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Novel Self-Assembly of *m*-Xylylene Type Dithioureas

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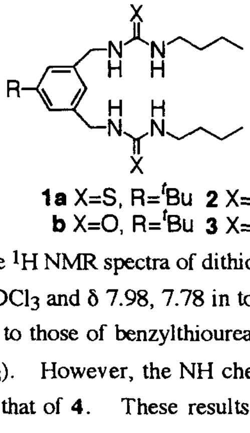
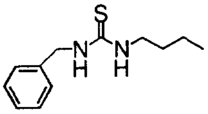
Abstract: *m*-Xylylene type dithioureas self-assemble to form an orthogonal dimer structure both in solution and solid state, wherein the four thiourea groups constitute a cyclic array of the closed network of the hydrogen bond through head-to-tail binding mode. This novel dimer structure was elucidated on the basis of ^{1}H NMR spectra, vapor pressure osmometry, and X-ray crystal structure analysis. © 1997 Elsevier Science Ltd.

In recent years, a number of molecules possessing urea or thiourea functional groups have been designed as neutral receptors for various anions.[1,2] Molecular recognition is achieved by multiple hydrogen bonding with the relatively acidic NH protons of these groups which are located in a well-defined position and direction. The potential hydrogen bond of these groups is also used to construct supramolecular structures.[3] During the course of our study in design and synthesis of urea/thiourea-based receptor molecules, we incidentally found the novel self-assembly behavior of *m*-xylylene type dithioureas **1a**, **2** and **3**, forming an orthogonal dimer structure both in solution and solid state through specific intermolecular hydrogen bonding between the thiourea groups.[4]



1a X=S, R=^{t}Bu **2** X=S, R=H
b X=O, R=^{t}Bu **3** X=S, R=Br



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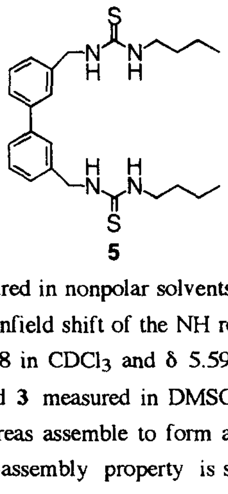

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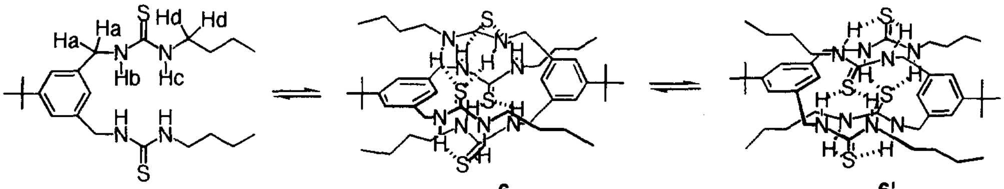
The ^{1}H NMR spectra of dithiourea **1a** (0.05 mol dm^{-3}, 30°C) measured in nonpolar solvents (δ 7.65, 7.40 in $CDCl_3$ and δ 7.98, 7.78 in toluene-d_8) displayed a remarkable downfield shift of the NH resonances compared to those of benzylthiourea **4** (0.05 mol dm^{-3}, 30°C, δ 6.01, 5.78 in $CDCl_3$ and δ 5.59, 5.35 in toluene-d_8). However, the NH chemical shifts of dithioureas **1a**, **2**, and **3** measured in DMSO-d_6 were similar to that of **4**. These results suggest that *m*-xylylene type dithioureas assemble to form aggregates through hydrogen bonding in nonpolar solvents. Moreover, this self-assembly property is specific to *m*-xylylene type dithioureas since biphenyl type dithiourea **5** did not show the downfield shift of the NH resonances (0.05 mol dm^{-3}, 30°C, δ 6.37, 6.01 in $CDCl_3$). Association of **1a** in solution through hydrogen bonding is also evidenced by the appearance of an NH stretching band in the infrared spectrum at 3240 cm^{-1}, which is low-frequency-shifted compared to the corresponding band of monothiourea **4** at 3400 cm^{-1} ($CHCl_3$, 0.05 mol dm^{-3}, r.t.).

In order to estimate the molecular weight of the aggregate of dithiourea **1a**, vapor pressure osmometric (VPO) measurements were undertaken in toluene at 60°C against a benzil standard. The observed molecular weight in the concentration range of 7 mmol dm^{-3} to 46 mmol dm^{-3} varied within a range of 832 to 861, which is consistent with a dimer (Mw(calcd.)=845). Below these concentrations the dimer appears to gradually dissociate. For example, the observed Mw was 707 at 0.9 mmol dm^{-3}. Similarly, dithiourea **1a** displayed concentration-dependent ^{1}H NMR spectra due to the self-assembly. The NMR measurements were carried out at 50°C in $CDCl_3$ in order to avoid the complexity arising from the slow conformational change in the dimer of **1a** described later. For example, when the concentration of **1a** was increased from 0.25 mmol dm^{-3} to 100 mmol dm^{-3}, the chemical shift of the two N-CH_2 protons Ha and Hd shifted from δ 4.78 and 3.19 to δ 4.97 and 2.79, respectively. Similarly, the aromatic proton flanked by the two thiourea side chains moved from δ 7.06 to δ 6.94. The dimerization constant $Ka(CDCl_3)=1.3\times10^3$ mol^{-1} dm^3 was obtained from these data by applying the method developed by Horman and Dreux.[5,6] There is a good agreement between the experimental data and the calculated dilution curve, which supports the monomer-dimer equilibrium and the absence of higher order aggregates.[7] We assume the structure **6** for the dimer of **1a** in solution, in which two molecules of dithiourea **1a** are orthogonally assembled by the hydrogen bond network between the four thiourea groups, on the basis of the upfield shift of the chemical shift of Hd at high concentrations, NOE experiments, and the structure observed in solid state. Namely, at high concentrations (e. g., 0.10 mol dm^{-3}, 50°C) strong NOE was observed for the aromatic protons on irradiation of Hd.



1a **6** **6'**

We also found that the ^{1}H NMR spectra of dithiourea dimer **6** displayed significant temperature-dependence; the signals for the two benzyl protons Ha, which are observed as a single peak at high temperature (toluene-d_8, 0.02 mol dm^{-3}, 90°C), split into two signals (δ 6.06 and 3.84) of AMX pattern at low temperature (-50°C) as shown in Figure 1. The other N-CH_2 protons Hd also split into two signals at δ 3.59 and 2.03 below 0°C because these protons are not equivalent in the dimeric structure **6**. The above phenomenon is explained in terms of equilibrium between two equivalent structures **6** and **6′** in which the relative orientation of all thiourea groups is reversed. This means that the equilibrium between **6** and **6′** is slow enough at low temperatures to distinguish non-equivalent methylene protons on the NMR time-scale. The energy barrier for this inversion is estimated from the coalescence temperature and the Δν values to be about 13 kcal mol^{-1} both in $CDCl_3$ and toluene-d_8. These values may well be regarded as the sum of the enthalpy of N-H· · ·S=C hydrogen bonds.[8]

Single crystals of **1a** suitable for X-ray diffraction were obtained from an ethanol solution.[9] The structure analysis shows that **1a** self-assembles to form an orthogonal dimer structure (Figure 2). The four thiourea groups of the dimer constitute a novel cyclic array of the closed network of the hydrogen bond through a head-to-tail binding mode; the intermolecular S· · ·N distances are 3.41 and 3.49 Å.

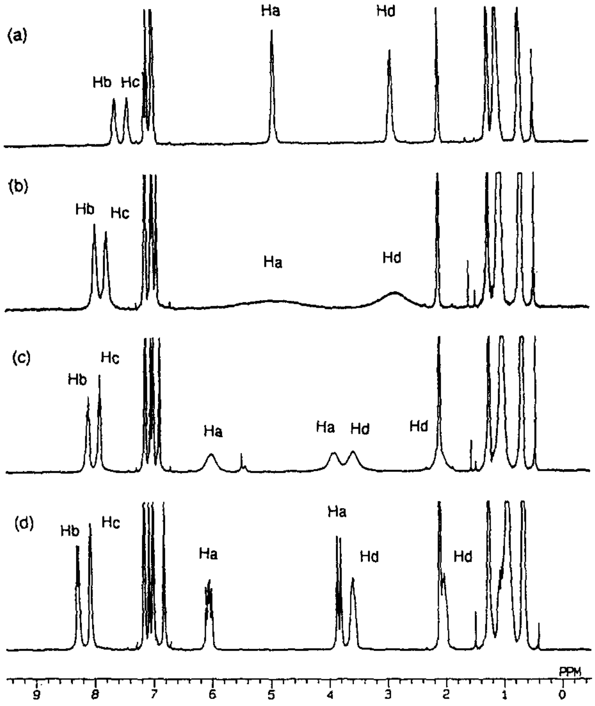


Figure 1. ^{1}H NMR spectra (270 MHz, 0.02 mol dm^{-3}) of **1a** in toluene-d_8 at (a) 90 °C, (b) 30 °C, (c) 0 °C, (d) -50 °C.

We have thus demonstrated that *m*-xylylene type dithioureas self-assemble to form a novel orthogonal dimer structure in which four thiourea groups constitute a cyclic array of the closed network of the hydrogen bond. Such motif will lend itself to the construction of supramolecular structures like catenanes, because the hydrogen-bonded orthogonal geometry has recently been shown to play a crucial role in the hydrogen bond-templated synthesis of such structures.[10]

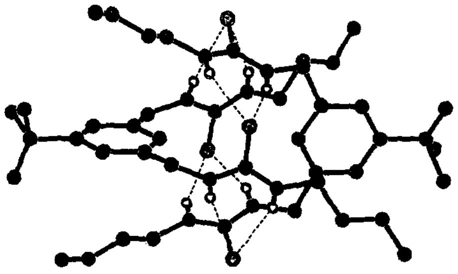


Figure 2. Structure of dimeric unit **6**. Hydrogens except for N-*H* and the disordered methyl carbons of the *tert*-butyl group having equal occupancies are omitted for clarity.

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4. Although Umezawa reported the synthesis of thiourea **2** and its excellent binding ability toward phosphate anion, its self-aggregation behavior was not referred to (ref. 2).
5. Horman, I.; Dreux, B. *Helv. Chim. Acta* **1984**, *67*, 754-764.
6. Similarly, the dimerization constants of **2** and **3** were determined to be 2.4×10^3 and 1.4×10^3 mol^{-1} dm^3, respectively.
7. Umezawa reported that a diurea analogous to **1b** self-associated in $CHCl_3$ with a dimerization constant of 130 mol^{-1} dm^3 based on the VPO measurement (ref. 2). However, we were unable to assure the dimerization of diurea **1b** in $CDCl_3$ at 30°C by the ^1H NMR spectrometry. For example, when the concentration of **1b** was increased from 0.15 mol dm^{-3} to 9 mol dm^{-3}, N-CH_2 protons of the butyl chain first upfield shifted from δ 3.13 to δ 2.60 and then downfield shifted to δ 2.89 at 21 mol dm^{-3}. Such non-linear concentration dependence precluded the calculation of the association constant on the assumption that monomer-dimer equilibrium is dominant in this concentration range.
8. Though there seems to be no report, to our knowledge, on the thermodynamics of this type of hydrogen bond, it might be within the range of 1-2 kcal mol^{-1} in view of the enthalpy of N-H· · ·O=C hydrogen bond; Schneider, H-J. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 1417-1436.
9. *Crystal data* for **1a**; $C_{11}H_{19}N_2S$, M =211.34, tetragonal, space group $I4_1/a$, a = 16.707(5), c = 18.982(5) Å, V = 5298.3(22) Å^3, Z = 16, D_c = 1.060 g cm^{-3}. The data collection was done at 293 K using graphite monochromated Mo-Ka radiation (λ= 0.71069 Å). The structure was solved by direct methods (SHELXS86) and refined by full-matrix least-squares techniques (SHELXL93) to R = 0.070 (Rw = 0.206) for 1730 independent reflections having $I > 2\sigma(I)$. Due to the disorder of the *tert*-butyl group and the large thermal parameters of the side-chain terminals, the structure data are not good enough to discuss the bond lengths and angles in detail. However, the crystallographic analysis certainly confirms the novel hydrogen-bonded dimer structure. Full crystallographic details are deposited in the Cambridge Crystallographic Data Centre.
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