Hydrogen bonding networks in chiral thiourea organocatalysts. Evidence on the importance of the aminoindanol moiety

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ABSTRACT The crystal structures of four chiral thioureas, which are normally used as organocatalysts, are reported by the first time. Each compound is assembled in the crystal in a different way according to their chiral moiety in the thiourea skeleton, being dependent on the presence or the absence of the OH group in the aminoindanol or aminoindane moiety, respectively. Thiourea **1**, which contains an aminoindane group, is assembled into a zigzag chain linked via N-H $\cdots$ S hydrogen bonds. Thiourea **2**, with an aminoindanol and a phenyl group,

interacts mainly through O-H $\cdots$ S and N-H $\cdots$ S bonds in a very congested structure. Thiourea **3** disposes in a zigzag chain mainly through S $\cdots$ OH bonds and in further superposed zigzag chains through NH $\cdots$ S hydrogen bonds. The compound **4** is coordinated in a coplanar organization via O $\cdots$ H-N interactions, forming very tight dimers, which are further arranged in chain of dimers through O-H $\cdots$ S interactions.

The general trends in the patterns of packing of these four compounds are compared to those commonly observed in the crystalline solids of other thiourea and urea structures. The different arrangements adopted by our chiral thioureas in the solid state are rationalized and discussed in terms of molecular structure, remarking the importance of the OH group in the aminoindanol scaffold in the determination of the preferred solid assembly. A comparison correlating the crystal structures, specifically the interactions in the crystal network and the configuration adopted by the thioureas, with the catalytic efficiency previously observed by the same structures, is included.

1. Introduction

With the main aim of designing and controlling new crystal structures with appealing architectures, non-covalent interactions have played a crucial role in the progress of supramolecular chemistry. This approach is still an active challenging area of research. Although it is well-known that hydrogen bonds are much weaker than covalent unions, in the last decade these unions have become a key tool in crystal engineering¹ and in asymmetric catalysis,² because of the possibility of forming highly directional and strong associations, based on a cooperative effect.³ Among all the molecules involved in this field, ureas and thioureas have been the subject of extensive studies in the design of new three-dimensional crystal structures.

Furthermore, ureas⁴⁻⁹ and thioureas¹⁰⁻¹⁴ have been extensively used as anion binding groups in synthetic receptors because of their ability to form strong hydrogen bonding with a great variety of anions.

Although, at this point the prediction of the exact crystal structure of a given molecule remains as an elusive goal,¹⁵ the capacity of (thio)ureas to form robust intermolecular interactions in the solid state, allowing the control of the crystal packing, has stimulated the growth of this field and the search for new hydrogen bond-based motifs. More important is the fact that it is able to take advantage of this strong hydrogen bond capacity to use these molecules as active hydrogen bond catalysts.² In this manner, we have centered part of our investigation using thiourea building blocks to promote several asymmetric organocatalytic reactions.¹⁶⁻²¹

However, in contrast to the most explored urea structures in crystal engineering,²²⁻²⁴ crystalline solids of thiourea derivatives have been so far less explored, but some systematic crystallographic studies based on single crystals and powder X-ray data have been performed,²⁵⁻³⁰ despite the fact that they can also form relatively strong and directional hydrogen bonding interactions.³¹ A proof of fact of their well-known capacity as hydrogen bond donor, is their extensive use in asymmetric organocatalysis as a powerful chiral catalyst.³²⁻³⁶ Therefore, the lack of background using thiourea scaffolds for crystal design prompted us to study our own chiral thiourea catalysts from a crystalline point of view and in order to see a possible correlation between the behavior in the solid state and that observed in solution when they are used as organocatalysts.

We report the crystal structures of these four chiral thioureas **1-4** derived from the aminoindane or aminoindanol skeleton and bearing the bulky bis(trifluoromethyl)phenyl or a simple phenyl

group. Their crystalline structures are analyzed in terms of the expected behavior observed by other thioureas or ureas.

Figure 1. Thioureas **1-4** used in the comparative crystalline study.

For comparative purpose, we have selected the results achieved with these catalysts in the Friedel-Crafts alkylation reaction between indole **5** and nitrostyrene **6** at low temperature (Table 1),¹⁸ although the same tendency can be observed in other reactions explored by us when these catalysts have been used.¹⁶⁻²¹

Table 1. Thiourea-catalyzed Friedel-Crafts alkylation reaction.^a

Catalyst	Time (h)	yield (%)	ee (%)
1	120	24	Racemic
2	120	12	Racemic
3	120	28	10
4	72	40	82

^a Experimental conditions: To a mixture of catalyst **1-4** (0.02 mmol), nitroalkene **6** (0.1 mmol) in CH₂Cl₂ (500 μ L) in a test tube at room temperature was added indole **5** (0.15 mmol) After the reaction time, compound **7** was isolated by flash chromatography.

To the best of our knowledge only two precedent characterization of enantiomerically pure thioureas by X-ray diffraction studies have been carried out.^{37,38} The present study represents the first correlation study between the crystal structures of potential organocatalysts in the solid state, supporting the outcome obtained in catalytic reactions and complementing the architectonic chemistry observed so far in the literature for these attractive structures. Moreover, this is the first example where chiral thiourea crystals are analyzed from a solid state engineering point of view.

2. Results and Discussion

Small differences have been described between ureas and thioureas in crystal engineering networks. These come from the differences between the oxygen and the sulfur atom in the system, and whereas the thiocarbonyl group is a weaker hydrogen-bond acceptor than the carbonyl one, this property is compensated by the strongest acidity of the NH donors in thioureas.³⁹ This leads to significant variations between these two molecules in their conformational behavior and hydrogen bonding preferences. From an experimental point of view, these preferences afford the formation of straight chains formed in ureas, with the molecules approaching each other through their C=O vector, and to zigzag chains in thioureas because the molecules approach obliquely in order to optimize the electrostatic interactions between the NH protons and the negative charge of the sulfur atom (Figure 2).

Figure 2. Normal spatial approach in (thio)ureas.

Taking this into account, we started studying the structure of catalyst **1** with the aminoindane chiral group. Compound **1** crystallizes in the monoclinic system and $P2_1$ space group with two independent molecules in the asymmetric unit, corresponding to the $1R$ enantiomer. The conformational disposition in both molecules is *trans,trans*. In these two molecules the planes formed between the thiourea SCN_2 moieties are situated almost perpendicular to each other, with an angle of 98.2° , and the sulfur atom points out towards the NH groups of the other thiourea molecule (Figure 3).

Figure 3. a) Molecular structure of one molecule of thiourea **1**. b) Disposition of the two independent molecules with intermolecular contacts.

The structure corresponds with hydrogen-bonded chains between the two NH proton donors and the S atom in other adjacent thiourea molecule. In these layers, the S atom of thiourea acts as a proton acceptor with bifurcated hydrogen bonds with the NHs of the adjacent thiourea skeleton which acts as a proton donor, in a very organized network. This effect is the most typical behavior observed in urea architectures due to the most polar character of the C=O bond compared with C=S bond and the corresponding more favorable self-association in urea structures.⁴⁰ This behavior can be also rationalized in terms of *ab initio* methods, which support differences in energy for the N-H $\cdots$ S compared with N-H $\cdots$ O interaction in the chain dimers, being weaker in thioureas than in ureas.^{41,42}

This spatial arrangement is persistent in the space and allows a coplanar approach of the thiourea blocks in the plane defined by each thiourea chain, being symmetric each two layers and separated by a distance of about 3.8 Å between the two first planes and 4.3 Å between the second and third plane. Moreover, the aminoindane skeleton is shifting its relative position each two layers in order to accommodate the chiral part of the structure (see Figures 4 and 5).

Figure 4. Zigzag chain union with a *trans,trans* arrangement.

Figure 5. Zigzag movement observed for chiral thiourea **1**.

According to this arrangement there are two distinct hydrogen bonds (Table 2), those between the two independent molecules with values N1-H03...S1 of 2.58(3) and N1-H04...S1 of 2.70(3) Å, and angles close to the linearity, 162(2)°, and those related by symmetry with the next layer, N1-H01... S2_1 2.67(3) Å, angle of 155(2)° and N2-H02...S2_1 2.46(3) Å, angle of 172(3)° (\$1 x-1, y, z\$).

Table 2. Hydrogen bond parameters for compound **1**.

D-H	H...A	D...A	<(DHA)	
0.76(3)	2.70(3)	3.436(3)	162(2)	N4-H04...S1
0.81(3)	2.58(3)	3.361(2)	162(2)	N3-H03...S1
0.81(3)	2.46(3)	3.257(2)	172(3)	N2-H02...S2_1 (\$1 = x-1, y, z\$)
0.86(3)	2.67(3)	3.464(2)	155(2)	N1-H01...S2_1 (\$1 = x-1, y, z\$)

In contrast to the straight chains shown in ureas along the C=O vector, since the electron density is found around the axial position of the C=O bond, in thiourea **1** it is possible to observe the preferential zigzag movement⁴³ that the oblique C=S group is describing in the space. This

oblique contact occurs in order to optimize the electrostatic interactions between the NH protons and the negative charge over the S atom, disposed in an equatorial belt around the S atom.⁴⁴ Additionally, close contacts (~ 2.65 Å) within the layers exist between a F atom of the CF₃ group with the *orto*-H (C-H $\cdots$ FCF₂) by the same side of two consecutive aryl rings, and this interaction is observed each two groups. Surprisingly, the distances from the NH to the S atom are different along the chain polymer. In the dimers, belonging to the asymmetric unit, the distance from the most acidic H atom is higher (2.70(3) Å) than the distance to the less acidic H atom (2.58(3) Å). However, in the symmetry translated molecules the distance from the most acidic H atom is shorter (2.46(3) Å) than the one with the less acidic H atom (2.67(3) Å).

Interestingly, this *trans,trans* disposition is in agreement with the poor capacity of activation shown by this thiourea in organocatalytic reactions. Since, as observed by us, the absence of the OH group in its skeleton makes this structure a less efficient catalyst than **4** (see entries 1 and 4, Table 1).^{16-19,21} Computational calculations reported by us demonstrated the participation of the OH in the activation of the nitroalkene (Figure 6) and its important role in the Friedel-Crafts alkylation mechanism, justifying the lack of reactivity observed when catalyst **1** is used.¹⁹

Figure 6. Crucial role of the *cis* OH group in the aminoindanol moiety

Thiourea **2** contains the aminoindanol group in a *cis,trans* arrangement related to the NH groups and instead of the more bulky and electron withdrawing CF₃ groups there are hydrogen atoms.

The crystal structure of thiourea **2** is shown in Figure 7. It crystallizes with only one molecule per asymmetric unit in the monoclinic chiral $P2_1$ space group. The structure corresponds with the $1R,2S$ enantiomer. The protons of the nitrogen atoms point out to opposite direction, *cis,trans* disposition, which is not the ideal situation for an efficient hydrogen bond donor catalyst since this avoids the right bidentate coordination of the electrophiles (as shown in Figure 6).^{19,45} There are two main short contacts between adjacent molecules and correspond to the $\text{OH}\cdots\text{S}$ hydrogen bond of 2.55(2) Å and $\text{S}\cdots\text{HN}$ bond of 2.56(2) Å, with angles very close to linearity of 173.6(19) and 160.1(16)°, respectively (see Table 3). This is a non-common disposition in thiourea molecules, because the dimer formation takes place through shoulder-to-shoulder $\text{NH}\cdots\text{S}$ hydrogen bonds. The presence of the OH group in the aminoindanol moiety is crucial for this different pattern.

Figure 7. a) Molecular structure of thiourea **2** *cis,trans*. b) Dimer formation through $\text{OH}\cdots\text{S}$ and $\text{NH}\cdots\text{S}$ hydrogen bonds.

Table 3. Hydrogen bond parameters for compound **2**.

D-H	H...A	D...A	<(DHA)	
0.822(19)	2.56(2)	3.3432(15)	160.1(16)	N1-H01...S1_\$1 (\$1 = -x+1, y+1/2, -z)
0.82(2)	2.55(2)	3.3667(14)	173.6(19)	O1-H0...S1_\$2 (\$2 = -x+1, y-1/2, -z)

The packing diagram of **2** shows all the molecules located in a parallel fashion and connected by the main OH $\cdots$ S and NH $\cdots$ S hydrogen bonds and other secondary bonds between several protons with the nitrogen or the carbon atoms of the aromatic rings, thus forming a three-dimensional network (Figure 8).

Figure 8. Packing diagram of thiourea **2** showing the hydrogen bond network.

Schreiner and co-workers reported that the strength of the interaction also depended on the rigidity of the catalyst, which at the same time is related with the entropy of the catalyst to be ordered for the suitable interaction with the electrophile.⁴⁵ Moreover, it was proposed that the presence of an electron-withdrawing group in the *para*-position of the aromatic ring provides a most positive polarization of the hydrogen atoms in the *ortho*-position allowing an attractive interaction between the H $\cdots$ S (Figure 9). This interaction can influence on the rotation of the phenyl group, avoiding it and consequently, favoring the catalysis.

Figure 9. Attractive interaction avoiding the rotation of the phenyl groups

Interestingly, the *cis,trans* configuration found in the crystal structure of thiourea **2** is consistent with the lack of the CF_3 groups in the aromatic ring, which would allow the rotation of the aromatic ring supporting, at the same time, the almost lack of reactivity also observed with this catalyst (entry 2, Table 1). Moreover, the nitroalkene **5** prefers to be coordinated through a bidentate coordination, as pioneering observed by Etter and co-workers,⁴⁶ providing a more rigid TS among the three species involved in the process,¹⁹ which in this case, with thiourea **2**, is less probable. This fact would also support the lack of enantiomeric excess when this catalyst is used. Thiourea **3** contains the aminoindanol group in a *trans,trans* disposition related to the NH groups and the bulky 3,5- $(\text{CF}_3)_2\text{C}_6\text{H}_3$ moiety. Compound **3** crystallizes with only one molecule in the asymmetric unit in the orthorhombic chiral $\text{P}2_12_12_1$ group. The structure corresponds with the 1*R*,2*R* enantiomer. It can be observed that one of the NH groups is slightly turned over the perpendicularity. This distorted *trans,trans* disposition, also makes difficult the formation of hydrogen bonds between these two NH groups and the sulfur atom. The crystal structure of thiourea **3** is shown in Figure 10.

Figure 10. Molecular structure of thiourea **3**, and formation of dimers through OH $\cdots$ S hydrogen bonds.

This twisted *trans,trans* arrangement found in **3** supports the lack of reactivity observed with this catalytic structure in our reactions (entry 3, Table 1), since this disposition of the NHs would difficult the right bidentate activation of the electrophile in our Michael addition reactions, as previously described,^{16-21,47} and more entropic energy would be required to order the catalyst in the TS.⁴⁵ Moreover, the *trans*-disposition of the OH group in the aminoindanol moiety would not allow the right activation of the nitroalkene as previously supported with computation calculations (Figure 11),¹⁹ and as abovementioned in Figure 6.

Figure 11. Non appropriate coordination of the nitro group

Interestingly, we did not observe the formation of the interaction between both NHs of the thiourea with the S atom of the consecutive one in **3**. In contrast, the layers are formed by coordination of the OH group with the less acidic NH of other thiourea ($\text{H-O}\cdots\text{H-N}$) (2.15(5) Å) by the same side. Therefore, it is possible to observe the formation of a chain with the zigzag shape with the molecules perfectly orientated in totally coplanar organization (Figure 12). In this arrangement, a short $\text{H}\cdots\pi$ interaction to the centroid of the phenyl ring of the aminoindanol moiety of 2.67 Å is observed.

Figure 12. Arrangement of thiourea **3** through short $\text{H-O}\cdots\text{H-N}$ bonds and $\text{H}\cdots\pi$ interaction.

Additionally, there are also short intermolecular hydrogen bonds between the sulfur atom of the thiourea and the proton of the OH group, $\text{O1-H0}\cdots\text{S1}$ 2.42(5) Å (Table 4), which affords the formation of another zigzag chain (Figure 13a). These two zigzag chains are superposed originating a three-dimensional array as shown in Figure 13b.

Figure 13. a) Formation of other zigzag chain through S...OH bonds. b) Superposed zigzag chains.

Table 4. Hydrogen bond parameters in thiourea **3**.

D-H	H...A	D...A	<(DHA)	
0.86(5)	2.42(5)	3.206(4)	153(5)	O1-H0...S1_\$1
0.76(5)	2.15(5)	2.897(6)	172(6)	N2-H2...O1_\$2

The structure of thiourea **4**, with the OH group in the *cis* relative position is displayed in Figure 14a. It crystallizes with only one molecule in the asymmetric unit in the orthorhombic chiral P2₁2₁2 group and with half molecule of dichloromethane. The structure corresponds with the 1*S*,2*R* enantiomer. It is interesting to observe three different hydrogen bonding types. The first one is confined in the very congested union between two faced thioureas and formed by OH coordination with two NH of the facing thiourea (Figure 14b). The distance between the OH and the most acidic NH is 2.35(3) Å, while the less acidic one is placed at 2.10(3) Å. This

conformational preference is rare since the bulkiness of the organic substituents is expected to govern the arrangement of the final structure giving rise to a less hindered coordination.²⁶

Figure 14. a) Molecular structure of thiourea 4. b) Dimer formation of thiourea 4.

In order to explain this uncommon association within both thiourea molecules, we could invoke a favorable π - π staking between the two bis(trifluoromethyl)phenyl groups, with a short distance of 3.514 Å, and between the phenyl rings of the two aminoindanol moieties, with a distance of 3.561 Å. This couple of molecules interact with the OH groups of other adjacent couple of thiourea molecules through the sulfur atom, O-H $\cdots$ S 2.56(4) Å, and some short F $\cdots$ H contacts of 2.610 Å, forming a chain of thiourea dimers (Figure 15).

Figure 15. Formation of chains with thiourea dimers **4**.

These interactions would be in agreement with a recent mechanistic proposal reported by us in which an external Brønsted acid would activate our thiourea catalyst enhancing the reactivity and the enantioselection of the catalytic system.¹⁸ Additionally, the planarity of the aminoindanol moiety and the orientation of the OH group joined to the directional disposition of both NHs are in agreement with our mechanistic hypothesis regarding the bifunctional character played by this structure in the Michael reactions depicted in Figure 16.^{16-19,21} This crystal structure supports the high capacity of this catalyst to promote different reactions in comparison with the other three structures studied.⁴⁸

Figure 16. Bifunctional mode of action by thiourea 4.

Consequently, the pattern in which thiourea 4 is packed is different to those observed in crystalline solids of previously published thioureas.²⁴⁻²⁸ Additionally, this packing is also different from those found with the other thioureas 1-3 described here. The difference mainly relies in the strong hydrogen bonding between the hydroxyl group of the aminoindanol and the NHs protons of the thiourea. These contacts are specially relevant in the mode of action of these hydrogen bond donor catalysts, since it makes possible the *trans,trans* disposition of the NH groups for the right activation of the substrates in the catalytic processes (Figure 6 and 16). Hydrogen bond parameters for compound 4 are summarized in Table 5.

Table 5. Hydrogen bond parameters in thiourea **4**.

D-H	H...A	D...A	<(DHA)		
0.73(3)	2.10(3)	2.840(2)	164(3)	N2-H2...O1_\$1	(\$1 -x, -y+1, z)
0.81(3)	2.35(3)	3.101(2)	150(3)	N1-H1...O1_\$1	(\$1 -x, -y+1, z)
0.80(4)	2.56(4)	3.2980(16)	162(3)	O1-H0...S1_\$2	(\$2 -x+1/2, y-1/2, -z+1)

FT-IR spectroscopy analysis is one of most widely used techniques to support possible hydrogen bond interactions between at least two organic molecules, providing information about hydrogen bonds in the solid state.^{28,49} Functional groups OH and NH, participating or not in hydrogen bonding, can be monitored by IR spectroscopy. The IR spectra for thioureas **1-4** are collected in the supporting information of this article and the main bands in Table 6. It is remarkable that the frequency values of N–H and O–H stretching vibration modes are significantly lower than those corresponding to non-associated N–H and O–H groups in thioureas. In all the thioureas several bands appear in the range 1125-1550 cm⁻¹ and they correspond to $\nu(\text{C}=\text{S})$ and $\nu(\text{C}-\text{N})$ vibrations modes. The spectrum of thiourea **1** exhibits a broad band at 3222 cm⁻¹, which is in agreement with the presence of N–Hs coordinated in the solid state, as we have found in the solid state structure with strong S $\cdots$ HN interactions. Thioureas **2** and **3** showed two closely N–H stretching bands at 3401 and 3212 cm⁻¹, and 3313 and 3231 cm⁻¹, respectively, as a consequence of the rotamers with NH in *cis,trans* (**2**) or distorted *trans,trans* (**3**) as shown above for these crystal structures.⁵⁰ The absorptions related with the OH $\cdots$ S coordination are also observed in thioureas **2** and **3** at 3401 cm⁻¹ (a narrow band) and at 3373 cm⁻¹ (a narrow band), respectively. For thiourea **4** the $\nu(\text{N}-\text{H})$ band appears at 3238 cm⁻¹, indicating a higher degree of hydrogen bonding, in a similar order to thiourea **1**, since with both N-H in *trans* a major association is

expected. Additionally, in thiourea **4** the absorption related with the OH $\cdots$ S coordination is also observed around 3100 cm⁻¹ (a broad band).⁵¹ The narrow bands in **2** and **3** are related with a less associated OH group in the packing of these molecules in sharp contrast with the broad band found in **4**. All these data also support the hydrogen bonds observed in the crystal structures.

Table 6. Main IR bands for thioureas **1-4** (cm⁻¹)

Thiourea	Conformation	$\nu(\text{O-H})$	$\nu(\text{N-H})$	$\nu(\text{C=S})$ and $\nu(\text{CN})$
1	<i>trans,trans</i>	-	3222(br)	1125-1560(s)
2	<i>cis,trans</i>	3401(s)	3401(br), 3212(br)	1127-1590(s)
3	<i>distorted trans,trans</i>	3373(s)	3313(br), 3231(br)	1122-1560(s)
4	<i>trans,trans</i>	3100(br)	3238(br)	1130-1530(s)

Conclusions

The crystal structures of four chiral thiourea organocatalysts are described by the first time. This study illustrates different packing modes determined by the presence or the absence of the OH group and its relative configuration in the aminoindanol skeleton. Additionally, the importance of the presence of a bulkiest substituent in the other amine group of the thiourea is compared. The OH group present in the aminoindanol skeleton has been also found crucial, with the *cis* configuration, for the success of the catalytic examples previously studied.⁴⁸ Different modes of coordination have been reported through hydrogen bonds which exhibit different connectivity in the solid state. In this sense, H-O $\cdots$ H-N, O-H $\cdots$ S or N-H $\cdots$ S have been identified as the main intermolecular hydrogen bond interactions. These bonds successfully assemble the molecules in the crystal structure. The interactions in the crystal network seem to be in agreement with the

catalytic behavior previously observed by the same structures in Michael addition reactions. The differences and similarities with other model systems containing a thiourea or urea skeleton have been also discussed. Our study extends and complements the works so far reported concerning thioureas, since this is the first work focused on chiral organocatalytic structures. These results could open a new interesting line of research related to the study of other chiral thiourea and urea scaffolds, which has not been previously considered in the literature. Moreover, this contribution could become an important precedent for further researches.

EXPERIMENTAL SECTION

General experimental methods and instrumentation. Purification of reaction products was carried out either by filtration or by flash chromatography using silica-gel (0.063-0.200 mm). Analytical thin layer chromatography was performed on 0.25 mm silica gel 60-F plates. ESI ionization method and mass analyzer type MicroTof-Q were used for the ESI measurements. ^1H and $^{13}\text{C}\{^1\text{H}\}$ -APT NMR were recorded at room temperature on a BRUKER AVANCE 400 spectrometer (^1H , 400 MHz; ^{13}C , 100.6 MHz) or on a BRUKER AVANCE II 300 spectrometer (^1H , 300 MHz; ^{13}C , 75.5 MHz) in CDCl_3 as solvent. Chemical shifts were reported in the δ scale relative to residual CHCl_3 (7.28 ppm) for ^1H NMR and to the central line of CDCl_3 (77 ppm) for ^{13}C NMR. The IR spectra were recorded with two different spectrometers, one with Fourier transform, a Fourier Nicolet Avatar 360 FI-IR, and a Perkin Elmer FT-IR spectrometer equipped with a universal ATR sampling accessory.

General Procedures

Thioureas **1**, **3** and **4** have been prepared as previously described by us.¹⁷ Thiourea **2** has been synthesized by a similar procedure.

General procedure for the preparation of thiourea 2

To a stirred solution of phenyl isothiocyanate (1.1 mmol) in CH₂Cl₂ (5 mL), commercially available chiral (1*R*,2*S*)-*cis*-1-amino-2-indanol (1 mmol) was added in one portion. After stirring the resulting solution at room temperature overnight, the solvent was evaporated under reduced pressure and the product purified by flash chromatography (SiO₂, hexane/EtOAc 7:3). Thiourea **2** was obtained as a white solid in 89% yield. ¹H NMR (CDCl₃) δ (ppm): 8.14 (br s, 1H), 7.45-7.15 (m, 9H), 6.77 (d, *J* = 7.9 Hz, 1H), 5.98 (dd, *J* = 7.8, 5.2 Hz, 1H), 4.83-4.75 (m, 1H), 3.20 (dd, *J* = 16.7, 5.3 Hz, 1H), 2.90 (dd, *J* = 16.7, 1.7 Hz, 1H), 2.32 (br s, 1H). ¹³C-APT NMR (CDCl₃) δ (ppm): 180.65 (1C), 140.0 (1C), 139.9 (1C), 136.3 (1C), 130.0 (2C), 128.4 (1C), 127.2 (1C), 126.9 (1C), 125.4 (1C), 124.7 (2C), 124.6 (1C), 73.42 (1C), 63.15 (1C), 39.68 (1C). HRMS (ESI+) calcd C₁₆H₁₆N₂NaOS 307.0876; found 307.0882 [M + Na].

Crystal Structure Determinations

Crystals for thioureas **1-4** have been obtained by slow diffusion of *n*-hexane into a dichloromethane solution. Data were recorded with an APEX-II CCD for compound **4** or an Xcalibur diffractometer for compounds **1**, **2** and **3**. The crystals were mounted in inert oil on glass fibers and transferred to the cold gas stream of the diffractometer. Data were collected using monochromated Mo-Kα radiation (λ = 0.71073 Å) in ω -scans. Absorption corrections based on multiples cans were applied by using the SADABS program (**4**),⁵² or spherical harmonics implemented in SCALE3 ABSPACK scaling algorithm (**1-3**).⁵³ The structures were solved by direct methods and refined on F² by using the SHELXL-97 program.⁵⁴ All non-hydrogen atoms were refined anisotropically. All hydrogen atoms were located in the Fourier map. The crystallographic details are summarized in Table 7.

Table 7. X-ray data for compounds **1-4**.

Compound	1	2	3	4 ·1/2CH ₂ Cl ₂
Formula	C ₁₈ H ₁₄ F ₆ N ₂ S	C ₁₆ H ₁₆ N ₂ OS	C ₁₈ H ₁₄ F ₆ N ₂ OS	C _{18.50} H ₁₅ ClF ₆ N ₂ O
<i>M_r</i>	404.37	284.37	420.37	462.83
Habit	colorless prism	colorless prism	colorless plate	colorless prism
Crystal size (mm)	0.38x0.34x0.26	0.44x0.24x0.20	0.41x0.20x0.05	0.38x0.36x0.30
Crystal system	Monoclinic	Monoclinic	Orthorhombic	Orthorhombic
Space group	P2 ₁	P2 ₁	P2 ₁ 2 ₁ 2 ₁	P2 ₁ 2 ₁ 2
Cell constants:				
<i>a</i> (Å)	7.9961(2)	10.612(2)	4.7304(8)	10.4055(4)
<i>b</i> (Å)	16.3151(4)	6.1475(12)	11.420(9)	12.4576(5)
<i>c</i> (Å)	13.8271(3)	10.714(2)	32.857(16)	14.7926(6)
α (°)	90	90	90	90
β (°)	96.032(3)	96.76(3)	90	90
γ (°)	90	90	90	90
<i>V</i> (Å ³)	1793.86(8)	694.1(2)	4141.9(14)	1917.53(13)
<i>Z</i>	4	2	4	4
<i>D_x</i> (Mg m ⁻³)	1.497	1.361	1.573	1.603
μ (mm ⁻¹)	0.244	0.230	0.254	0.378
<i>F</i> (000)	824	300	856	940
<i>T</i> (°C)	-173	-173	-173	-173
2 θ _{max}	51	51	51	51
No. of refl.:				
measured	14146	16352	4191	20202
independent	6430	2574	2931	3584
Transmissions	0.9129-0.9392	0.9056-0.9555	0.9029-0.9874	0.8696-0.8950
<i>R</i> _{int}	0.0278	0.0268	0.0509	0.0165
Parameters	600	245	309	327
Restraints	1	1	0	0
Goodness of fit on <i>F</i> ²	1.027	1.059	1.008	1.072
<i>wR</i> (<i>F</i> ² , all Refl.)	0.0761	0.0513	0.0901	0.0794
<i>R</i> (<i>I</i> > 2 σ (<i>I</i>))	0.0353	0.0219	0.0623	0.0299
max. $\Delta\rho$ (e Å ⁻³)	0.238	0.169	0.251	0.469

ASSOCIATED CONTENT

Supporting information

CCDC 1478178 (**1**), 1478179 (**2**), 1478180 (**4**) and 1478181 (**3**) contain the supplementary crystallographic data for all compounds. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by e-mailing data_request@ccdc.cam.ac.uk, or by

contacting The Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

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REFERENCES

- 1 For a pivotal review concerning this topic, see: Custelcean, R. *Chem. Commun.* **2008**, 295; and references therein cited.
- 2 Pihko, P. M. (Ed.) in *Hydrogen Bonding in Organic Synthesis*. Wiley-VCH: Weinheim, **2009**.
- 3 Prins, L. J.; Reinhoudt, D. N.; Timmerman, P. *Angew. Chem. Int. Ed.* **2001**, *40*, 2382-2426.
- 4 Koulov, A. V.; Lambert, T. N.; Shukla, R.; Jain, M.; Boon, J. M.; Smith, B. D.; Li, H.; Sheppard, D. N.; Joos, J.-B.; Clare, J. P.; Davis, A. P. *Angew. Chem. Int. Ed.* **2003**, *42*, 4931-4933.

- 5 McNally, B. A.; Koulov, A. V.; Lambert, T. N.; Smith, B. D.; Joos, J.-B.; Sisson, A. L.; Clare, J. P.; Sgarlata, V.; Judd, L. W.; Magro, G.; Davis, A. P. *Chem. Eur. J.* **2008**, *14*, 9599-9606.
- 6 Judd, L. W.; Davis, A. P. *Chem. Commun.* **2010**, *46*, 2227-2229.
- 7 Hussain, S.; Brotherhood, P. R.; Judd, L. W.; Davis, A. P. *J. Am. Chem. Soc.* **2011**, *133*, 1614-1617.
- 8 Haynes, C. J. E.; Moore, S. J.; Hiscock, J. R.; Marques, I.; Costa, P. J.; Félix, V.; Gale, P. A. *Chem. Sci.* **2012**, *3*, 1436-1444.
- 9 Moore, S. J.; Haynes, C. J. E.; González, J.; Sutton, J. L.; Brooks, S. J.; Light, M. E.; Herniman, J.; Langley, G. J.; Soto-Cerrato, V.; Pérez-Tomás, R.; Marques, I.; Costa, P. J.; Félix, V.; Gale, P. A. *Chem. Sci.* **2013**, *4*, 103-117.
- 10 Busschaert, N.; Wenzel, M.; Light, M. E.; Iglesias-Hernández, P.; Pérez-Tomás, R.; Gale, P. A. *J. Am. Chem. Soc.* **2011**, *133*, 14136-14148.
- 11 Moore, S. J.; Wenzel, M.; Light, M. E.; Morley, R.; Bradberry, S. J.; Gómez-Iglesias, P.; Soto-Cerrato, V.; Pérez-Tomás, R.; Gale, P. A. *Chem. Sci.* **2012**, *3*, 2501-2509.
- 12 Busschaert, N.; Bradberry, S. J.; Wenzel, M.; Haynes, C. J. E.; Hiscock, J. R.; Kirby, I. L.; Karagiannidis, L. E.; Moore, S. J.; Wells, N. J.; Herniman, J.; Langley, G. J.; Horton, P. N.; Light, M. E.; Marques, I.; Costa, P. J.; Félix, V.; Frey, J. G.; Gale, P. A. *Chem. Sci.* **2013**, *4*, 3036-3045.
- 13 Haynes, C. J. E.; Busschaert, N.; Kirby, I. L.; Herniman, J.; Light, M. E.; Wells, N. J.; Marques, I.; Félix, V.; Gale, P. A. *Org. Biomol. Chem.* **2014**, *12*, 62-72.
- 14 Kirby, I. L.; Pitak, M. B.; Wilson, C.; Galea, P. A.; Coles, S. J. *CrystEngComm* **2015**, *17*, 2815-2826.
- 15 Dunitz, J. D. *Chem. Commun.* **2003**, 545-548.

- 16 Herrera, R. P.; Sgarzani, V.; Bernardi, L.; Ricci, A. *Angew. Chem. Int. Ed.* **2005**, *44*, 6576-6579.
- 17 Herrera, R. P.; Monge, D.; Martín-Zamora, E.; Fernández, R.; Lassaletta, J. M. *Org. Lett.* **2007**, *9*, 3303-3306.
- 18 Marqués-López, E.; Alcaine, A.; Tejero, T.; Herrera, R. P. *Eur. J. Org. Chem.* **2011**, 3700-3705.
- 19 Roca-López, D.; Marqués-López, E.; Alcaine, A.; Merino, P.; Herrera, R. P. *Org. Biomol. Chem.* **2014**, *12*, 4503-4510.
- 20 Schön, E.-M.; Marqués-López, E.; Herrera, R. P.; Alemán, C.; Díaz Díaz, D. *Chem. Eur. J.* **2014**, *20*, 10720-10731.
- 21 Juste-Navarro, V.; Marqués-López, E.; Herrera, R. P. *Asian J. Org. Chem.* **2015**, *4*, 884-889.
- 22 MacDonald, J. C.; Whitesides, G. M. *Chem. Rev.* **1994**, *94*, 2383-2420.
- 23 Schwiebert, K. E.; Chin, D. N.; MacDonald, J. C.; Whitesides, G. M. *J. Am. Chem. Soc.* **1996**, *118*, 4018-4029.
- 24 Burne, P.; Turner, D. R.; Lloyd, G. O.; Clarke, N.; Steed, J. W. *Cryst. Growth Des.* **2008**, *8*, 3335-3344.
- 25 McBride, M. T.; Luo, T.-J. M.; Palmore, G. T. R. *Cryst. Growth Des.* **2001**, *1*, 39-46.
- 26 Custelcean, R.; Gorbunova, M. G.; Bonnesen, P. V. *Chem.–Eur. J.* **2005**, *11*, 1459-1466.
- 27 Succaw, G. L.; Weakley, T. J. R.; Han, F.; Doxsee, K. M. *Cryst. Growth Des.* **2005**, *5*, 2288-2298.
- 28 Wishkerman, S.; Bernstein, J.; Hickey, M. B. *Cryst. Growth Des.* **2009**, *9*, 3204-3210.
- 29 Paisner, K.; Zakharov, L. N.; Doxsee, K. M. *Cryst. Growth Des.* **2010**, *10*, 3757-3762.

- 30 Štrukil, V.; Igre M. D.; Fábian, L.; Eckert-Maksić, M.; Childs, S. L.; Reid, D. G.; Duer, M. J.; Halasz, I.; Mottillo, C.; Frišćić, T. *Green Chem.* **2012**, *14*, 2462-2473.
- 31 Allen, F. H.; Bird, C. M.; Rowland, R. S.; Raithby, P. R. *Acta Crystallogr., Sect. B* **1997**, *53*, 680-695.
- 32 Taylor, M. S.; Jacobsen, E. N. *Angew. Chem. Int. Ed.* **2006**, *45*, 1520-1543.
- 33 Doyle, A. G.; Jacobsen, E. N. *Chem. Rev.* **2007**, *107*, 5713-5743.
- 34 Zhang, Z.; Schreiner, P. R. *Chem. Soc. Rev.* **2009**, *38*, 1187-1198.
- 35 Kotke, M.; Schreiner, P. R. in *Hydrogen Bonding in Organic Synthesis*, Pihko, P. M. (Ed.), Wiley-VCH: Weinheim, **2009**, pp. 141-351.
- 36 Jakab, G.; Schreiner, P. R. in *Comprehensive Enantioselective Organocatalysis*, Dalko, P. (Ed.), Wiley-VCH: Weinheim, **2013**, pp. 315-341.
- 37 Štrukil, V.; Igre M. D.; Fábian, L.; Eckert-Maksić, M.; Frišćić, T. *Chem. Eur. J.* **2012**, *18*, 8464-8473.
- 38 Mittal, N.; Lippert, K. M.; De, C. K.; Klauber, E. G.; Emge, T. J.; Schreiner, P. R.; Seidel, D. *J. Am. Chem. Soc.* **2015**, *137*, 5748-5758.
- 39 Bordwell, F. G.; Algrim, D. J.; Harrelson, J. A. Jr. *J. Am. Chem. Soc.* **1988**, *110*, 5903-5904.
- 40 Scheerder, J.; Engbersen, J. F. J.; Casnati, A.; Ungaro, R.; Reinhoudt, D. N. *J. Org. Chem.* **1995**, *60*, 6448-6454.
- 41 Masunov, A.; Dannenberg, J. J. *J. Phys. Chem. A* **1999**, *103*, 178-184.
- 42 Masunov, A.; Dannenberg, J. J. *J. Phys. Chem. B* **2000**, *104*, 806-810.
- 43 Zhao, X.; Chang, Y.-L.; Fowler, F. W.; Lauher, J. W. *J. Am. Chem. Soc.* **1990**, *112*, 6627-6634.
- 44 Custelcean, R.; Engle, N. L.; Bonnesen, P. V. *CrystEngComm* **2007**, *9*, 452-455.

- 45 Wittkopp, A.; Schreiner, P. R. *Chem. Eur. J.* **2003**, *9*, 407-414.
- 46 Etter, M. C.; Urbańczyk-Lipkowska, Z.; Zia-Ebrahimi, M.; Panunto, T. W. *J. Am. Chem. Soc.* **1990**, *112*, 8415-8426.
- 47 Alcaine, A.; Marqués-López, E.; Merino, P.; Tejero, T.; Herrera, R. P. *Org. Biomol. Chem.* **2011**, *9*, 2777-2783.
- 48 Sonsona, I. G.; Marqués-López, E.; Herrera, R. P. *Beilstein J. Org. Chem.* **2016**, *12*, 505-523.
- 49 Bencivenni, L.; Cesaro, S. N.; Pieretti, A. *Vibrat. Spectrosc.* **1998**, *18*, 91-102.
- 50 Gosavi, R. K.; Agarwala, U.; Rao, C. N. R. *J. Am. Chem. Soc.* **1967**, *89*, 235-239.
- 51 Gorman, M. *J. Chem. Edu.* **1957**, *34*, 304-306.
- 52 SADABS, version 2.03, Bruker AXS, Inc., Madison, WI, **2000**.
- 53 CrysAlisPro, Agilent Technologies, Version 1.171.35.11. *Multi-scans absorption correction with SCALE3 ABSPACK scaling algorithm.*
- 54 Sheldrick, G. M. *SHELXL-97, Program for Refinement of Crystal Structures*, University of Göttingen, Göttingen, **1997**.