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REACTION OF 2,3,5,6,7,8-HEXAHYDROQUINOXALINE WITH THIOUREA DERIVATIVES: ANALYSIS OF THE STRUCTURE AND CONFORMATIONAL STATE OF [4.4.3]PROPELLANE

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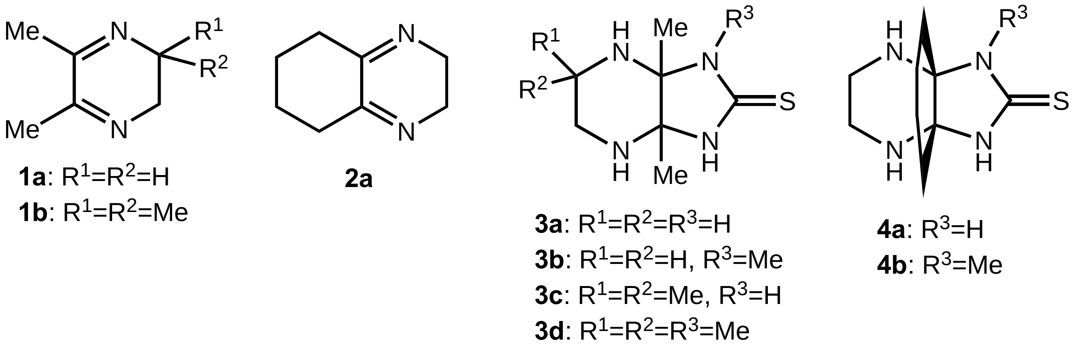
Abstract – The reaction of 2,3,5,6,7,8-hexahydroquinoxaline with thiourea derivatives yields a propellane-type tetraazaindene structure, whose conformation was established by 2D NMR analysis and molecular orbital calculations, and verified by single-crystal X-ray diffraction analysis. Further, the result obtained from X-ray analysis of this propellane-type tetraazaindene structure indicated that the crystalline state was stabilized by specific hydrogen bonds; four hydrogen bonds were of the type >C=S•••H–N, four of N–H•••N type between the imidazolidine moieties, and two of >C=S•••H–C type.

Propellane-type structures[1-3] possess three rings sharing one C-C covalent bond. Owing to their characteristic stereochemistry, their structural properties, such as bond distances and bond angles, have been well studied.[4,5] A natural product containing an aza-propellane core, actumine has been isolated from *Sinomenium acutum*[6] and found to exhibit selective T cell cytotoxicity,[7] anti-amnesic activity,[8] and anti-HBV (hepatitis type B virus) activity.[9] An efficient total synthesis of actumine has also been reported.[10]

In a previous study,[11] the reaction of dihydropyrazines (**1a**, **1b**, and **2a**),[12] having DNA strand-breakage activity,[13] with thiourea/methylthiourea provided tetraazaindene derivatives (TAIs) (**3a**, **3b**, **3c**, **3d**, **4a**, and **4b**; Figure 1). Based on X-ray crystallographic data and molecular orbital (MO) calculations, we proposed that the initial stage of cyclization may be triggered by the pericyclic ene reaction between the

NH=C–SH moiety of isothiourea and the C=N moiety of dihydropyrazine.[11] Herein we have investigated the conformation of the tetraazaindene moiety in the propellane-type structure (**4a**) by 2D-NMR spectroscopy, MO calculations,[14-17] and X-ray crystallographic analysis.[18-20]



1a: $R^1=R^2=H$
1b: $R^1=R^2=Me$

2a

3a: $R^1=R^2=R^3=H$
3b: $R^1=R^2=H$, $R^3=Me$
3c: $R^1=R^2=Me$, $R^3=H$
3d: $R^1=R^2=R^3=Me$

4a: $R^3=H$
4b: $R^3=Me$

Figure 1. Structures of compounds **1-4**

The reaction of 2,3,5,6,7,8-hexahydroquinoxaline (**2a**) with thiourea yielded the tetraazaindene propellane-type compound **4a**, whose structure was established by NMR spectroscopy, ^{1}H-^{1}H correlation spectroscopy (COSY), and heteronuclear multiple quantum coherence (HMQC) and heteronuclear multiple bond connectivity (HMBC) spectroscopic techniques. Collectively, these techniques indicate the presence of a symmetrical propellane structure in **4a**. Figure 2 shows that the conformation of **4a** was successfully confirmed by the following nuclear Overhauser effect spectroscopic (NOESY) correlations: H-8b and H-11b (1.61 ppm)/H-5a and H-6a (2.52 ppm), H-9b and H-10b (1.40 ppm)/NH-3 and NH-1 (8.01 ppm), and H-5b and H-6b (2.65 ppm)/NH-3 and NH-1 (8.01 ppm). Therefore, the predicted structure of **4a** indicates that both of its six-membered rings adopted boat conformations. Given the long NOESY correlation: H-8b and H-11b/H-5a and H-6a, we assumed that boat conformations were strain. To further confirm the structure of **4a**, MO calculations and single-crystal X-ray diffraction analysis were performed.

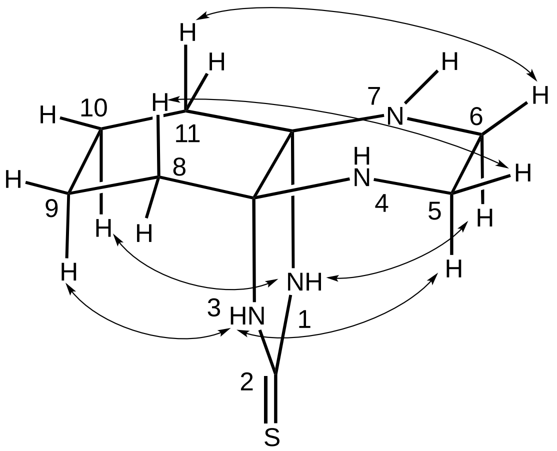
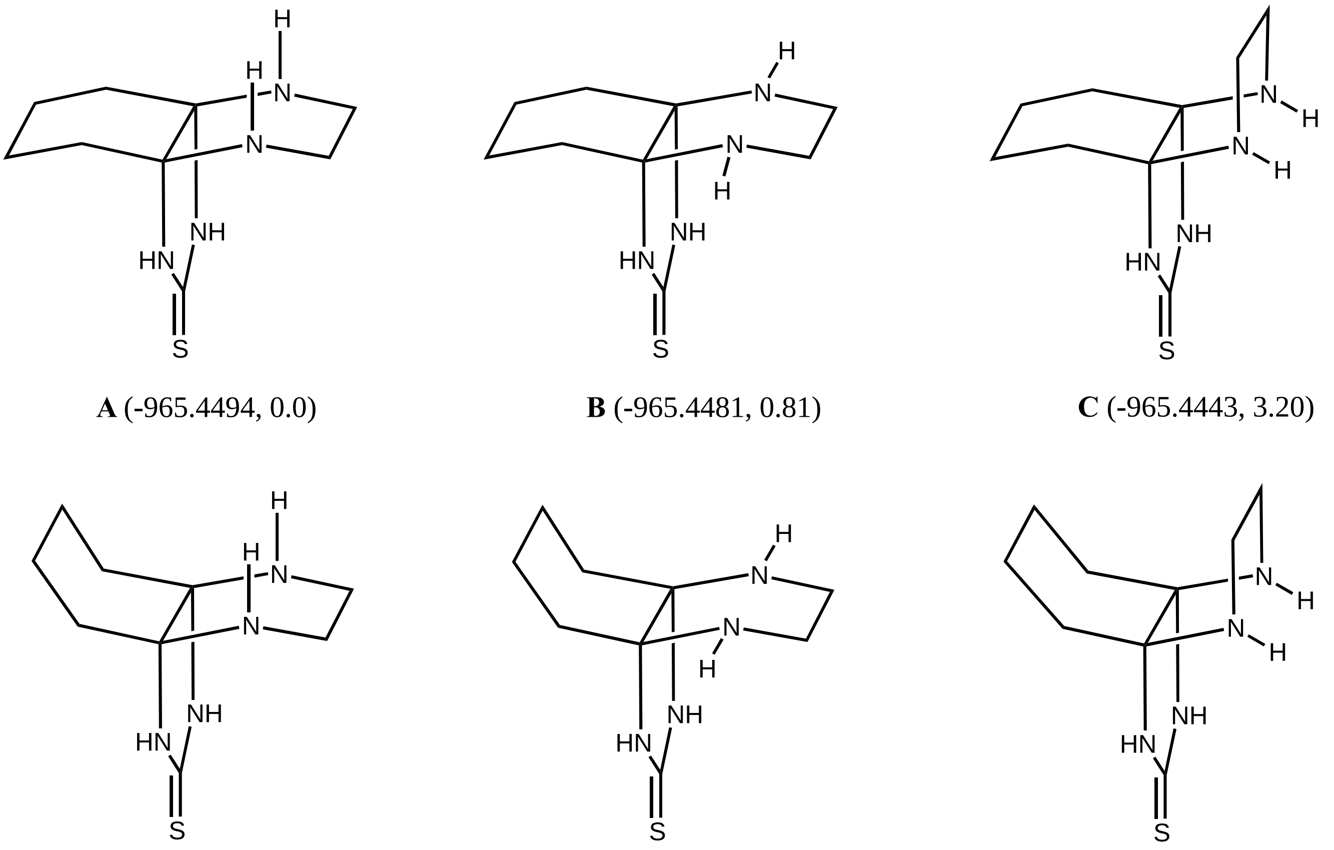


Figure 2. Nuclear Overhauser effect (NOE) correlation for predicting the conformation of **4a**

Thus, the NMR results indicated the formation of a symmetrical propellane structure. Figure 3 shows six possible conformations of **4a**. Geometry optimization of these conformations was conducted using density functional theory (DFT) at the B3LYP/6-31G(d) level of theory.[14,15] By comparing the heats of formation of these conformations, conformation **A** was predicted to be the most stable among the six possible conformations (Figure 3).



A (-965.4494, 0.0) **B** (-965.4481, 0.81) **C** (-965.4443, 3.20)

D (-965.4465, 1.81) **E** (-965.4480, 0.88) **F** (-965.4343, 9.48)

Figure 3. Calculated heats of formation (B3LYP/6-31G(d), $^*\Delta\Delta H_f$ (kcal/mol)) of six possible conformations of **4a**. $^*\Delta\Delta H_f$ (kcal/mol) = (conformation **A** – predicted conformations) × 627.5; 1 hartree = 627.5 kcal/mol

Based on the NMR analysis and MO calculations, we propose that the hydrogen atoms of NH-4 and NH-7 interact with the sulfur atom of the thiocarbonyl group. To investigate this issue in greater detail, the conformations and steric features of **4a** were examined by single-crystal X-ray diffraction analysis.[18-20] The ORTEP diagram shown in Figure 4 illustrates that **4a** has a propellane-type tetraazaindene structure. Bond distances and angles relating to the C-C covalent bond (C (3a)–C (7a)) sharing three rings of **4a** are listed in Table 2.

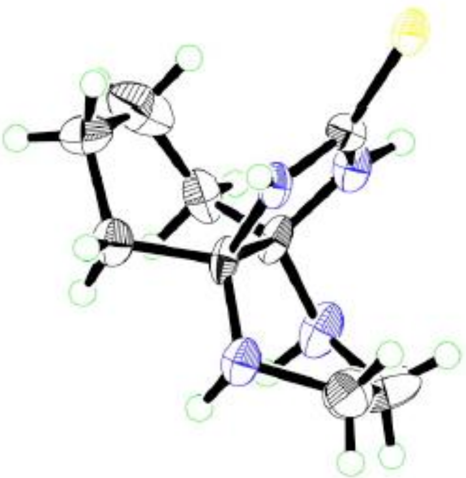


Figure 4. ORTEP diagram of **4a**

Table 2. Bond distances and angles of **4a**

Bond distances (Å)		Bond angle (°)			
C (3a)-N (3)	1.461	N (3)-C (3a)-N (4)	109.65	N (4)-C (3a)-C (8)	108.45
C (3a)-N (4)	1.461	N (3)-C (3a)-C (8)	111.21	N (4)-C (3a)-C (7a)	113.52
C (3a)-C (8)	1.520	N (3)-C (3a)-C (7a)	101.80	C (8)-C (3a)-C (7a)	112.11
C (3a)-C (7a)	1.581	N (1)-C (7a)-N (7)	110.18	N (7)-C (7a)-C (11)	108.43
C (7a)-N (1)	1.458	N (1)-C (7a)-C (11)	110.93	N (7)-C (7a)-C (3a)	113.41
C (7a)-N (7)	1.458	N (1)-C (7a)-C (3a)	102.21	C (11)-C (7a)-C (3a)	111.60
C (7a)-C (11)	1.527				

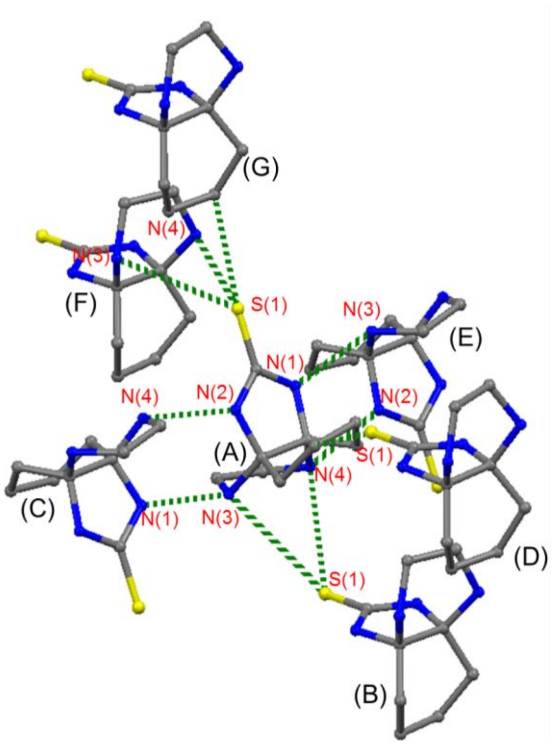


Figure 5. Weak interactions in the crystal structure of the propellane-type compound **4a**

Table 3. Hydrogen bond interactions (S•••H–N, N•••H–N, and S•••H–C) in the crystal structure of the propellane-type compound **4a**

A•••H–D	A•••D (Å)	∠A•••H–D (°)
S (1) (B) •••H–N (3) (A)	3.685	155.31
S (1) (B) •••H–N (4) (A)	3.558	159.18
N (3) (A) •••H–N (1) (C)	3.015	161.29
N (4) (C) •••H–N (2) (A)	2.988	168.22
S (1) (D) •••H–C (A)	3.615	130.14
N (4) (A) •••H–N (2) (E)	2.988	168.22
N (3) (E) •••H–N (1) (A)	3.015	161.29
S (1) (A) •••H–N (3) (F)	3.685	155.31
S (1) (A) •••H–N (4) (F)	3.558	159.18
S (1) (A) •••H–C (G)	3.615	130.14

*Atoms A and D are the hydrogen bond acceptor and donor, respectively.

Figure 5 shows the crystal structure of **4a** and the associated intermolecular interactions from the surrounding molecules, based on the single-crystal X-ray diffraction analysis. Hydrogen bonds with acceptor and donor are categorized distances of 2.2-2.5 Å as “strong, mostly covalent”, 2.5-3.2 Å as “moderate, mostly electrostatic”, 3.2-4.0 Å as “weak, electrostatic”.[21] Furthermore, when the ∠A•••H–D angle is smaller than 90°, it is thought that hydrogen bonding is not operative.[22,23]

Table 3 shows the intermolecular hydrogen bonds in the **4a** crystal. It is evident that the **4a** molecule forms ten intermolecular hydrogen bonds. Specifically, four hydrogen bonds are of >C=S•••H–N, four of N–H•••N type between the imidazolidine moieties, and two of >C=S•••H–C type. We propose that these hydrogen bonds contribute to the stabilization of the crystalline state of **4a**. To elucidate the stability of the >C=S•••H–N-type hydrogen bond interaction in **4a**, geometry optimization of the composite of the adjoining subunits (A) and (B) (Figure 5), containing two >C=S•••H–N-type hydrogen bonds, was conducted using DFT at the B3LYP/6-31G(d) level of theory. The composite of the adjoining (A) and (B) units was more stable because its energy was 5.5 kcal/mol lower than twice the heat of formation of one molecule of **4a**.

In this study, the propellane-type compound **4a** was synthesized and its conformation was elucidated both experimentally and theoretically. We demonstrated that the structure of **4a** in its crystalline state was stabilized by intermolecular hydrogen bonds between its theoretically most stable structures. Thus, we conclude that MO calculations can reliably predict the molecular structure of this propellane-type compound. This knowledge would be useful for future studies of similar propellane-type compounds and tetraazaindene derivatives.

EXPERIMENTAL

MATERIALS AND INSTRUMENTS

The reported melting points are uncorrected. ^{1}H NMR and ^{13}C NMR spectra were obtained on a JNM-ECA 500 (500 MHz) spectrometer using TMS (tetramethylsilane) as the internal standard. Mass spectra were obtained using a JMS-DX303HF instrument. Chemicals for the synthesis of 2,3,5,6,7,8-hexahydroquinoxaline (**2a**) were purchased from Wako Pure Chemical Industries, Ltd.

GENERAL EXPERIMENTAL PROCEDURE

3a,7a-Tricyclo[3.4.4]butanohexahydro-1*H*-imidazo[4,5-*b*]pyrazine-2(3*H*)-thione (**4a**) was synthesized by the reaction of thiourea and 2,3,5,6,7,8-hexahydroquinoxaline (**2a**).[11] Single crystals of **4a** were obtained by recrystallization from MeOH-DMSO; **4a** demonstrated good solubility in a small amount of DMSO but poor solubility in MeOH. Therefore, a large amount of MeOH was added to **4a** that was dissolved in a small amount of DMSO. MeOH was then gradually evaporated, which gave crystals of **4a**.

3a,7a-Tricyclo[3.4.4]butanohexahydro-1*H*-imidazo[4,5-*b*]pyrazine-2(3*H*)-thione (4a): colorless prisms. Yield 68.0%. mp 163–165 °C (dec.). ^{1}H NMR (500 MHz, DMSO) δ: 1.29 (2H, H-9a, and H-10a), 1.38 (2H, H-8a, and H-11a), 1.40 (2H, H-9b, and H-10b), 1.61 (2H, H-8b, and H-11b), 2.05 (2H, br, NH-4, and NH-7), 2.52 (2H, H-5a, and H-6a), 2.65 (2H, H-5b, and H-6b), 8.01 (2H, NH-1, and NH-3). ^{13}C NMR (125 MHz, DMSO) δ: 20.8 (C9 and C10), 32.8 (C8 and C11), 40.1 (C5 and C6), 74.9 (C3a and C7a), 182.7 (C=S). FAB-MS (*m/z*): 213.2 (M^++1). *Anal.* Calcd for $C_9H_{16}N_4S \cdot 0.5H_2O$: C, 48.84; H, 7.74; N, 25.31: Found: C, 48.56; H, 7.60; N, 25.46.

MOLECULAR ORBITAL (MO) CALCULATIONS

Semi-empirical MO calculations were performed through the CS Chem3D Pro interface and WINMOPAC3.5 using MOPAC2002 on an Intel personal computer.[16,17] Structures optimized using semi-empirical methods (AM1-, PM5-, or PM6-) were used as the starting geometries for the DFT calculations.[14,15] The energies were corrected using zero-point vibrational energy (scaled by a factor of 0.9804). Calculations incorporating solvent effect in DMSO, which is a solvent for NMR, used the polarizable continuum model (PCM) method included in the GAMESS software package.[15] As a result of the calculation, there was almost no influence of the solvent effect. The data calculated on the B3LYP/6-31G(d) level are available upon request from the author.

SINGLE-CRYSTAL X-RAY ANALYSIS

A colorless prism crystal having approximate dimensions of 0.500 × 0.500 × 0.500 mm was mounted on a glass fiber. All measurements were made on a Rigaku RAXIS RAPID imaging plate area detector with graphite monochromated Mo-Kα radiation. The data were collected at a temperature of 23±1 °C to a maximum 2θ value of 54.9°. The structures were solved by direct method (SIR-2011),[18] and hydrogen atoms were placed at the calculation. A full-matrix least-squares technique was used with anisotropic thermal parameters for non-hydrogen atoms and riding model for hydrogen atoms. All the calculations were performed using the Crystal Structure[19,20] crystallographic software package.

4a: $C_9H_{16}N_4S_1$, orthorhombic, space group *Pbca*, a = 15.0969 (6), b = 12.9742 (5), c = 10.7906 (5) (Å), V = 2113.56 (15) (Å^3), Density (calc.) 1.334, Density (obs.) 1.334 g cm^{-3}, Z = 8, R = 0.0438, Unique data used = 2411, Rw = 0.1752, Goodness of Fit = 1.000. The crystallographic data are deposited at CCDC 1859308.

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