, **12**, 2445–2454
10 S. Ranjan, R. Devarapalli, S. Kundu, S. Saha, S. Deolka, V. R. Vangalac and C. M. Reddy, *IUCrJ*, 2020, **7**, 173–183
11 C. R. Groom, I. J. Bruno, M. P. Lightfoot, *Acta Crystallogr.*, 2016, **B72**, 171–179
12 P. Metrangolo, H. Neukirch, T. Pilati and G Resnati, *Acc. Chem. Res.*, 2005, **38**, 386-395
13 C. B. Aakeröy, P. D. Chopade, and J. Desper, *Cryst. Growth Des.*, 2011, **11**, 5333–5336
14 P. Metrangolo and G. Resnati, *Cryst. Growth Des.*, 2012, **12**, 5835–5838
15 A. Priimagi, G. Cavallo, P. Metrangolo and G. Resnati, *Acc. Chem. Res.*, 2013, **46**, 2686-2695
16 A. Mukherjee, S. Tothadi and G. R. Desiraju, *Acc. Chem. Res.*, 2014, **47**, 2514–2524
17 D. Secci, A. Bolasco, M. D'Ascenzio, F. Sala, M. Yánez, and S. Carradori, *J. Heterocyclic Chem.*, 2012, **49**, 1187-1195
18 N. A. Weires, J. Boster and J. Magolan, *EurJoc*, 2012, **33**, 6508-6512
19 P. Sang, Y. Xie, J. Zou and Y. Zhang, *Org. Lett.*, 2012, **15**, 3894-3897
20 J. Feng, S. Handa, F. Gallou and B. H. Lipshutz, *Angew.Chem.Int.Ed.*, 2016, **55**, 8979-8983
21 M. C. Burla, R. Caliandro, B. Carrozzini, G. L. Cascarno, C. Cuocci, C. Giacovazzo, M. Mallamo, A. Mazzone and G. Polidori, *J. Appl. Cryst.*, 2015, **48**, 306-309
22 G. M. Sheldrick, *Acta Cryst.*, 2015, **A71**, 3-8
23 L. J. Farrugia, *J. Appl. Cryst.*, 2012, **45**, 849-854
24 T. Hastie, R. Tibshirani and J. Friedman, *The Elements of Statistical Learning, Data Mining, Inference, and Prediction*, Springer, 2008
25 S. Wold, K. Esbensen and P. Geladi, *Chemometrics and Intelligent Laboratory Systems*, 1987, **2**, 37-52
26 Dell Inc. Dell Statistica (data analysis software system), version 13. software.dell.com, 2016
27 A. Kálmán, L. Párkányi, Gy. Argay, *Acta Crystallogr.*, 1993, **49**, 1039–1049
28 A. Kálmán A, L. Párkányi, Isostructurality of organic crystals. In: M. Hargittai, I. Hargittai, editors *Advances in molecular structure research* 3 Greenwich JAI Press, 1997, 189–226
29 A. Kálmán In: W. Gans, editor *Fundamental principles of molecular modeling*, New York Plenum Press, 1996
30 L. Párkányi, ISOS: Software for isostructurality calculation. http://www.chemcryst.hu/isos/
31 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. Cryst.*, 2008, **41**, 466-470
32 A. L. Spek, *Acta Cryst.*, 2020, **E76**, 1-11
33 N. Rashid, M. K. Tahir, S. Kanwal, N. M. Yusof and B. M. Yamin, *Acta Crystallogr.*, 2007, **E63**, o1402
34 M. S. Krishnamurthy, N. Fathima, H. Nagarajaiah and N. S. Begum, *Acta Crystallogr.*, 2013, **E69**, o1689
35 M. S. Krishnamurthy and N. S. Begum, *Acta Crystallogr.*, 2015, **E71**, o387
36 M. Azam, A. A. Khan, S. I. Al-Resayes, M. S. Islam, A. K. Saxena, S. Dwivedi, J. Musarrat, A. Trzesowska-Kruszynska and R. Kruszynski, *Spectrochim. Acta*, 2015, **A142**, 286
37 F.-F. Jian, H.-Q. Yu, Y.-B. Qiao, T.-L. Liang and P.-S. Zhao, *Acta Crystallogr.*, 2007, **E63**, o321
38 R. T. Stibrany, J. A. Potenza, *CSD Communication* (Private Communication), 2010
39 F.-F. Jian, H.-Q. Yu, Y.-B. Qiao, P.-S. Zhao and H.-L. Xiao, *Acta Crystallogr.*, 2006, **E62**, o5194
40 N. Rashid, M. K. Tahir, N. M. Yusof and B. M. Yamin, *Acta Crystallogr.*, 2007, **E63**, o1260
41 IUCr definition of isostructurality: https://dictionary.iucr.org/Isostructural_crystals
42 S. Ranjan, R. Devarapalli, S. Kundu, S. Saha, S. Deolka, V. R. Vangalac, C. M. Reddy, *IUCrJ*, 2020, **7**, 173-183

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Easy recognition and numerical description of isostructurality; how different the similar structures can be; supramolecular aspects of isostructurality.

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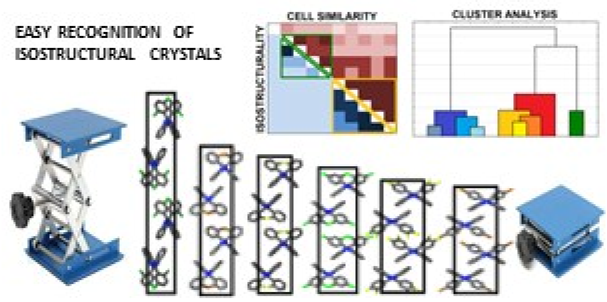

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