DOI: 10.1021/cg100589n

CRYSTAL GROWTH & DESIGN Article
2010, Vol. 10
3757–3762

A Robust Thiourea Synthon for Crystal Engineering

Kathryn Paisner, Lev N. Zakharov, and Kenneth M. Doxsee*

Department of Chemistry, University of Oregon, Eugene, Oregon 97403

Received May 3, 2010; Revised Manuscript Received May 21, 2010

ABSTRACT: Crystallographic characterization of a series of bis-thiourea derivatives derived from *N*,*N*′-bis(3-aminopropyl)-piperazine revealed a highly conserved intramolecular hydrogen bonding pattern, with intramolecular S(6) [or, in one case, S(8)] hydrogen bonding interactions between each heterocyclic nitrogen atom and one proton of the adjacent propylthioureido substituent. These intramolecular hydrogen-bonding interactions lend an overall spiral-like structure to the molecules, rather reminiscent of the form of a spiral galaxy. These monomeric units assemble into infinite chains via the formation of intermolecular $R_2^2(8)$ cyclic thiourea dimers, with the exception of a phenyl derivative, which crystallized as a monomeric bis(dimethyl sulfoxide) solvate. The S(6) intramolecular hydrogen bond motif was maintained in the phenylthioureido derivatives of both *N*-(3-aminopropyl)morpholine and 3,3′-diamino-*N*-methyl-dipropylamine. The robustness of the "spiral galaxy" motif and its apparent ability to direct intermolecular interactions suggest its potential utility as a useful new synthon for solid-state design.

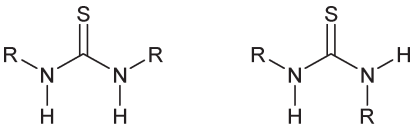
Introduction

While the solid-state behavior of urea derivatives is reasonably well-understood,[1,2] allowing exploitation for a variety of increasingly sophisticated chemical applications,[3,4] development of a comparable level of understanding of the factors dictating the solid-state structures of substituted thioureas has remained more elusive.[5] As a likely consequence of the more pronounced conformational pliability of the thioureas, for which both *s-cis* and *s-trans* geometries are frequently encountered (Scheme 1),[6] solid-state trends are more tenuous than for the conformationally less adaptable ureas, and few reliable solid-state "synthons" have been established.[5,7] Nevertheless, the strong hydrogen-bonding ability of thioureas has shown utility in areas ranging from anion complexation[8−11] and organocatalytic synthesis[12−15] to nonlinear optics,[16] and we believe that improving our understanding of and control over the solid-state behavior of thioureas will lend greater utility to this very promising functional group in the development of new materials with predictable, designed structures and properties.

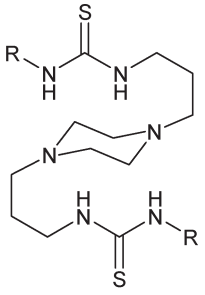
The identification of reliable solid-state structural motifs is central to our effort to establish control over the solid-state structure of substituted thioureas. In a crystallographic survey of tris-thiourea derivatives derived from tris(2-aminoethyl)amine,[17] through which we documented striking structural diversity critically dependent on seemingly small changes in molecular structure, a lead was established for a reliable, solid-state feature. Amidst a highly variable set of molecular conformations and inter- and intramolecular hydrogen-bonding interactions, donation of an intramolecular hydrogen bond from one of the thiourea groups to the central, tertiary nitrogen, resulting in a five-membered ring, was ubiquitous. While this S(5) motif[18] appeared to contribute little to the overall solid-state organization of this particular group of thioureas, its invariable presence suggested further examination of compounds designed to facilitate this type of intramolecular interaction.

While the tris(2-aminoethyl)amine derived thioureas allowed for rather efficient intramolecular hydrogen-bonding,

Scheme 1. Conformations of *N*,*N*′-Disubstituted Thioureas[6]



Scheme 2. Thioureas Derived from *N*,*N*′-Bis(3-aminopropyl)piperazine



1a: R = n-propyl
1b: R = n-pentyl
1c: R = isopropyl
1d: R = *tert*-butyl
1e: R = phenyl
1f: R = benzyl

we felt that extension of the connecting "tether" could further enhance this interaction by allowing for more optimal orientation of the hydrogen-bond donating and accepting groups. With this in mind, we chose to examine thioureas prepared from *N*,*N*′-bis(3-aminopropyl)piperazine (Scheme 2) as candidates for solid-state investigation, with these bis-thiourea systems being of additional interest in that the flexibility of the piperazine ring could, we felt, lead to the formation of dimeric structures similar to those reported earlier by us[19] and others.[20]

*To whom correspondence should be addressed. Phone: (541) 346-2846. E-mail: doxsee@uoregon.edu.

Published on Web 06/10/2010

In contrast to the great diversity of solid-state structures found for the tris-thiourea derivatives, these bis-thiourea derivatives derived from *N*,*N*′-bis(3-aminopropyl)piperazine displayed startlingly similar structures, seemingly regardless of the nature of the pendant "R" groups. As we discuss below, the bis-thiourea derivatives (**1a**−**f**) adopt conformations allowing both "arms" to form hydrogen bonds to the central piperazine moiety, leading to molecular structures reminiscent of a "spiral galaxy." Herein, we report the synthesis and solid-state structural analysis of these thioureas, and, for comparison, an acyclic version and a single-armed morpholine analogue. Given the predictable formation of solid-state structures in these systems, and in the face of the current dearth of reliable thiourea synthons, we believe that this "spiral galaxy" motif will provide significant assistance to the efforts of those engaged in crystal engineering with these intriguing and useful molecules.

Experimental Section

General. All reagents were used as purchased, from Aldrich or TCI, without further purification. Tetrahydrofuran (THF) was dried with molecular sieves before use; all other solvents were technical-grade and used as received. Representative procedures and partial characterizations are presented here; full experimental details and characterization for all new compounds are provided as Supporting Information.

Preparation of *N*,*N*′-Bis[3-(*N*′′-isopropylthioureido)propyl]piperazine (1c). Isopropyl isothiocyanate (0.52 mL, 0.0048 mol) was added to a solution of *N*,*N*′-bis(3-aminopropyl)piperazine (0.50 mL, 0.0024 mol) in THF (10 mL) at room temperature. The mixture was stirred overnight, and then the solvent was removed on a rotary evaporator, providing the crude product as a powdery-white solid (crude yield 100%). ^{1}H NMR analysis revealed no impurities other than residual solvent, and an analytical sample was prepared simply by triturating a small amount of the crude product with methylene chloride (in which it has only limited solubility), isolation of the solid by filtration, and drying in vacuo for approximately 96 h. Recrystallization from a mixture of ethanol and hexanes afforded crystals suitable for single crystal X-ray diffraction analysis, mp 151−153 °C. IR (KBr): ν_{max} 3224 (NH), 1558 (C═S) cm^{-1}; ^{1}H NMR (DMSO-d_6, 300 MHz): δ 7.38 (bs, 2H, NH), 7.29 (d, 2H, NH), 4.35 (bs, 2H), 3.47 (bs, 4H), 2.46 (m, 12H), 1.75 (m, 4H), 1.24 (d, 12H); ^{13}C NMR (DMSO-d_6, 75.156 MHz): δ 180.8 (C═S), 55.4 (N−CH_2), 52.7 (N−CH_2), 44.8 (N−CH_2), 41.8 (N−CH_2), 25.9 (CH), 22.3 (CH_3). Anal. Calcd for $C_{18}H_{38}N_6S_2$: C, 53.69; H, 9.51; N, 20.87; S, 15.93; found: C, 53.79; H, 9.19; N, 20.68; S, 16.34 (by difference).

Preparation of *N*,*N*′-Bis[3-(*N*-benzylthioureido)propyl]piperazine (1f). Benzyl isothiocyanate (1.29 mL, 0.0096 mol) was added to a solution of *N*,*N*′-bis(3-aminopropyl)piperazine (1.00 mL, 0.0048 mol) in THF (15 mL), at room temperature. The mixture was stirred overnight, and then the solvent was removed on a rotary evaporator, providing the crude product as a powdery-white solid (crude yield 100%). ^{1}H NMR analysis revealed no impurities other than residual solvent, and an analytical sample was prepared simply by triturating a small amount of the crude product with methylene chloride (in which it has only limited solubility), isolation of the solid by filtration, and drying in vacuo for approximately 96 h. Recrystallization from a mixture of ethanol and water afforded crystals suitable for single crystal X-ray diffraction analysis, mp 147−148 °C. IR (KBr): ν_{max} 3238 (NH), 1527 (C═S) cm^{-1}; ^{1}H NMR (DMSO-d_6, 300 MHz): δ 7.85 (bs, 2H, NH), 7.48 (bs, 2H, NH), 7.29 (m, 10H), 4.65 (bs, 4H), 3.35 (bs, 4H), 2.25 (m, 12H), 1.61 (m, 4H); ^{13}C NMR (DMSO-d_6, 75.156 MHz): δ 183.0 (C═S), 140.2 (C), 128.9 (CH), 127.9 (CH), 127.5 (CH), 55.9 (N−CH_2), 53.4 (N−CH_2), 47.7 (N−CH_2), 42.6 (N−CH_2), 26.7 (CH_2). Anal. Calcd for $C_{26}H_{38}N_6S_2$: C, 62.61; H, 7.68; N, 16.85; S, 12.86; found: C, 62.77; H, 7.65; N, 16.82; S, 12.76 (by difference).

Preparation of *N*-[3-(*N*′-Phenylthioureido)propyl]morpholine (2). Phenyl isothiocyanate (0.84 mL, 0.0071 mol) was added to a solution of *N*-(3-aminopropyl)morpholine (1.00 mL, 0.0071 mol) in THF, at room temperature. The mixture was stirred overnight, and then the solvent was removed on a rotary evaporator, providing the crude product as a powdery-white solid (crude yield 100%). An analytical sample was prepared by crystallization from hot acetone, yielding colorless, octahedral crystals with an average diameter of 2.5−5.0 mm, which were washed with acetone and air-dried. Recrystallization from either acetone or a mixture of acetonitrile and water afforded crystals suitable for single crystal X-ray diffraction analysis, mp 126−127 °C. IR (KBr): ν_{max} 3162 (NH), 1529 (C═S) cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.62 (bs, 1H, NH), 7.44 (t, 2H, CH), 7.30 (t, 1H, CH), 7.23 (d, 2H, CH), 3.81 (bs, 2H), 3.24 (bs, 4H), 2.39 (m, 2H), 2.27 (bs, 4H), 1.75 (m, 2H); ^{13}C NMR ($CDCl_3$, 75.156 MHz): δ 180.7 (C═S), 137.5 (CH), 130.6 (CH), 127.3 (CH), 125.3 (CH), 66.8 (O−CH_2), 59.8 (N−CH_2), 54.2 (N−CH_2), 46.6 (N−CH_2), 24.9 (CH_2). Anal. Calcd for $C_{14}H_{21}N_3OS$: C, 60.18; H, 7.58; N, 15.04; O, 5.73; S, 11.48; found: C, 60.35; H, 7.46; N, 15.02; S, 11.28; O, 5.89 (by difference).

Preparation of *N*,*N*′-Bis[3-(*N*-phenylthioureido)propyl]-*N*′′-methylamine (3). Following the procedure used for **2**, treatment of *N*,*N*′-bis(3-aminopropyl)methylamine with phenyl isothiocyanate provided **3** in quantitative yield. Colorless crystals, suitable for single crystal X-ray diffraction analysis, were grown from dichloroethane/hexanes. An analytical sample was prepared by recrystallization from acetone; the powdery-white solid was washed with acetone and allowed to air-dry overnight, mp 138−140 °C. IR (KBr): ν_{max} 3391, 3161 (NH), 1534 (C═S) cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.10 (bs, 2H, NH), 7.38 (t, 4H), 7.21 (m, 8H), 3.55 (q, 4H), 2.18 (t, 4H), 1.44 (m, 4H); ^{13}C NMR ($CDCl_3$, 75.156 MHz): δ 180.2 (C═S), 136.7 (CH), 130.0 (CH), 126.9 (CH), 125.4 (CH), 56.3 (N−CH_2), 45.5 (N−CH_2), 41.9 (N−CH_3), 25.4 (CH_2). Anal. Calcd for $C_{21}H_{29}N_5S_2$: C, 60.69; H, 7.03; N, 16.85; S, 15.43; found: C, 60.56; H, 6.84; N, 16.67; S, 15.15.

Structure Determination. X-ray diffraction data were collected on a Bruker Smart Apex diffractometer at 173(2) K using MoKα radiation (λ = 0.71073 Å).[21] Absorption corrections were applied by SADABS.[22] Structures were solved using direct methods completed by subsequent difference Fourier syntheses, and refined by full matrix least-squares procedures on F^2. All non-H atoms were refined with anisotropic thermal parameters. For all compounds except **1a**, the H atoms were found on the residual density maps and refined with isotropic thermal parameters. For compound **1a**, the H atoms involved in H-bonds were found on the residual density map and refined with isotropic thermal parameters, while the other H atoms were treated in calculated positions. The crystallographic data and some details of data collection, solution, and refinement of the crystal structures are given in Table 1. All calculations were performed using the SHELXTL 6.10 package.[23]

Results and Discussion

The piperazine-derived bis-thioureas are prepared by treatment of *N*,*N*′-bis(3-aminopropyl)piperazine with two equivalents of the desired isothocyanate and may be obtained in quantitative yield and high purity simply by evaporation of the reaction solvent. Each of the bis-thioureas is highly crystalline, and recrystallization easily affords samples suitable for single crystal X-ray structural analysis.

Despite the propensity of thioureas to display significant solid-state conformational variability, *N*,*N*′-bis(3-aminopropyl)-piperazine derivatives (**1a**−**e**) uniformly form essentially identical S(6) intramolecular hydrogen bonds,[18] illustrated by the representative molecular structures of **1a** and **1b** (Figure 1).

The six-membered rings formed through these intramolecular hydrogen bonds, roughly perpendicular to the plane defined by the piperazine ring (Figure 2 and Table 2), appear relatively strain-free, as evidenced by the three nicely staggered methylene units, which are essentially superimposable on a portion of a chair-form cyclohexane ring.

The length of the intramolecular N···H contact increases in proportion to the relative size of the substituent (Table 2), while no obvious trend is apparent in either the N−H bond length or in the N···H−N angle. Interestingly, even the *tert*-butyl-substituted thiourea **1d** forms this intramolecular

Table 1. Crystal Data and Details of Structure Determination for Bisthioureas 1a−f, 2, and 3

parameter	1a	1b	1c	1d	1e	1f	2	3
formula	$C_{18}H_{38}N_6S_2$	$C_{22}H_{46}N_6S_2$	$C_{18}H_{38}N_6S_2$	$C_{20}H_{42}N_6S_2$	$C_{28}H_{46}N_6O_2S_4$	$C_{26}H_{38}N_6S_2$	$C_{14}H_{21}N_3OS$	$C_{21}H_{29}N_5S_2$
formula wt	402.665	458.771	402.665	430.718	626.964	498.750	279.40	415.61
habit	plate	block	block	plate	needle	block	block	block
size (mm)	0.38 × 0.16 × 0.02	0.28 × 0.23 × 0.08	0.38 × 0.35 × 0.24	0.35 × 0.18 × 0.06	0.42 × 0.06 × 0.05	0.34 × 0.17 × 0.08	0.40 × 0.29 × 0.18	0.32 × 0.26 × 0.17
T (K)	173(2)	173(2)	173(2)	173(2)	173(2)	173(2)	173(2)	173(2)
Xtl system	triclinic	triclinic	monoclinic	triclinic	monoclinic	triclinic	monoclinic	monoclinic
space grp	$P\bar{1}$	$P\bar{1}$	$P2_1/n$	$P\bar{1}$	$P2_1/c$	$P\bar{1}$	$P2_1/n$	$P2_1/c$
a (Å)	7.9711(6)	7.5087(9)	11.6092(12)	8.5296(9)	6.3651(4)	7.8621(8)	9.4941(8)	7.5140(7)
b (Å)	8.9324(6)	9.4482(12)	14.2683(15)	8.9162(10)	27.4003(17)	8.9516(9)	15.9450(13)	16.7692(15)
c (Å)	9.7837(7)	9.4581(12)	13.8136(15)	9.0911(10)	9.8447(6)	10.6574(11)	10.5815(8)	18.0518(17)
α (deg)	69.193(1)	85.891(2)	90	64.991(1)	90	71.844(2)	90	90
β (deg)	66.872(1)	76.883(2)	102.133(1)	88.749(2)	108.800(1)	75.928(2)	110.839(1)	92.693(1)
γ (deg)	65.622(1)	82.603(2)	90	71.490(1)	90	68.330(2)	90	90
volume (Å^3)	567.79(7)	647.42(14)	2237.0(4)	589.05(11)	1625.37(17)	655.33(12)	1497.1(2)	2272.1(4)
Z, Z'	1, 0.5	1, 0.5	4, 1	1, 0.5	2, 0.5	1, 0.5	4, 1	4, 1
μ (mm^{-1})	0.249	0.226	0.253	0.244	0.327	0.230	0.213	0.250
reflections measured	5522 [R_{int} = 0.0198]	7305 [R_{int} = 0.0230]	24732 [R_{int} = 0.0337]	6814 [R_{int} = 0.0295]	10083 [R_{int} = 0.0345]	7381 [R_{int} = 0.0202]	17175 [R_{int} = 0.0310]	26099 [R_{int} = 0.0361]
ind reflns	2000	2800	4886	2549	3498	2842	3275	4971
reflns/restraints/ parameters	2000/0/126	2800/0/228	4886/0/387	2549/0/211	3498/0/273	2842/0/230	3275/0/256	4971/0/369
R, wR (%) ($I > 2\sigma(I)$)	5.57, 14.42	3.88, 9.64	3.36, 9.07	3.99, 9.85	3.97, 8.76	3.59, 9.51	4.10, 10.89	3.67, 9.34
GOF	1.07	1.05	1.05	1.01	1.05	1.01	1.027	1.046
max/min resid density (e Å^{-3})	0.698/−0.247	0.284/−0.152	0.310/−0.185	0.347/−0.178	0.335/−0.232	0.363/−0.156	0.518/−0.292	0.292/−0.181

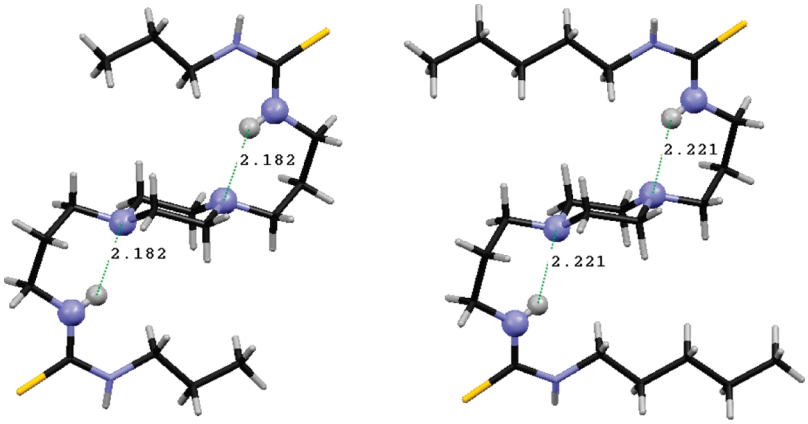


Figure 1. Molecular structures of **1a** and **1b**, showing intramolecular hydrogen bonds.

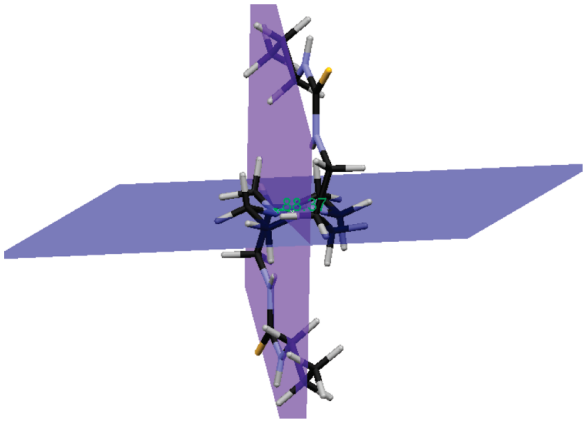


Figure 2. Least-squares planes through the piperazine ring and one of the hydrogen-bonded ring in **1a**.

hydrogen-bond, although it is considerably longer (2.32 Å). This can be contrasted to the observations of Custelcean et al.,[7] who reported that the solid-state conformation of certain *N*,*N*′-dialkylthioureas could be controlled by the bulkiness of the two alkyl substituents. In that work, an *N*-*tert*-butyl-*N*′-ethylthiourea adopted the *trans*, *trans* conformation—as did all other *N*-*tert*-butyl thioureas, if the N′ substituent was bulkier than a simple methyl group—and not the *trans*, *cis* conformation found in thiourea **1d**.

The benzyl derivative (**1f**) displays a solid-state structure that superficially closely resembles that of compounds **1a**−**e** (Figure 3). However, closer examination reveals a fundamental difference − it is the more remote thiourea NH group that donates the hydrogen bond to the piperazine nitrogen in this derivative, forming an *eight*-membered S(8) ring rather than the six-membered S(6) ring seen for each of the other derivatives. Interestingly, this variation in intramolecular hydrogen bonding is accommodated with surprisingly little perturbation of the gross molecular structure, as comparison of Figures 1 and 3 attests. More quantitatively, the intramolecular hydrogen-bonding data for **1f** presented in Table 2 largely parallel the data for compounds **1a**−**e**, differing primarily in a slightly shorter hydrogen bond and, more noticeably, in the N···H−N angle, which, given the

larger hydrogen-bonding ring size, is able to more closely approach linearity (164°).

Equally independent of significant substituent effects, the intermolecular contacts of thioureas **1a**−**d** and **1f** are also surprisingly similar. (The phenyl derivative, **1e**, crystallized as a DMSO solvate, thus changing dramatically the nature of the solid-state packing. This derivative is discussed separately below.) Because the formation of the "spiral galaxy" motif forces both thiourea moieties into the *trans,cis* conformation, with the *trans* N−H participating in intramolecular hydrogen-bonding, the sulfur atom and the *cis* N−H are ideally located to form an eight-membered cyclic $R_2^2(8)$ dimer[18] with a neighboring molecule, a common solid-state thiourea structural motif. In thioureas **1a**−**d** and **1f**, the formation of this cyclic dimer on each face of the molecule results in long chains of identically configured molecules (Figure 4a), which pack in a parallel arrangement (Figure 4b,c). The S···H(N) contact in these structures ranges from 2.61 Å (the lowest of the two distances leading to the average of 2.62 reported in Table 2) to 2.73 Å, and demonstrates no apparent correlation with substituent size (Table 2).

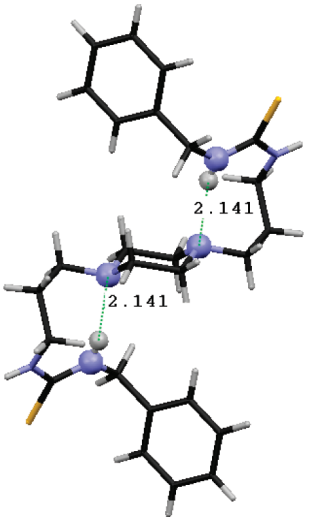


Figure 3. Molecular structures of **1f**, showing intramolecular hydrogen bonds.

Interchain interactions are limited to rather long aliphatic H−H and H−S contacts (e.g., the S atom of *n*-pentyl derivative **1b** is 3.00 Å from one of the piperazine H atoms) and appear to be completely absent in the *t*-butyl derivative, **1d**, for which the closest H−H "contact," at 2.50 Å, is between a *t*-Bu methyl group and the central methylene of one of the tethering C_3 groups. The Kitaigorodski packing indices[24,25] for these compounds (Table 2), calculated using the PLATON program, also appear to highlight the great overall structural similarity among the various derivatives, increasing slightly with increasing size of the R group.

The phenyl derivative, compound **1e**, crystallized from a mixture of DMSO and ethyl acetate as a bis(DMSO) solvate, in which molecules of **1e** are present not as hydrogen-bonded chains, but rather as isolated individual molecules, with the two *s-cis* thiourea groups each "capped" by a hydrogen-bonded DMSO molecule (Figure 5). The contact between the DMSO oxygen atom and the thiourea hydrogen atom is quite short, at 2.01 Å, and the thiourea sulfur atom and a relatively acidic α-proton on the DMSO molecule, at a distance of 2.98 Å, also appear to be engaged in a somewhat weaker hydrogen-bonding interaction.[26,27]

Although not depicted in Figure 5, each DMSO oxygen atom also interacts with the modestly acidic[28] aromatic hydrogen *ortho* to the thiourea moiety on a neighboring molecule of **1e** (distance 2.58 Å), a type of hydrogen bonding that has been observed in both proteins and small organic molecules.[28−30] Each thiourea sulfur atom also falls within weak hydrogen-bonding distance of the *para* hydrogen on an adjacent molecule (distance 2.94 Å). Compound **1e** displays negligible solubility in all solvents examined except the polar aprotic DMSO, DMF, and *N*-methylpyrrolidinone, and even in these, it displays only sparing solubility at elevated temperatures. Should it prove possible to crystallize **1e** from a less strongly hydrogen-bonding solvent, we would anticipate it to adopt the general structure displayed by **1a**−**d** (Figure 4), and we are continuing our efforts to confirm this expectation.

Table 2. Selected Structural Data for Bisthioureas 1a−f, 2, and 3

parameter	1a	1b	1c[a]	1d	1e	1f	2	3
substituent	*n*-propyl	*n*-pentyl	*i*-propyl	*t*-butyl	phenyl	benzyl		
				Intramolecular H-Bonding				
N···N (Å)	2.911(3)	2.929(2)	2.94(1)	3.009(2)	3.011(2)	2.946(2)	2.925(2)	2.813(2)
N···H (Å)	2.18(3)	2.22(2)	2.25(3)	2.32(2)	2.49(2)	2.14(2)	2.27(2)	2.08(2)
N−H (Å)	0.87(3)	0.83(2)	0.83(1)	0.88(2)	0.79(2)	0.82(2)	0.82(2)	0.86(2)
N···H−N (deg)	142(3)	143(2)	141(3)	135(2)	125(2)	164(2)	138(2)	142(2)
interplanar angle (deg)	88.37	87.81	89.30	87.23	71.72	73.43	87.45	
				Intermolecular $R_2^2(8)$ H-Bonding				
S···H (Å)	2.65(3)	2.69(2)	2.62(1)	2.73(2)		2.65(2)	2.54(2)	2.48(5)[a]
N−H (Å)	0.83(3)	0.81(2)	0.83(2)	0.80(2)		0.81(2)	0.80(2)	0.86(2)[a]
S···H−N (deg)	163(3)	164(2)	163(2)	170(2)		165(2)	166(2)	165(2)[a]
S ··· H−N−CS (deg)	145.10	126.82	156.70	174.51		158.51	169.88	163.28[a]
S ··· H−N−C (deg)	21.57	42.16	19.42	7.49		31.31	13.42	8.52[a]
				Thiourea Unit				
H−N−C=S (deg) (cis)	11.84	13.81	9.62	2.42	5.13	3.63	8.77	12.68/9.93[b]
H−N−C=S (deg) (trans)	173.28	166.22	175.85	179.00	176.52	171.93	166.37	170.49/178.51[b]
C=S (Å)	1.692(3)	1.700(2)	1.702(3)	1.702(2)	1.696(2)	1.703(2)	1.698(2)	1.703(2)/1.688(2)[b]
C−N (Å) (cis)	1.340(3)	1.337(2)	1.34(1)	1.350(2)	1.355(2)	1.345(2)	1.348(2)	1.360(2)/1.352(2)[b]
C−N (Å) (trans)	1.340(3)	1.340(2)	1.34(1)	1.342(2)	1.336(2)	1.338(2)	1.330(2)	1.319(2)/1.330(2)[b]
packing index	66.2	67.5	66.9	69.0	67.9	68.6	66.6	65.0

[a] Average of values for the two symmetry-inequivalent functional groups. [b] Thiourea unit engaged in intramolecular H-bonding/thiourea unit engaged only in intermolecular H-bonding.

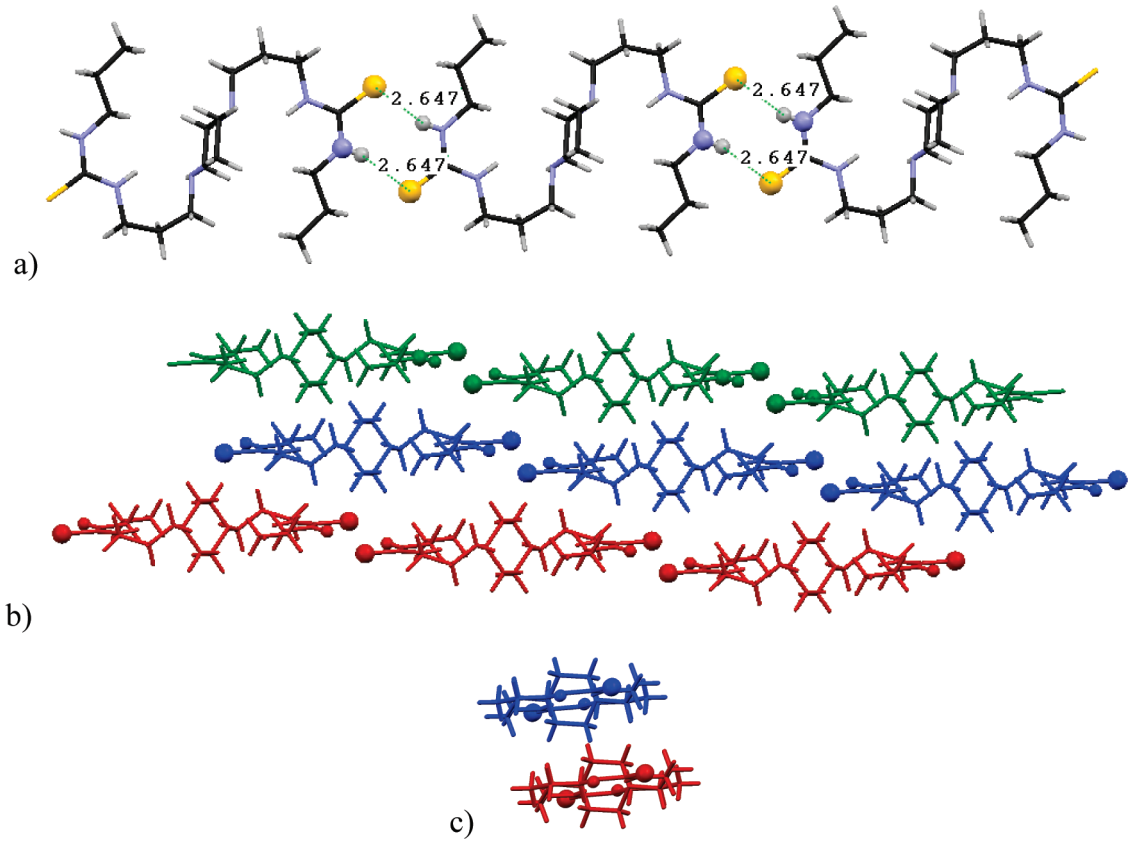


Figure 4. (a) Infinite chain of cyclic dimers of **1a**; (b) side view of infinite chains (three individual hydrogen-bonded chains in red, blue, and green for clarity); (c) end view of rows of infinite chains (two individual hydrogen-bonded chains in red and blue for clarity).

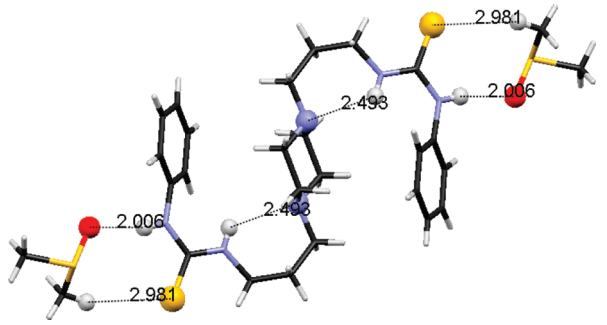


Figure 5. Molecular structures of **1e**, showing intramolecular hydrogen bonds and hydrogen-bonded DMSO solvates.

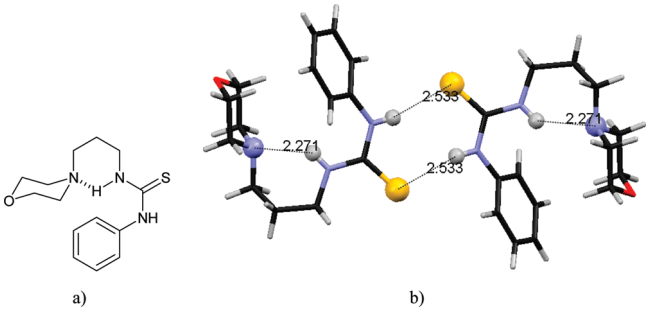


Figure 6. (a) Molecular and (b) crystal structure of **2**, showing intra- and intermolecular hydrogen bonds.

Given the overwhelming consistency of the "spiral galaxy" motif among the bis-thiourea derivatives of *N*,*N*′-bis(3-aminopropyl)piperazine, in which the intramolecular S(6) hydrogen bond was highly "conserved," we extended our investigation to other compounds offering the potential for formation of a six-membered, intramolecular hydrogen-bonding contact. Most generally, this simply requires a tertiary amine[31] separated from the thiourea by a three-carbon alkyl chain.

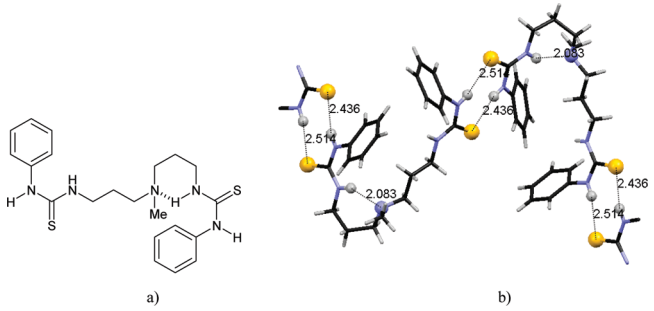


Figure 7. (a) Molecular and (b) crystal structure of **3**, showing intra- and intermolecular hydrogen bonds.

Compound **2** (Figure 6a) was prepared from *N*-(3-aminopropyl)morpholine and phenyl isothiocyanate. Unlike **1e**, morpholine derivative **2** was reasonably soluble in conventional organic solvents and was easily recrystallized from acetone or aqueous acetonitrile. Single crystal X-ray diffraction analysis revealed that **2** behaved exactly as expected (Figure 6b), displaying both the six-membered, intramolecular contact and the eight-membered intermolecular cyclic dimer seen in compounds **1a**−**d** and **1f**.

The intramolecular N···H contact in **2**, at 2.27 Å, is significantly shorter than that observed in **1e**, 2.49 Å, despite the similar structure of these compounds. This shorter contact may either be allowed by or result from a twisting of the

phenyl substituent in **2** away from the face of the morpholine ring (19.4° angle between two least-squares planes), whereas in **1e**, the phenyl substituent is almost perfectly parallel to the face of the piperazine ring, with a torsion angle of only 4.1°. As in **1a**−**d** and **1f**, **2** forms an eight-membered cyclic $R_2^2(8)$ dimer with an adjacent thiourea (Figure 6b and Table 2). Because the morpholine ring possesses only a single thiourea-containing "arm," only discrete dimers are formed rather than the infinite chains depicted in Figure 4. However, relatively short intermolecular contacts are evident between the morpholine oxygen and two methylene hydrogen atoms on a neighboring molecule, at 2.67 and 2.54 Å.

An additional test of the reliability of the six-membered, intramolecular hydrogen-bond interaction as a solid-state synthon for thioureas was provided through the synthesis of compound **3**, in which the heterocyclic unit was replaced, in essence, by the single central tertiary amine group. Despite this significant change in molecular structure, the intra- and intermolecular hydrogen-bonding interactions displayed by compound **3** are remarkably similar to those observed in compounds **1a**−**d** and **1f**.

Crystallizing in the $P2_1/c$ space group, and featuring the "spiral galaxy"-type intramolecular S(6) motif between one of its thiourea "arms" and the central, tertiary nitrogen atom, compound **3** also forms infinite chains of cyclic dimers, as each thiourea "arm" forms two hydrogen bonds with a single, neighboring molecule. The length of the intramolecular N···H contact is 2.08 Å, correlating well with the trend in bond length vs substituent size observed in **1a**−**f**, and the intermolecular hydrogen bond lengths are similarly typical of those seen in the other derivatives, at 2.51 and 2.44 Å. In addition to these hydrogen bonding interactions, a short intramolecular contact is apparent between one aryl proton and the face of the other aromatic ring (2.76 A from the mean plane of the aromatic ring), consistent with other reports of C−H···π interactions.[30,32]

Conclusion

We have discovered a new, solid-state structural motif, the "spiral galaxy," common among all reported thioureas derived from *N*,*N*′-bis(3-aminopropyl)piperazine. We have also demonstrated that the robustness of this synthon extends to other thioureas that possess the requisite structural characteristics: a three-carbon chain, separating an N-substituted thiourea moiety and a tertiary amine. The "spiral galaxy" motif also appears to direct intermolecular hydrogen bonding, at least in the *N*,*N*′-bis[3-(*N*′′-substitutedthioureido)propyl]-piperazine compounds examined in this paper. We are continuing to examine the generality of the "spiral galaxy" motif in directing intermolecular hydrogen bonding and, consequently, crystal packing in a diverse array of thioureas, in order to explore its use as a synthetic building block in solid-state design.

Supporting Information Available: Additional experimental details, full characterization, and X-ray crystallographic information files (CIF) are available for compounds **1a**−**f**, **2**, and **3**. This information is available free of charge via the Internet at http://pubs.acs.org.

References

(1) Nguyen, T. L.; Fowler, F. W.; Lauher, J. W. *J. Am. Chem. Soc.* **2001**, *123*, 11057–11064.
(2) Kane, J. J.; Liao, R.-F.; Lauher, J. W.; Fowler, F. W. *J. Am. Chem. Soc.* **1995**, *117*, 12003–12004.
(3) Kishikawa, K.; Nakahara, S.; Nishikawa, Y.; Kohmoto, S.; Yamamoto, M. *J. Am. Chem. Soc.* **2005**, *127*, 2565–2571.
(4) George, S.; Nangia, C.-K.; Lam, T. C.; Mak, W.; Nicoud, J.-F. *Chem. Commun.* **2004**, 1202–1203.
(5) Custelcean, R. *Chem. Commun.* **2008**, *3*, 295–307.
(6) Bryantsev, V. S.; Hay, B. P. *J. Phys. Chem. A* **2006**, *110*, 4678−4688. Throughout this manuscript, we adopt the standard convention of using the "cis" and "trans" descriptors to define the relative positions of the sulfur atom and the hydrogen atom attached to the thiourea nitrogen.
(7) Custelcean, R.; Gorbunova, M. G.; Bonnesen, P. V. *Chem.−Eur. J.* **2005**, *11*, 1459–1466.
(8) Wei, T.-B.; Wei, W.; Cao, C.; Zhang, Y.-M. *Phosphorus, Sulfur Silicon Relat. Elem.* **2008**, *183* (5), 1218–1228.
(9) Rashdan, S.; Light, M. E.; Kilburn, J. E. *Chem. Commun.* **2006**, *44*, 4578–4580.
(10) Wittkopp, A.; Schreiner, P. R. *Chem.—Eur. J.* **2003**, *9*, 407.
(11) Koch, K. R. *Coord. Chem. Rev.* **2001**, *216−217*, 473–488.
(12) Fuerst, D. E.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2005**, *127*, 8964.
(13) Takemoto, Y. *Org. Biomol. Chem.* **2005**, *3*, 4299.
(14) Taylor, M. S.; Jacobsen, E. N. *Angew. Chem., Int. Ed.* **2006**, *45* (10), 1520–1543.
(15) Connon, S. J. *Chem.−Eur. J.* **2006**, *12* (21), 5418–5427.
(16) Jin, Z.-M.; Zhao, B.; Zhou, W.; Jin, Z. *Powder Diffr.* **1997**, *12*, 47–48.
(17) Paisner, K.; Zakharov, L.; Doxsee, K. M., manuscript in preparation.
(18) Etter, M. C.; MacDonald, J. C.; Bernstein, J. *Acta Crystallogr.* **1990**, *B46*, 256–262.
(19) Succaw, G. L.; Weakley, T. J. R.; Han, F.; Doxsee, K. M. *Cryst. Growth Des.* **2005**, *5*, 2288–2298.
(20) Tobe, Y.; Sasaki, S.; Mizuno, M.; Hirose, K.; Naemura, K. *J. Org. Chem.* **1998**, *63*, 7481–7489.
(21) *SMART and SAINT*; Bruker AXS Inc., Madison, WI, USA, 2000.
(22) Sheldrick, G. M. *SADABS*; University of Göttingen: Germany, 1995.
(23) Sheldrick, G. M. *Acta Crystallogr.* **2008**, *A64*, 112–122.
(24) Kitaigorodski, A. I. *Molecular Crystals and Molecules*; Academic Press: New York, 1973.
(25) Spek, A. L. *Acta Crystallogr.* **1990**, *A46*, C34.
(26) Li, W.-K.; Zhou, G.-D.; Mak, T. C. W. *Advanced Structural Inorganic Chemistry*; Oxford University Press: New York, 2008, p 404.
(27) Ohba, S.; Miyamoto, H.; Fujioka, A.; Ikeuchi, T.; Lehn, J.-M. *Acta Crystallogr.* **2005**, *E61*, o182–o184.
(28) Jeffrey, G. A. *Crystallogr. Rev.* **2003**, *9*, 135–176.
(29) Nanda, V.; Schmiedekamp, A. *Prot. Struct. Funct. Bioinform.* **2007**, *70*, 489–497.
(30) Desiraju, G. R.; Steiner, T. *The Weak Hydrogen Bond in Structural Chemistry and Biology*; Oxford University Press: Oxford, 1999; pp 175−185.
(31) While not explored in this work, it is likely that other heteroatom acceptors could serve the same role as a tertiary amine.
(32) Madhavi, N. N. L.; Bilton, C.; Howard, J. A. K.; Allen, F. H.; Nangia, A.; Desiraju, G. R. *New J. Chem.* **2000**, *24*, 1–4.