



Cite this: *Org. Biomol. Chem.*, 2024, 22, 5301

Received 4th May 2024,
Accepted 11th June 2024

DOI: 10.1039/d4ob00723a

rsc.li/obc

The chalcogen-bonding interactions formed at both sides of the thiocarbonyl group in thiourea were investigated. In particular, the role of these chalcogen-bonding interactions in the *trans-trans* conformation of thiourea was evaluated *via* single-crystal X-ray diffraction analysis and DFT calculations. The obtained results indicate that the Se...S...Se dual chalcogen-bonding interactions play a stronger role in controlling the planar structure than the S...S...S interactions.

Thiourea derivatives have been recognized as privileged organocatalysts and ligands for a variety of organic transformations.¹ For the development of thiourea-based organocatalysts with high catalytic performance and stereoselectivity, their stereostructures are of crucial importance.

Thiourea derivatives such as *N,N'*-diaryl thiourea, possess four rotatable C-N single bonds (a, a', b, and b' in Fig. 1A), which results in a rich conformational variety. For example, rotation of the b and b' bonds leads to *trans-trans*, *cis-trans*, and *cis-cis* conformations,^{2,3} while rotation around the a and a' bonds in the case of derivatives that bear R substituents causes a different substituent geometry as typically shown in the *trans-trans* conformation.

Among the conformations of thiourea, the *trans-trans* conformation is expected to show superior catalytic activity and molecular recognition ability by virtue of the hydrogen-bonding interactions involving both N-H groups. Therefore, establishing conformational control over thiourea to obtain the *trans-trans* conformation has attracted considerable attention. Wittkopp and Schreiner have developed a series of *N,N'*-diaryl thiourea derivatives including 1, which bears electron-withdrawing CF₃

Formation of chalcogen-bonding interactions and their role in the *trans-trans* conformation of thiourea[†]

Takumi Inoue,^a Nami Morita,^a Yui Amijima,^a Rika Sakai,^a Shohei Hamada,^a Seikou Nakamura,^b Yusuke Kobayashi^b and Takumi Furuta^a 

groups (Fig. 1B).⁴ It has been proposed that thiourea 1 adopts the *trans-trans* conformation due to the formation of intramolecular hydrogen-bonding interactions between the sulfur atom of the thiocarbonyl group and the acidic C-H groups at the *ortho*-position of the aniline moieties.

However, to the best of our knowledge, controlling the conformation of thiourea to favor the *trans-trans* conformation remains largely unexplored, apart from the aforementioned examples.

Chalcogen-bonding interactions represent attractive noncovalent interactions between chalcogen atoms (sulfur, selenium, and tellurium) and heteroatoms including oxygen and

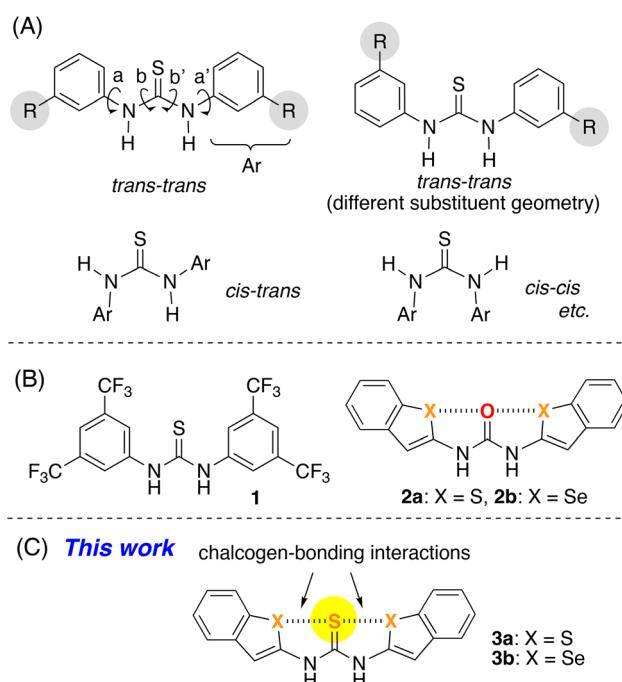


Fig. 1 (A) Conformations of *N,N'*-diaryl thiourea derivatives bearing substituents (R). (B) Previously reported urea and thiourea derivatives with *trans-trans* conformation. (C) This work.

^aLaboratory of Pharmaceutical Chemistry, Kyoto Pharmaceutical University, Yamashina-ku, Kyoto 607-8414, Japan. E-mail: furuta@mb.kyoto-phu.ac.jp

^bLaboratory of Pharmacognosy, Kyoto Pharmaceutical University, Yamashina-ku, Kyoto 607-8414, Japan

[†]Electronic supplementary information (ESI) available: Experimental procedure, spectroscopic data, computational details. CCDC 2348537. For ESI and crystallographic data in CIF or other electronic format see DOI: <https://doi.org/10.1039/d4ob00723a>



nitrogen.⁵ We have previously reported strategies to establish conformational control over urea derivatives **2a** and **2b**, which bear benzothiophene and benzoselenophene moieties, to obtain the *trans-trans* conformation with S...O...S and Se...O...Se arrangements by virtue of intramolecular chalcogen-bonding interactions (Fig. 1B).⁶ With this approach to establish conformational control in hand, we envisioned that the stereostructure of the corresponding thioureas **3a** and **3b** could also be controlled to favor the *trans-trans* conformation (Fig. 1C). However, it can be expected that the conformational flexibility is increased in the *N,N'*-diaryl thiourea derivative relative to the *N,N'*-diaryl urea derivative.^{2c} Furthermore, the electronic repulsion between the heavy chalcogen atoms might induce adverse effects toward the formation of chalcogen-bonding interactions. Thus, in an initial step, we investigated the formation of chalcogen-bonding interactions at both sides of the thiocarbonyl group in the *trans-trans* conformation. Herein, the formation of chalcogen-bonding interactions in **3a** and **3b** and the evaluation of their role in the formation of the planar structure of the *trans-trans* conformation are described.

Thioureas **3a** and **3b** were prepared *via* benzothiophene and benzoselenophene isothiocyanate intermediates (Scheme 1). First, benzochalcogenophene carboxylic acids **4a** and **4b**, which bear sulfur and selenium atoms, respectively, were converted into the corresponding *N*-Boc derivatives (**5a** and **5b**) *via* a Curtius rearrangement. Deprotection of the Boc groups under acidic conditions led to hydrochloride salts **6a** and **6b**, which were subjected to treatment with thiophosgene to give isothiocyanates **7a** and **7b**. Upon treatment of **7a** and **7b** with 1.5 equivalent of **6a** and **6b** in the presence of *i*Pr₂EtN in CH₂Cl₂ at -20 °C, the corresponding thioureas (**3a** and **3b**) were obtained in 35% and 33% yield, respectively.

The stereostructure of **3a** was determined unambiguously by an X-ray diffraction (XRD) analysis of a single crystal obtained from acetone.⁷ As shown in Fig. 2A, the three sulfur atoms are aligned on the same side of the molecule. The distances between the sulfur atoms of the benzothiophene and the thiocarbonyl moieties (3.0429(9) and 3.0810(9) Å, respectively) are both shorter than the sum of the van der Waals radii (3.6 Å) of two sulfur atoms. These short contacts indicate that chalcogen-bonding interactions are formed at both sides of the thiocarbonyl group, resulting in an S...S...S arrangement

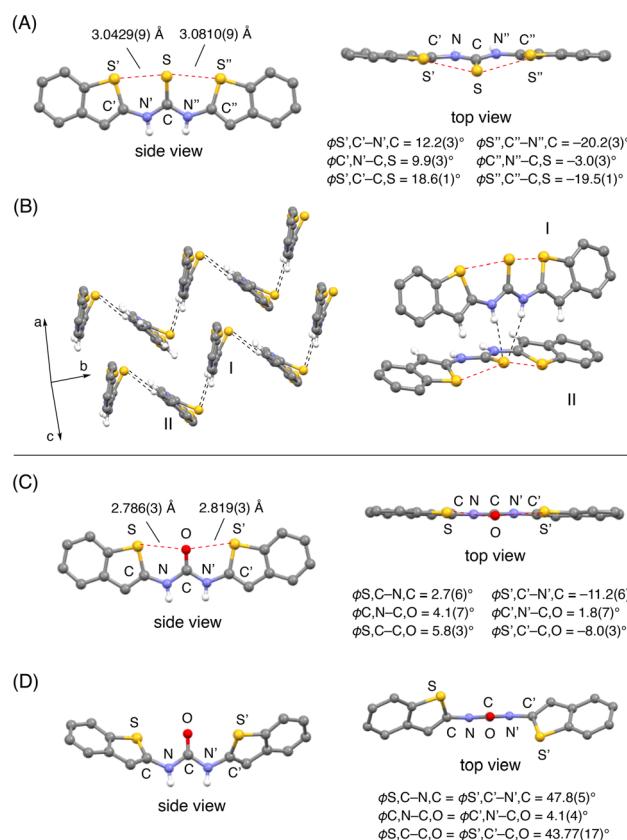


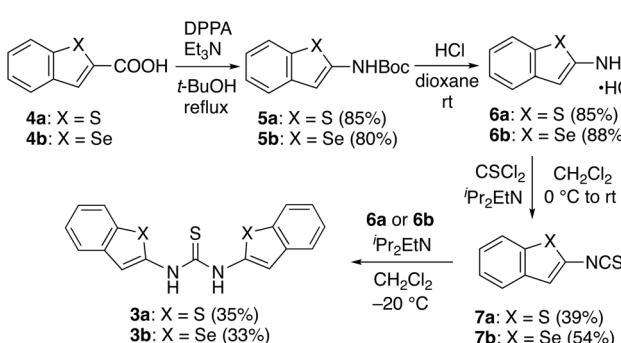
Fig. 2 (A) Crystal structure of **3a**. (B) Packing of **3a** and associated molecules I and II. (C) Crystal structure of a single crystal of **2a** obtained from acetone, exhibiting chalcogen-bonding interactions. (D) Crystal structure of a single crystal of **2a** obtained from THF without chalcogen-bonding interactions. Only the hydrogen atoms of the N-H groups are depicted for clarity. The red and black dotted lines indicate chalcogen-bonding interactions and hydrogen-bonding interactions, respectively.

(red dotted lines). Due to these chalcogen-bonding interactions, the benzothiophene rings and the thiocarbonyl group are located almost on the same plane, albeit that a small twist of the thiocarbonyl group was observed (ϕ S',C'-C,S = 18.6(1)°; ϕ S",C"-C,S = -19.5(1)°) (Fig. 2A, top view).

This planar structure of **3a** is a typical feature for the urea derivatives bearing the chalcogen-bonding interactions. In our previous study, the crystal structures of urea **2a** with and without chalcogen-bonding interactions were determined.⁸ In the structure of **2a** without chalcogen-bonding interactions, the dihedral angles between the carbonyl group and the benzothiophene moieties were significantly higher (ϕ S,C-C,O = ϕ S',C'-C,O = 43.77(17)°) (Fig. 2D). On the other hand, **2a** with chalcogen-bonding interactions exhibited the planar structure (Fig. 2C).

Accordingly, the planar structure with the small twist of the thiocarbonyl group in **3a** supports the formation of chalcogen-bonding interactions.

It is also interesting to compare the dihedral angles of the thiocarbonyl group in **3a** (ϕ S',C'-C,S = 18.6(1)°; ϕ S",C"-C,S = -19.5(1)°) with those in **2a** with chalcogen-bonding inter-



Scheme 1 Synthesis of thioureas **3a** and **3b**.



actions (ϕ S,C-C,O = 5.8(3) $^\circ$; ϕ S',C'-C,O = -8.0(3) $^\circ$) (Fig. 2C). The larger dihedral angles in **3a** might be due to (i) the presence of a repulsive interaction between the sulfur atoms in the thiocarbonyl group and the aromatic rings as initially expected, and/or (ii) the formation of intermolecular hydrogen-bonding interactions in the crystal. As shown in Fig. 2B, **3a** assembles through intermolecular hydrogen-bonding interactions between the sulfur atom of the thiocarbonyl group and the N-H groups (black dotted lines) as shown for the representative molecules I and II (Fig. 2B).

To investigate the conformations of **3a** and **3b** in solution, nuclear Overhauser effect (NOE) studies were carried out in THF-*d*₈ and in DMSO-*d*₆, respectively. In both cases, NOE correlations were observed between the N-H protons and the protons at the 3,3'-positions (Fig. 3).⁹ These results suggest that both compounds adopt the *trans-trans* conformation with S...S and Se...S...Se arrangement in solution.

To gain further insight into the chalcogen-bonding interactions, the crystal structure of **3a** and the DFT-optimized structure were subjected to an NBO analysis¹⁰ at the ω B97XD/6-311G(d,p) level¹¹ under SMD(DMSO) conditions (Fig. 4A). The analysis of the crystal structure of **3a** supports the presence of the chalcogen-bonding interactions at both sides of the sulfur atom of the thiocarbonyl group, indicating orbital overlap between the sulfur s-type lone pair (LP1)¹² and the antibonding orbitals of the C-S bonds (σ^*_{C-S}), which were calculated to have second-order perturbation energies of 1.01 and 1.16 kcal mol⁻¹, respectively. The overlap between the sulfur p-type lone pair (LP2)¹² and the antibonding orbitals of the C-S bonds (σ^*_{C-S}) with energies of 3.81 and 4.37 kcal mol⁻¹, respectively, was also confirmed (Fig. 4A). The NBO analysis of the DFT-optimized structure revealed similar stabilization energies (shown in parenthesis in Fig. 4A).

The noncovalent interaction (NCI) plot index analysis¹³ of the crystal structure of **3a** also supports the presence of the chalcogen-bonding interactions at both sides of the thiocarbonyl group (indicated by the green areas between S' and S and between S and S'' in Fig. 4B). Furthermore, the quantum theory of atoms in molecules (QTAIM) analysis¹⁴ of the crystal structure showed electron-density values (ρ = 0.0172 and 0.0164 a.u.) at the bond critical points (BCPs), which is comparable to those previously reported for chalcogen-bonding interactions (Fig. 4C).¹⁵ The depletion of electron density at the BCPs, which suggests that the interactions are noncovalent, is also supported by positive Laplacian values ($\nabla^2\rho_{S-S}$: 0.0665, $\nabla^2\rho_{S''-S}$: 0.0623). Moreover, the positive values of H_{S-S}

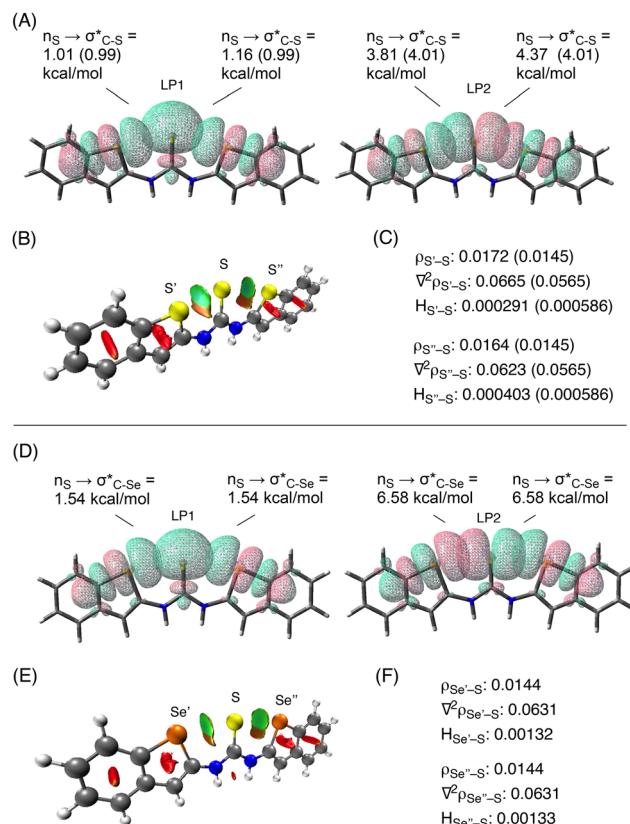


Fig. 4 (A) NBO analysis of the crystal structure of **3a**. Data in parenthesis refer to the values of the optimized structure. (B) NCI plot isosurfaces of the crystal structure of **3a**. (C) Results of the QTAIM analysis of the crystal structure of **3a**. Data in parenthesis refer to the values of the optimized structure. (D) NBO analysis of the optimized structure of **3b**. (E) NCI plot isosurfaces of the optimized structure of **3b**. (F) Results of the QTAIM analysis of the optimized structure of **3b**. The calculations were performed at the ω B97XD/6-311G(d,p) level under SMD(DMSO) conditions.

(0.000291) and $H_{S''-S}$ (0.000403) indicate that the interactions are electrostatic in nature. In their entirety, these results confirm the formation of chalcogen-bonding interactions between the sulfur atoms in **3a**.

To evaluate the chalcogen-bonding interactions between the selenium and the sulfur atoms in **3b**, the structure was optimized and analyzed at the ω B97XD/6-311G(d,p) level¹¹ under SMD(DMSO) conditions. The NBO, NCI, and QTAIM data supported the formation of chalcogen-bonding interactions (Fig. 4D-F). It is worth noting that the chalcogen-bonding interactions calculated *via* NBO analysis for **3b** are stronger than those calculated for **3a** (1.54 kcal mol⁻¹ for LP1 and 6.58 kcal mol⁻¹ for LP2 in **3b** vs. 0.99 kcal mol⁻¹ for LP1 and 4.01 kcal mol⁻¹ for LP2 in optimized **3a**).¹⁶

Therefore, the population of the *trans-trans* conformation of **3b** with the Se...S...Se arrangement can be expected to be larger than that of **3a** with the S...S...S arrangement.

This prediction was supported by the conformational analysis of *trans-trans* **3a** and **3b** on the basis of the calculated S, C-N,C and S',C'-N',C dihedral angles and the Se,C-N,C and

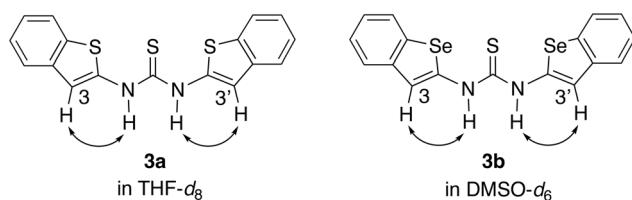


Fig. 3 NOE correlations of **3a** (in THF-*d*₈) and **3b** (in DMSO-*d*₆).



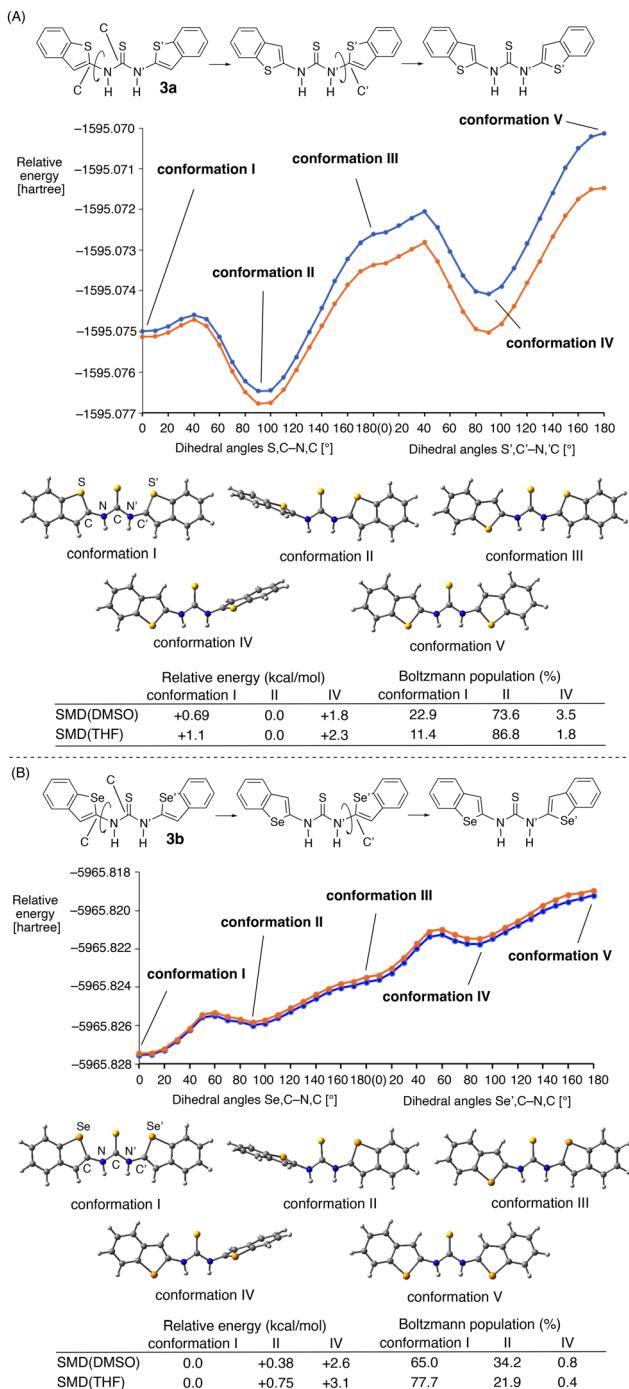


Fig. 5 (A) Conformational analysis of **3a** on the basis of the S,C–N,C and S',C'-N',C dihedral angles (blue dotted line: SMD(DMSO), orange dotted line: SMD(THF)), structures obtained under SMD(DMSO) conditions, as well as relative energies and Boltzmann population of the conformations. (B) Conformational analysis of **3b** on the basis of the Se,C–N,C and the Se',C'-N',C dihedral angles (blue dotted line: SMD(DMSO), orange dotted line: SMD(THF)), structures obtained under SMD(DMSO) conditions, as well as relative energies and Boltzmann population of the conformations. The calculations were performed at the ω B97XD/6-311G(d,p) level.

Se',C'-N',C dihedral angles (Fig. 5). In the case of **3a**, the *trans-trans* planar conformation I with the S...S...S arrangement should be present, as indicated by the NOE study (Fig. 3).

However, even in the presence of chalcogen-bonding interactions, conformation I was calculated to be less stable (+0.69 kcal mol⁻¹ at the ω B97XD/6-311G(d,p) level under SMD (DMSO) conditions) than conformation II, wherein the benzothiophene ring adopts a perpendicular arrangement relative to the C=S group (Fig. 5A). The Boltzmann population for conformations I, II, and IV was calculated to be 22.9, 73.6, and 3.5% under SMD(DMSO) conditions. In the calculations under SMD(THF) conditions, the conformations exhibit the same order of stability.

In contrast, the *trans-trans* conformation I of **3b** with the Se...S...Se arrangement was by 0.38 and 0.75 kcal mol⁻¹ more stable than conformation II under SMD(DMSO) and SMD (THF) conditions, respectively (Fig. 5B). The Boltzmann populations were calculated to be 65.0% and 77.7% under SMD (DMSO) and SMD(THF) conditions, respectively. This reversal of the order of stability between conformations I and II could potentially be attributed to the formation of stronger chalcogen-bonding interactions between the selenium and the sulfur atoms than between the sulfur atoms in **3a**. These results confirm the formation of chalcogen-bonding interactions at both sides of the thiocarbonyl group in the *trans-trans* conformation, and, in particular, that the sulfur–selenium interactions contribute more strongly to the control of the planar structure of the thiourea.

Conclusions

The formation of chalcogen-bonding interactions in the *trans-trans* conformation of thiourea derivatives was demonstrated by performing experimental X-ray diffraction and theoretical analyses. The Se...S...Se interaction in **3b** was found to be stronger than the S...S...S interaction in **3a**. A conformational analysis revealed that the population of the *trans-trans* planar conformation of **3b** is higher than that of **3a**. This conformational preference could provide a theoretical basis for the development of advanced thiourea-based catalysts. Further studies on the conformational analysis including *cis-trans* and *cis-cis* conformations, as well as the derivatization of these chalcogen-containing thioureas, including their application as organocatalysts are currently in progress in our laboratory.

Data availability

The data supporting this article have been included as part of the ESI.†

Author contributions

T. I.: investigation, writing of the original manuscript draft. N. M., Y. A., and R. S.: investigation. S. H., S. N., and Y. K.: investigation, formal analysis. T. F.: supervision, conceptualization.



Conflicts of interest

There are no conflicts to declare.

Acknowledgements

This work was financially supported by a Grant-in-Aid for Scientific Research (B) (21H02611 and 24K02158). This work was the result of using shared research equipment(s) (Bruker/Avance NEO 500 MHz spectrometer and JEOL/JMS-GCmateII) supported by MEXT and Kyoto Pharmaceutical University.

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