Supramolecular equivalence of ethynyl, chloro, bromo and iodo groups. A comparison of the crystal structures of some 4-phenoxyanilines

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Paper

4-(4′-Iodo)phenoxyaniline is isostructural to the corresponding bromo, chloro and ethynyl derivatives in contrast to 4-iodoaniline which is not isostructural to its bromo, chloro and ethynyl counterparts. This difference is rationalised in terms of conditional isomorphism.

Introduction

Since the earliest days of crystal engineering, it has been appreciated that the role of a functional group in determining the crystal structure of a small organic molecule may be considered as arising from geometrical or chemical factors.[1] Does a functional group behave like a group of a certain shape and size or like a group with certain interaction preferences? Such questions are difficult to answer because these geometrical and chemical components of supramolecular recognition are often inextricably intertwined.[2] The phenomenon of isostructurality is important in assessing these dual roles of functional groups in crystal packing.[3] Accordingly, when isostructurality is observed it may be considered as arising from geometrical factors (shape and size) or from chemical factors (intermolecular interactions). Kitaigorodskii's theory of close packing emphasises the importance of size and shapes, in other words, the geometrical factors. Nangia and Desiraju have stated that the importance of these factors depends on the size of the relevant molecules.[4] Interaction-based isostructurality in geometrically dissimilar molecules is less common but two recent elegant examples are worth mentioning: Kálmán, Fábián and Argay have reported hydrogen bond based isostructurality between two molecules that differ in volumes by as much as one third,[5] while Jones and Vancea showed that equivalence between N–H···Br⁻ and C–H···Br⁻ interactions leads to isostructurality in a pair of molecules that have rather different shapes.[6] The present study reports and discusses the crystal structures of a set of (4′-substituted)-4-phenoxyanilines, **1a–1d** and is a continuation of our earlier work on the corresponding 4-substituted anilines **2a–2d**.[7]
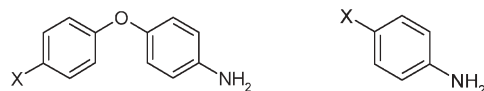
Experimental

1. Synthesis

Melting points were recorded on a DSC (Universal V2.6D TA instruments). ^{1}H NMR spectra were recorded on a Bruker-AC-200 spectrometer (CDCl$_3$). All reactions were carried out using standard techniques and literature procedures. All compounds were purified by column chromatography and crystals for X-ray work were obtained from 1 : 1 EtOAc–hexane.

4-(4′-Ethynyl)phenoxyaniline (**1a**) was prepared in three steps. 4-Iodophenol and 4-nitrofluorobenzene were stirred with KOH in DMSO at room temperature for 16 h. 4-(4′-Iodo)phenoxynitrobenzene was formed and subjected to reduction with N$_2$H$_4$ and Pd/C in EtOH at room temperature for 2 h. Compound **1a** was then obtained by Sonogashira coupling followed by hydrolysis with KOH in MeOH. mp: 64.39 °C, ^{1}H NMR. 7.54 (d, *J* 8,2H), 6.98 (m, 4H), 6.81 (d, *J* 8, 2H), 3.75 (s, 2H), 3.13 (s, 1H).

4-(4′-Chloro)phenoxyaniline (**1b**) was prepared as above. mp: 103.18 °C, ^{1}H NMR. 7.35 (d, *J* 8, 2H), 6.86 (d, *J* 8, 2H), 6.77 (d, *J* 8, 2H), 6.59 (d, *J* 8, 2H), 4.99 (s, 2H).

4-(4′-Bromo)phenoxyaniline (**1c**) was prepared analogously. mp: 109.28 °C, ^{1}H NMR. 7.46 (d, *J* 8, 2H), 6.78 (m, 4H), 6.59 (d, *J* 8, 2H), 5.03 (s, 2H).

4-(4′-Iodo)phenoxyaniline (**1d**) was obtained as an intermediate in the synthesis of **1a**. mp: 93.34 °C, ^{1}H NMR. 7.62 (d, *J* 8, 2H), 6.84 (d, *J* 8, 2H), 6.76 (d, *J* 8, 2H), 6.58 (d, *J* 8, 2H), 5.01 (s, 2H).

2. X-ray crystallography

X-ray data for compounds **1a**, **1b**, **1c** and **1d** were collected on a SMART diffractometer using Mo Kα radiation (λ = 0.71073 Å). The intensities were integrated using SAINT[8] and the absorption correction was applied using SADABS.[9] Structure solution and refinement were carried out using SHELXL programs built in with the SHELXTL (Version 6.12) package.[10] All non-hydrogen atoms were refined with anisotropic displacement parameters. The aromatic hydrogen atoms were generated by a riding model on idealized geometries with $U_{iso}(H) = 1.2\ U_{eq}(C)$. The amino H-atoms were located from difference Fourier maps and refined independently. For **1c**, the amino H-atoms were located from difference Fourier maps. The positional parameters were refined freely but the isotropic displacement parameter was fixed at $U_{iso}(H) = 1.5\ U_{eq}(N)$. It was noted that the geometry at the N-atom was pyramidal and not planar.

3. Computational

All simulations were carried out with version 4.8 of the Cerius^2 molecular modeling environment[11] running on Silicon

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Scheme 1
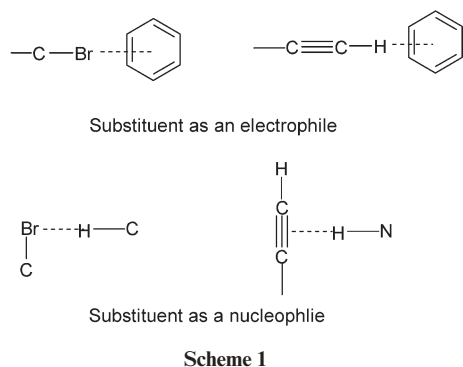
Graphics workstations. The hypothetical crystal structural generation was undertaken using the Cerius² polymorph predictor (PP) module with one molecule in the asymmetric unit. The experimental molecular conformation was used in five different space groups ($Pna2_1$, $P2_1$, $Pca2_1$, $Pnma$ and $P2_1/c$) These space groups were chosen because they are the experimental space groups ($Pnma$, $P2_1$ and $Pna2_1$) or variations ($Pca2_1$ and $P2_1/c$). It is always a good idea in polymorph prediction calculations to use $P2_1/c$ as one of the selected space groups. The COMPASS force field was applied and force field charges were used. Default options were used throughout with the fine search in Monte Carlo simulation and for clustering. Rigid body minimisation was carried out for the lattice energy calculations without any modifications except for the use of van der Waals and Coulomb interactions.

Results and discussion

Anilines **2a**, **2b**, and **2c** are isostructural, with the ethynyl, chloro and bromo groups functioning as both electrophilic (X···Ar) and nucleophilic (C–H···X, N–H···X) centres in an interaction dominated structure (Scheme 1). However, 4-iodoaniline (**2d**) has a different crystal structure with close packing between the I-groups. This difference in behaviour was attributed by us previously to geometrical (volume) effects.[7] The volumes of the four groups under consideration are: Cl (18.1 Å³), Br (24.4 Å³), C≡C–H (28.8 Å³) and I (32.96 Å³). The formation of I···I contacts in **2d** was ascribed to the fact that the volume of the I-group might have crossed a threshold value so that a transition to another structure type occurs. Noting the
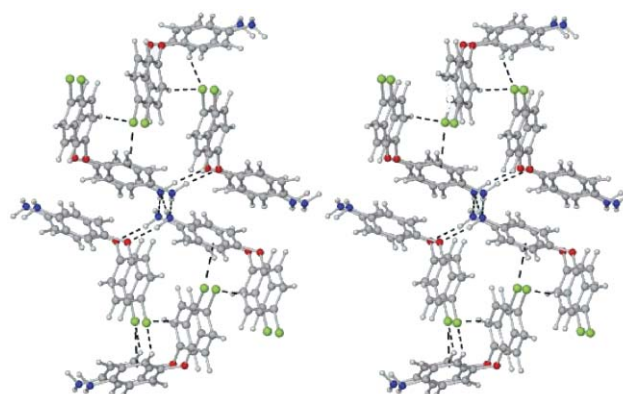

Fig. 1 Packing of chloro derivative, **1b**. Strong and weak hydrogen bonds are well insulated. Click here to access a 3-D image of Fig. 1.

remarks of Kitaigorodskii that *conditional isomorphism*[12] occurs in large molecules that differ in the presence/absence of small functional groups (methyl and nitro derivatives of methycoronene, naphthalenes β-substituted by methyl, hydroxyl, and amino groups), we decided to examine the crystal structure of the corresponding substituted phenoxyanilines **1a–1d**.

Table 1 gives the crystallographic and other data for compounds **1a–1d**. The four compounds are isostructural. Fig. 1 shows the packing of the chloro derivative, **1b**, and is representative. Strong and weak hydrogen bond donors and acceptors are well insulated from each other. The hydrogen bond metrics are given in Table 2. Formation of N–H···O interactions leaves an extra N–H group, which forms a cooperative N–H···N–H··· pattern, thereby saturating the hydrogen bonding potential of the –NH₂ and –O– fragments. The halogen (or ethynyl) groups act simultaneously as hydrogen bond acceptors (C–H···X) and as electropositive centres (C–X···Ar). This kind of intra-atomic cooperativity is by now very well-established[2,13] and is characteristic of the halogens, especially the heavier ones. The C–Cl···π and C–Br···π distances are virtually the same and the C–I···π distance is not much longer showing a preference for polarisation with increasing atomic number among the halogens (Fig. 2).

Pleasingly, the unit cell volumes of **1a–1d** mirror the volumes of X-group substituents. When a series of substituents with

Table 1 Crystallographic data for **1a–1d**. CCDC reference numbers 254527–254530. See http://www.rsc.org/suppdata/ce/b4/b416962j for crystallographic data in CIF or other electronic format

Compound	1a	1b	1c	1d
Chemical formula	$C_{14}H_{11}NO$	$C_{12}H_{10}ClNO$	$C_{12}H_{10}BrNO$	$C_{12}H_{10}INO$
Formula weight	209.24	219.66	264.12	311.11
Crystal system	Orthorhombic	Orthorhombic	Orthorhombic	Orthorhombic
Space group	$Pna2_1$	$Pna2_1$	$Pna2_1$	$Pna2_1$
T/K	100(2)	100(2)	100(2)	100(2)
a/Å	7.6907(8)	7.7106(13)	7.6970(9)	7.7243(12)
b/Å	25.275(3)	22.935(4)	23.105(3)	23.377(4)
c/Å	5.6861(6)	5.7440(10)	5.8734(7)	6.1145(9)
Z	4	4	4	4
V/Å³	1105.3(2)	1015.8(3)	1044.5(2)	1104.1(3)
D_c/Mg m⁻³	1.257	1.436	1.679	1.872
$F(000)$	440.0	456.0	528.0	600.0
μ/mm⁻¹	0.080	0.344	3.905	2.872
R_{int}	0.0181	0.0177	0.0260	0.0218
$\Delta\rho_{min,max}$/e A°⁻³	−0.158/0.168	−0.187/0.170	−0.350/0.350	−0.632/0.601
θ Range/°	1.61–25.65	1.78–26.00	1.76–25.98	1.74–26.38
Reflections collected	2784	3577	5935	9744
Unique reflections	1158	1892	2012	2086
Reflections with $I > 2\sigma(I)$	1094	1834	1919	2073
R_1 [$I > 2\sigma(I)$]	0.0302	0.0294	0.0206	0.0207
wR_2	0.0741	0.0750	0.0517	0.0497
GOF	1.053	1.091	1.013	1.221

Table 2 Interaction metrics for the compounds in this study

Compounds	Interactions	d/Å	D/Å	θ/°
1a	N–H···O	2.147	3.135(2)	165.8
	N–H···N	2.223	3.219(3)	168.6
	^{a}C–H···π (tri)	2.871	3.372	153.8
	^{a}C–H···π (tri)	2.876	3.811	144.7
	^{b}C–H···π (Ar)	2.271	3.347	172.1
1b	N–H···O	2.127	3.128(2)	171.2
	N–H···N	2.233	3.231(3)	169.8
	^{a}C–H···Cl	2.808	3.800	152.3
	^{a}C–H···Cl	2.749	3.746	152.9
	^{a}C–Cl···π (Ar)	3.429		168.0
1c	N–H···O	2.139	3.129(2)	166.8
	N–H···N	2.303	3.274(3)	161.2
	^{a}C–H···Br	2.823	3.803	150.5
	^{a}C–H···Br	2.896	3.887	152.3
	^{a}C–Br···π (Ar)	3.430		169.7
1d	N–H···O	2.150	3.140(4)	166.5
	N–H···N	2.385	3.372(5)	165.8
	^{a}C–H···I	2.978	3.941	148.3
	^{a}C–H···I	3.057	4.048	152.4
	^{a}C–I···π (Ar)	3.510		171.4

^{a} Phenyl C-atom. ^{b} Ethynyl C-atom, tri = bond to the π system of triple bond, Ar = bond to π system of the phenyl group. All C–H and N–H distances are neutron normalised to 1.083 and 1.009 Å.
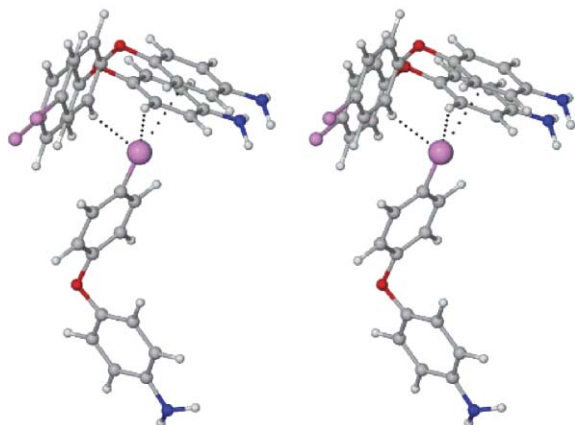

Fig. 2 Detailed view of intra-atomic cooperativity at the halogen atom in iodo derivative **1d**. The situation in the ethynyl derivative **1a** is equivalent. Notice that the halogen has a charge δ^+ in the polar region and δ^- in the equatorial region. Click here to access a 3-D image of Fig. 2.

different volumes (Cl, Br, I) and/or shapes (C≡CH) give isostructural compounds, it may be presumed that the chemical effects of these substituents in the packing are similar. We conclude that intra-atomic cooperativity of the type C–H···X···Ar (or C–H···C≡C–H···Ar) is the critical repeating synthon here. It is not that the N–H···O and N–H···N bonds are unimportant. But if the weak interaction patterns cannot be the same, other patterns of strong hydrogen bonds will be accessed leading to loss of isostructurality. This is what happened in compound **2d** in our earlier study.[7] The weak interactions are therefore *discriminants* between various packing types which may all be equivalent with regard to strong interactions.

The behaviour of phenoxyanilines **1a–1d** (all isostructural) when compared to the simpler anilines **2a–2d** (iodo derivative different) is an illustration of conditional isomorphism. Fig. 3 shows that the volume increments (relative to aniline) are between *ca.* 15% and *ca.* 26% for compounds **2a–2d**. However, the corresponding numbers (relative to 4-phenoxyaniline) are between *ca.* 4% and *ca.* 14% for compounds **1a–1d**. Simply put, when a substituent group does not have such a large effect on the volume (or shape) of a molecule, it is more likely to exert its
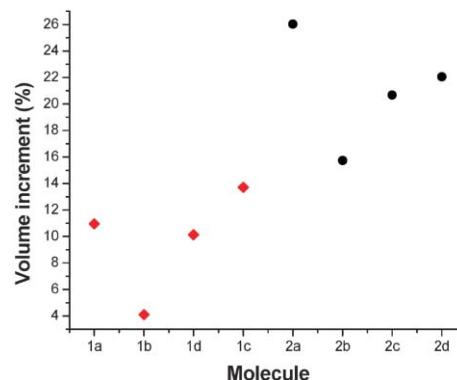
Fig. 3 Graph showing volume increment of anilines (●) and 4-phenoxyanilines (◆) caused by substitution with halogen or ethynyl groups.

intrinsic chemical effect. We emphasise that all substituent groups have their innate geometrical and chemical characteristics. Which of these is more apparent in any given crystal structure depends on other factors, one of which is the size of the molecules. Other volume measures of isostructurality have been described by Fábián and Kálmán[14] and it is clear that there are windows of molecular volume within which a certain packing is favoured but once this threshold is crossed another packing may be preferred.

A subtle comparison is provided by the ethynyl (**1a**, **2a**) and iodo (**1d**, **2d**) derivatives in the two series. The volumes of these groups are the closest among the four substituents considered but chemically, they are the furthest from each other. So, hydrogen bonding which is significant in **2a** (mp 100°C) is not so important in the non-isostructural **2d** (mp 42 °C). In the corresponding phenoxyanilines, however, all substituent groups are geometrically and chemically equivalent and the melting point order is reversed in keeping with the C_k (packing coefficient) values. Table 3 gives the melting points and C_k values for the eight compounds under consideration. This list is instructive.

Table 3 Melting points for the compounds in this study

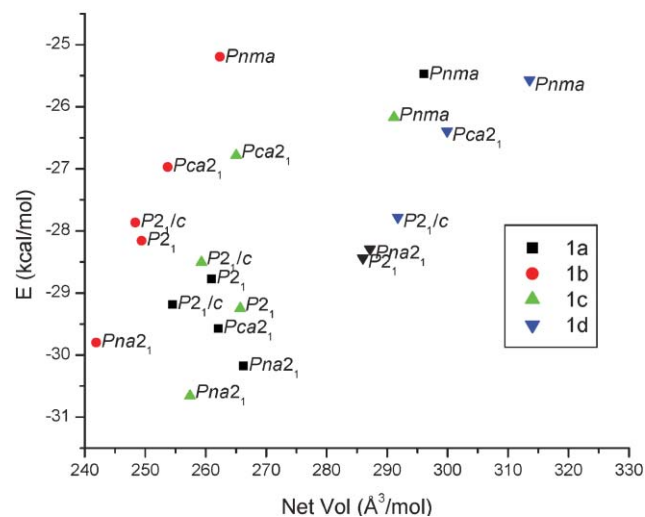| Present study			Previous study		
Compound	mp/°C	C_k/%	Compound	mp/°C	C_k/%
1a	64.39	70.5	**2a**	100	70.4
1b	103.18	73.6	**2b**	70	74.0
1c	109.28	73.3	**2c**	64	70.0
1d	93.34	71.6	**2d**	42	67.1

Fig. 4 Energy *vs.* net volume of calculated polymorphs for **1a–1d**.

Table 4 Details of polymorph prediction calculations[a]

			Cell values/Å, deg	Energy/ kcal mol^{-1}	Net volume/Å^3	Density/ g cm^{-3}	Structure description[c]
1a	Exp[b]	$Pna2_1$	7.445, 25.962, 5.511	−30.176	266.32	1.305	See Results and discussion.
	Predicted	$Pna2_1$	7.442, 25.982, 5.507	−30.176	266.23	1.305	Same as Exp.
		$P2_1$	13.073, 4.853, 8.856, 111.74	−28.773	260.94	1.331	Hydrogen bonds too long.
		$P2_1/c$	5.684, 19.804, 10.326, 61.14	−29.185	254.51	1.365	No strong hydrogen bonds. C–H···N present.
		$Pca2_1$	20.304, 5.787, 8.922	−29.574	262.07	1.326	No strong hydrogen bonds. C–H···O and C–H···N present.
		$Pnma$	9.170, 43.664, 5.915	−25.472	296.07	1.174	No strong hydrogen bonds. C–H···O present.
1b	**Exp**	$Pna2_1$	7.548, 22.617, 5.668	−29.798	241.89	1.508	See Results and discussion.
	Predicted	$Pna2_1$	7.547, 22.618, 5.668	−29.800	241.88	1.508	Same as Exp.
		$P2_1$	7.809, 5.606, 11.400, 87.96	−28.159	249.40	1.463	Similar to Exp but mismatch of weak hydrogen bonds.
		$P2_1/c$	16.033, 5.793, 10.712, 86.85	−27.865	248.36	1.469	Similar to Exp but hydrogen bonds are too long.
		$Pca2_1$	12.459, 9.712, 8.386	−26.972	253.70	1.438	No strong hydrogen bonds. N–H···π and C–H···O found.
		$Pnma$	9.696, 47.939, 4.515	−25.194	262.34	1.390	Corrugated sheet with Cl···Cl.
1c	**Exp**	$Pna2_1$	7.584, 23.095, 5.878	−30.659	257.39	1.704	See Results and discussion.
	Predicted	$Pna2_1$	7.584, 23.095, 5.878	−30.659	257.39	1.704	Same as Exp.
		$P2_1$	12.187, 5.510, 7.922, 92.46	−29.251	265.71	1.650	Similar to Exp but some Br-atom contacts too long.
		$P2_1/c$	20.476, 4.864, 10.885, 73.08	−28.508	259.29	1.691	N–H···Br formed instead of N–H···O in Exp.
		$Pca2_1$	14.030, 12.166, 6.210	−26.786	265.02	1.655	N–H···N present but no N–H···O.
		$Pnma$	9.686, 51.534, 4.666	−26.172	291.15	1.506	Two-molecule aggregate but hydrogen bonds too long.
1d	**Exp**	$Pna2_1$	7.752, 23.763, 6.232	−28.291	287.04	1.800	See Results and discussion.
	Predicted	$Pna2_1$	7.751, 23.171, 6.234	−28.292	287.16	1.799	Same as Exp.
		$P2_1$	4.957, 4.701, 24.616, 94.38	−28.436	285.98	1.806	N–H···N present but other N–H forms N–H···π instead of N–H···O. Weak I···I found.
		$P2_1/c$	27.567, 5.562, 8.148, 69.10	−27.782	291.78	1.771	Same as Exp but weak hydrogen bonds too long.
		$Pca2_1$	4.936, 25.131, 9.671	−26.392	299.92	1.722	Hydrogen bonds too long.
		$Pnma$	9.749, 47.780, 5.385	−25.568	313.56	1.648	N–H···N zigzag chain.

[a] Only the global minimum is mentioned in each case. [b] Exp means experimental structure after energy minimisation. [c] Interaction criteria: N–H···N and N–H···O, $d < 2.5$ Å; C–H···π, N–H···π and C–H···O, $d < 2.8$ Å; halogen···halogen lesser than sum of van der Waals radii.

Finally, we generated hypothetical crystal structures with the Polymorph Predictor software (Cerius^2) in five different space groups ($Pna2_1$, $P2_1$, $Pca2_1$, $Pnma$ and $P2_1/c$) for the four phenoxyanilines **1a–1d**. The results are summarised in Fig. 4 and Table 4. The experimental space group ($Pna2_1$) is the best option for **1a**, **1b** and **1c**. Interestingly, a $P2_1$ structure is the best structure for the iodo derivative **1d**, with the experimental structure being a close competitor. We note from Table 4 that several structures are unacceptable because the hydrogen bonds are unfavourably long. A limitation of this exercise is that the conformation of the molecule was restrained to the experimental one. However, if the molecular conformation were relaxed, the structural space that would need to be explored would be prohibitively large and beyond the scope of the present study. These computations may, in this sense, be considered almost as a benchmark of the software as they are of the structures. Still, the fact that compound **1d** has two possible structures (the experimental $Pna2_1$ and a hypothetical $P2_1$) and that it is this particular compound that has now become isostructural to its congeners in contrast to its cousin, **2d** is surely suggestive. Naturally, we screened compound **1d** exhaustively for polymorphs but we could not find any. We have not abandoned this search.

Conclusions

In the 4-substituted anilines, **2a–2d**, there are two structural possibilities: an interaction dominated structure shown by **2a**, **2b** and **2c** and a close-packing determined structure, shown by **2d**. The former is eminently suited to the ethynyl derivative **2a** and increasingly less so for the chloro and bromo derivatives **2b** and **2c**. The iodo substituent is so large and so chemically different from the ethynyl subsistent that **2d** takes a different structure. In the 4′-substituted-4-phenoxyanilines, **1a–1d**, however, the increased size of the molecule decreases the relative volume differences between the derivatives. The four compounds are therefore isostructural and adopt a packing where both interactions and close-packing are important. The chemical and geometrical aspects of the four substituents are all comparable with the internally cooperative C–H···X···Ar synthon being notable.

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