Novel Self-Assembly of *m*-Xylylene Type Dithioureas by Head-to-Tail Hydrogen Bonding

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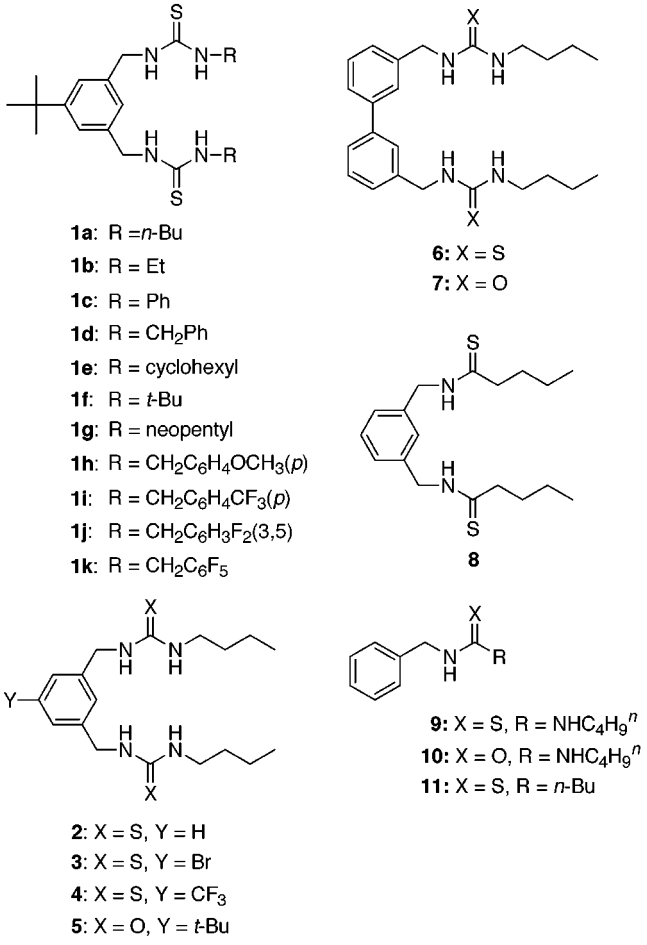
Dithiourea **1a** self-assembles to form an orthogonal dimer structure both in solution and in the solid state, wherein the four thiourea groups establish a closed network of hydrogen bonds through a head-to-tail binding mode. This novel dimer structure was elucidated on the basis of ^{1}H NMR spectra, vapor pressure osmometry, and X-ray crystal structure analysis. Furthermore, a series of *m*-xylylene type dithioureas were synthesized and their dimerization constants (K_a) in $CDCl_3$ were determined by dilution experiments using ^{1}H NMR spectroscopy. The magnitude of the K_a values are dependent on the steric bulk of the side chains, the acidity of the thiourea groups, and the weak intermolecular interaction between the benzene rings of the side chains and the *m*-xylylene spacer.

Introduction

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 establishing multiple hydrogen bonds with the relatively acidic NH protons of these groups which are located in a well-defined position and direction. The potential of establishing highly ordered hydrogen bond networks with these functional groups is also used to construct supramolecular structures both in solution[3a−d] and in the solid state.[3e−g] During the course of our study involving the design and synthesis of urea or thiourea-based anion receptors **1a** (see Chart 1) and **5**−**7** (possessing two urea or thiourea groups connected by a rigid spacer group), we discovered an unexpected self-assembly behavior specific to dithiourea **1a**.[4,5] Derivative **1a** was shown to form an orthogonal dimer structure both in solution and in the solid state by establishing specific intermolecular hydrogen bonds between the thiourea groups. The formation of aggregates of N,N′-disubstituted ureas and thioureas has been reported and shown to involve dimers[6a,b] and higher aggregates.[6a] For example, Scheerder reported that the

Chart 1



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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.[2]

(5) For a preliminary report of this work, see: Tobe, Y.; Sasaki, S.; Hirose, K.; Naemura, K. *Tetrahedron Lett.* **1997**, *38*, 4791−4794.

(6) (a) Jadzyn, J.; Stockhausen, M.; Zywucki, B. *J. Phys. Chem.* **1987**, *91*, 754−757. (b) Scheerder, J.; Engbersen, J. F. J.; Alessandro, C.; Ungaro, R.; Reinhoudt, D. N. *J. Org. Chem.* **1995**, *60*, 6448−6454.

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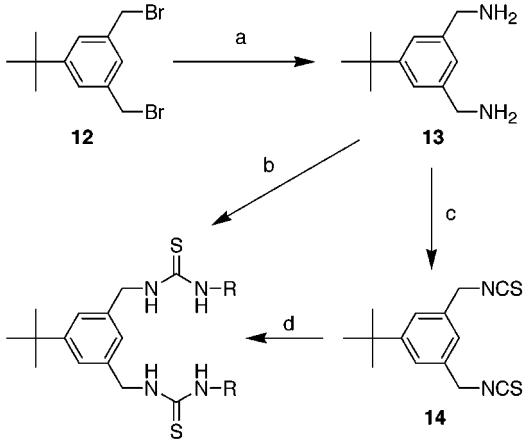
Scheme 1. Synthesis of *m*-Xylylene Type Dithioureas Possessing a *tert*-Butyl Group on the Benzene Ring[a]



1a, R = *n*-Bu
1b, R = Et
1c, R = Ph
1d, R = CH_2Ph
1e, R = cyclohexyl
1f, R = *t*-Bu
1g, R = neopentyl
1h, R = $CH_2C_6H_4OCH_3(p)$
1i, R = $CH_2C_6H_4CF_3(p)$
1j, R = $CH_2C_6H_3F_2(3,5)$
1k, R = $CH_2C_6F_5$

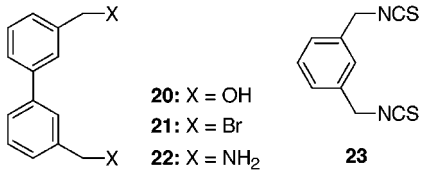
[a] Reagents and conditions: (a) (i) potassium phthalimide, DMF, 90 °C, (ii) $H_2NNH_2 \cdot H_2O$, EtOH, reflux, 57%; (b) RNCS, THF, reflux, 68−94%; (c) 1,1′-thiocarbonyldiimidazole, THF, room temperature, 32%; (d) RNH_2, THF, reflux, 74−94%.

dimerization constant of a simple N,N′-disubstituted thiourea is larger than that of the corresponding urea. This phenomenon is explained by assuming that the higher acidity of the thiourea hydrogens dominates the weaker hydrogen bond accepting ability of sulfur as compared to oxygen.[6b] However, the closed hydrogen-bonding structure of dimer of **1a** (comprised of four thiourea groups, which are aligned orthogonally to each other) was not known. Here we report the synthesis of *m*-xylylene dithioureas having a variety of aromatic and side-chain substituents and our experimental evidence for the aggregate formation of **1a**. Steric as well as electronic effects of the side chains were shown to influence the self-association behavior.

Results and Discussion

Synthesis of Thioureas 1a−k, 2−4, 6, and 9, Ureas 5, 7, and 10, and Thioamides 8 and 11. To investigate the novel self-assembly phenomenon of **1a** in detail, a series of dithioureas were prepared. Thus, compounds **1b−k** possess a variety of alkyl and aryl substituents in the side chain and a *tert*-butyl group on the spacer aromatic ring to secure solubility in $CDCl_3$. Moreover, **1d** and **1h−k** have aromatic rings with electron-donating or -withdrawing substituent(s) in the side chain. Thioureas **3** and **4**, on the other hand, have an electron-withdrawing substituent on the spacer ring. Dithioamide **8** was also examined to compare the functional group specificity. The known benzylic compounds **9**,[7] **10**,[8] and **11**[9] were prepared as the reference compounds.

The Gabriel reaction of bis(bromomethyl) compound **12**[10] gave diamine **13** in 57% yield (see Scheme 1), which was treated with commercially available isothiocyanates in THF to give dithioureas **1a−e** in 68−89% yield. Alternatively, diamine **13** was converted to diisothiocyanate **14** by treatment with 1,1′-thiocarbonyldiimidazole in 32% yield. Dithioureas **1f−k** were prepared by addition of the appropriate amines to **14** in 74−94% yield. To prepare bromide **3**, tribromide **15**[10] was converted to diamine **16** by the Gabriel reaction in 64% yield (see Scheme 2) followed by reaction with butyl isothiocyanate to give **3** in 72% yield. Trifluoromethyl derivative **4** was prepared from 4-(trifluoromethyl)aniline (**17**). Namely, iodination of **17** with ICl in AcOH followed by deamination via a diazonium salt gave 1,3-diiodo-5-(trifluoromethyl)benzene (**18**) in 33% yield. Replacement of iodo by cyano group was carried out by CuCN in HMPA, and subsequent reduction of the dicyanide with $LiAlH_4$ gave diamine **19** in 13% yield. Reaction with butyl isothiocyanate in THF gave the desired dithiourea **4** in 51% yield. Urea **5** was prepared from diamine **13** and butyl isocyanate in 56% yield. On the other hand, 3,3′-bis(hydroxymethyl)biphenyl (**20**)[11] was converted to diamine



20: X = OH
21: X = Br
22: X = NH_2
23

22 by bromination with phosphorus tribromide followed by the Gabriel reaction of dibromide **21**. Reaction of **22** with butyl isothiocyanate or butyl isocyanate gave biphenyl type thiourea **6** and urea **7** in 57% and 56% yield, respectively. Dithioamide **8** was prepared by the reaction between *m*-xylylene diisothiocyanate (**23**) and butylmagnesium bromide in 70% yield.

^{1}H NMR Study of the Self-Association of Dithiourea 1a. The self-association behavior of *m*-xylylene type dithiourea **1a** was investigated in detail and compared with that of urea **5**, biphenyl type dithiourea **6** and diurea **7**, dithioamide **8**, and the corresponding reference compounds **9−11**. The ^{1}H NMR chemical shifts of the NH protons of **1a** and **5−11** are summarized in Table 1. The ^{1}H NMR spectra of dithiourea **1a** in $CDCl_3$ displayed a large downfield shift of the NH resonances (H_a and H_b) compared to those of biphenyl type dithiourea **6** and monothiourea **9**. In the less polar solvent toluene-d_8, the observed chemical shifts of the NH resonances are even more remarkable (i.e. the difference of the chemical shift between **1a** and **9** is ca. 2.3 ppm). It should be noted that, despite the shielding effect of an aromatic solvent,[12] the NH signals of **1a** are shifted (>0.3 ppm) downfield relative to those observed in $CDCl_3$. However, the NH chemical shifts of **1a** when measured in DMSO-d_6 were similar to those of **6** and **9**. These results suggest that dithiourea **1a**, which has a *m*-xylylene unit as a spacer, assembles to form aggregates through hydrogen bonding

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(9) Katritzky, A. R.; Moutou, J.-T.; Yang, Z. *Synthesis* **1995**, 1497−1505.
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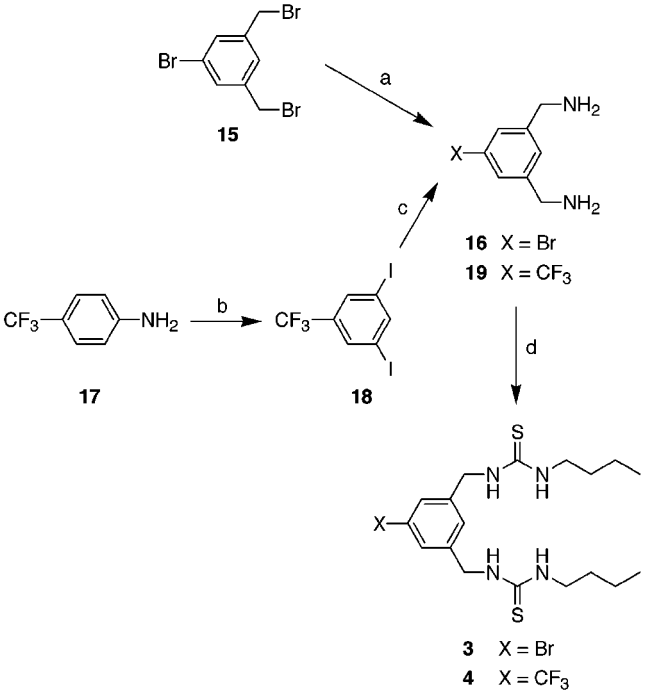
Scheme 2. Synthesis of *m*-Xylylene Type Dithioureas Possessing a Bromo or Trifluoromethyl Group on the Benzene Ring[a]



[a] Reagents and conditions: (a) (i) potassium phthalimide, DMF, 95 °C, (ii) $H_2NNH_2 \cdot H_2O$, EtOH, reflux, 64%; (b) (i) ICl, AcOH, 80 °C, (ii) $NaNO_2$, H_2SO_4, then H_3PO_2, −10 °C, 33%; (c) (i) CuCN, HMPA, 90 °C, (ii) $LiAlH_4$, ether, rt, 13%; (d) *n*-C_4H_9NCS, THF, reflux, 51−72%.

Table 1. ^{1}H NMR Chemical Shifts of NH Protons of Thioureas 1a, 6, and 9, Ureas 5, 7, and 10, and Thioamides 8 and 11[a]

compd	solvent	chem shift	
1a	$CDCl_3$[b]	7.40	7.65
	toluene-d_8[b]	7.78	7.98
	DMSO-d_6[b]	7.43	7.70
5	$CDCl_3$[d]	5.51	5.66
	DMSO-d_6[b]	5.84	6.17
6	$CDCl_3$[b]	6.01	6.37
	DMSO-d_6[b]	7.5[f]	7.81
7	DMSO-d_6[b,e]	5.89	6.29
8	$CDCl_3$[c]	7.45	
9	$CDCl_3$[c]	5.85	6.09
	toluene-d_8[c]	5.43	5.69
	DMSO-d_6[c]	7.44	7.74
10	$CDCl_3$[c]	4.68	5.01
	DMSO-d_6[c]	5.86	6.23
11	$CDCl_3$[b]	7.3−7.4[f]	

[a] Measured at 30 °C and at different concentrations to normalize the concentration of the ureido functional group to 0.1 M. [b] 0.05 M. [c] 0.1 M. [d] 0.02 M. [e] Compound **7** is hardly soluble in $CDCl_3$. [f] The N−H signals overlap with those of the aromatic protons.

in nonpolar solvents such as toluene. Although diurea **5** also exhibited the downfield shift of the NH resonances compared to those of monourea **10**, the chemical shift difference was not as remarkable as that observed between dithiourea **1a** and its reference compound **9**.[13] To further compare the functional group specificity toward the hydrogen bonding, *m*-xylylene type dithioamide **8** was also examined. However, despite the structural similarity with dithiourea **1a**, the NH chemical shift of **8** measured in $CDCl_3$ was similar to that of monothioamide reference **11**, indicating that the aggregate formation is specific to a dithiourea which is connected by the *m*-xylylene spacer.

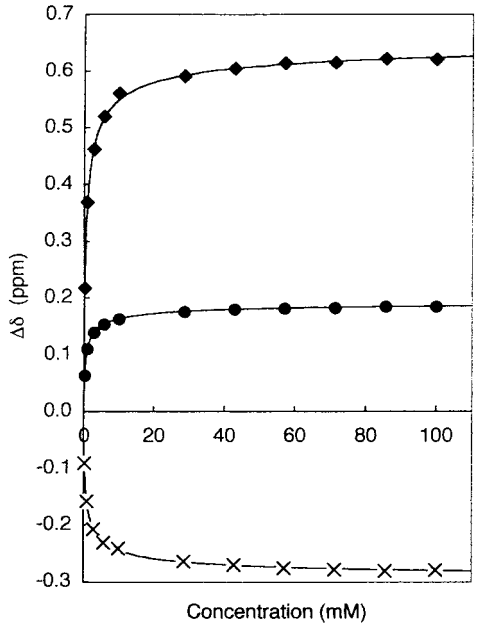


Figure 1. Concentration dependence of the chemical shift $\Delta\delta = \delta_{calcd}(\text{monomer}) - \delta_{obs}$ of benzylic protons H_c (×), methylene protons H_d (◆), and aromatic proton H_e (●) of **1a** in $CDCl_3$ at 50 °C.

Owing to the self-assembly, dithiourea **1a** displayed concentration-dependent ^{1}H NMR spectra. The NMR measurements were carried out within the concentration range of 0.1 M−0.25 mM at 50 °C in $CDCl_3$. The data were analyzed by assuming a monomer−dimer equilibrium by the curve fitting method developed by Horman and Dreux[14] (see Experimental Section), following the chemical shifts of H_c, H_d, and H_e as shown in Figure 1. There is a good agreement between the experimental data and the calculated dilution curve, which supports the fact that the monomer−dimer equilibrium is dominant in this concentration range and that higher order aggregates are negligible. The dimerization constant $K_a = 1.4 \times 10^3\ M^{-1}$ was thus obtained. The dimer formation of **1a** in solution is also supported by VPO studies, which is described later.

Concerning the dimerization-induced chemical shifts, when the concentration of **1a** was increased from 0.25 mM to 100 mM (in $CDCl_3$ at 50 °C), the methylene protons (H_d) of the butyl group adjacent to NH shifted upfield from δ 3.19 to 2.79. Moreover, strong NOE was observed for both of the anisochronous aromatic protons on irradiation of H_d (at 100 mM), while the corresponding NOE was not observed in DMSO-d_6. On the basis of these results, coupled with the X-ray crystallographic structure analysis described later, we propose that structure **24** (shown in Figure 2 for the dimer of **1a**) is

(13) Umezawa reported that a diurea analogous to **5**, which had long alkyl chains, self-associated in $CHCl_3$ with a dimerization constant of 130 M^{-1} based on the VPO measurement.[2] However, we were unable to ensure the dimerization of diurea **5** in $CDCl_3$ at 30 °C by ^{1}H NMR spectroscopy. For example, when the concentration of **5** was increased from 0.15 to 9 mM, the signal due to the N−CH_2 protons of the butyl chain shifted upfield from δ 3.13 to 2.86. However, the signal downfield shifted to δ 2.89 when the concentration increased up to 21 mM. Such concentration dependence precluded the calculation of the association constants on the assumption that monomer−dimer equilibrium is dominant in this concentration range.

(14) Horman, I.; Dreux, B. *Helv. Chim. Acta* **1984**, *67*, 754−764.

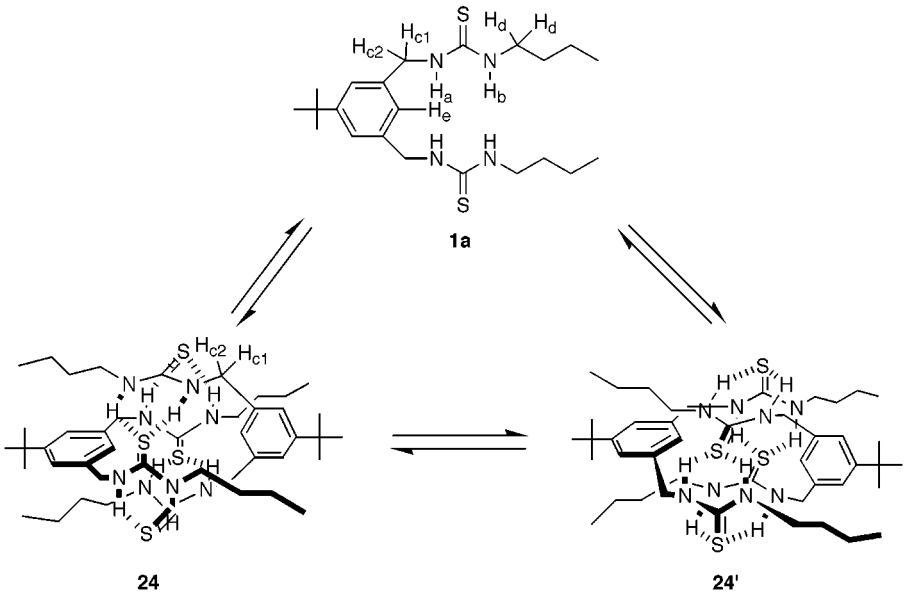


Figure 2. Monomer−dimer equilibrium of **1a** and switching the hydrogen bond network of dimer **24** and **24′** in solution.

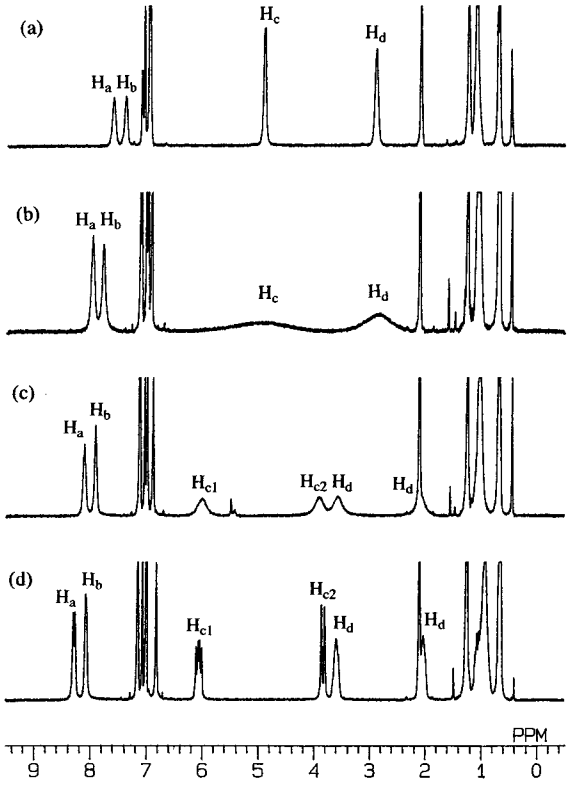


Figure 3. ^{1}H NMR spectra (270 MHz, 0.02 M) of **1a** in toluene-d_8 at (a) 90 °C, (b) 30 °C, (c) 0 °C, and (d) −50 °C.

formed in solution, in which two molecules of dithiourea **1a** are orthogonally assembled by the hydrogen bond network between the four thiourea groups.

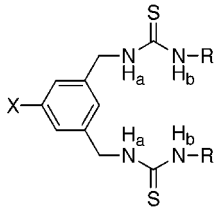
We also found that the ^{1}H NMR spectra of dithiourea dimer **24** displayed significant temperature-dependence. For example, the signals for the two benzylic protons H_c, which are observed as a single peak at high temperature (toluene-d_8, 0.02 M, 90 °C), split into two signals (δ 6.06 and 3.84) at low temperature (−50 °C) as shown in Figure 3. The proton H_{c1} and H_{c2} were tentatively assigned as shown in Figure 3 on the basis of the observed vicinal coupling constants and the dihedral angles of the H−N−C−H system in the solid-state structure of the dimer of **1a** (vide infra). Namely, it is revealed from X-ray crystal structure analysis that the dihedral angles H_a−N−C−H_{c1} and H_a−N−C−H_{c2} are 172 and 72°, respectively. Consequently, a large spin−spin coupling of H_{c1} with NH compared to that of H_{c2} is expected in view of the Karplus' equation (as it is applied to the H−C−C−H system),[15] though there seems to be no report, to our knowledge, on the relationship between the coupling constant and the dihedral angle in the H−N−C−H system. Thus, the signals at δ 6.06 (dd, J = 16.5, 10.3 Hz) and δ 3.84 (d, J = 16.5 Hz) were assigned to the protons H_{c1} and H_{c2}, respectively. The large downfield shift of H_{c1} is probably due to the anisotropic deshielding effect of the thiocarbonyl group,[16] because H_{c1} is positioned in the plane of thiourea group; the observed S−C(carbonyl)−C−H_{c1} dihedral angle is 1° in the solid state. The other N−CH_2 protons H_d also split into two signals at δ 3.59 and 2.03 below 0 °C. The large upfield shift of the one of H_d is due to the shielding effect of benzene ring caused by the dimer formation. These results indicate that both H_c and H_d are diastereotopic in the dimeric structure **24** and that the methylene protons are exchanging with a slow exchange rate. Although it has been well documented that the barriers to the rotation about the C−N bonds of thioureas are 13−14 kcal/mol in polar solvents,[17] the above phenomenon is not explained in terms of such conformational change. It is, on the other hand, reasonably explained by assuming an equilibrium between two equivalent structures **24** and **24′**, in which the relative orientation of all thiourea groups is reversed. At this moment, it is not clear whether the equilibrium between **24** and **24′** is due to synchronous flipping of all thiourea moieties in the dimer or to a dissociation (to **1a**)−

(15) Karplus, M. *J. Chem. Phys.* **1959**, *30*, 11−15.

(16) For the anisotropic deshielding effect of carbonyl group, see ref 12, p 88. Such large chemical shift difference of vicinal protons adjacent to an amide nitrogen is also seen in the spectra of cyclic compounds: (a) Bohlmann, F.; Schumann. D. *Tetrahedron Lett.* **1965**, 2435−2440. (b) Kang, J.; Hilmersson, G.; Santamaría, J.; Rebek, J., Jr. *J. Am. Chem. Soc.* **1998**, *120*, 3650−3656.

(17) (a) Martin, M. L.; Filleux-Blanchard, M. L.; Martin, G. J.; Webb, G. A. *Org. Magn. Reson.* **1980**, *13*, 396−402. (b) Haushalter, K. A.; Lau, J.; Roberts, J. D. *J. Am. Chem. Soc.* **1996**, *118*, 8891−8896.

Table 2. Dimerization Constants of Dithioureas[a]



compd	X	R	K_a (M^{-1})
1a	*t*-Bu	*n*-Bu	$(1.4 \pm 0.2) \times 10^3$
1b	*t*-Bu	Et	$(1.2 \pm 0.1) \times 10^3$
1c	*t*-Bu	Ph	*b*
1d	*t*-Bu	CH_2Ph	$(5.9 \pm 0.4) \times 10^2$
1e	*t*-Bu	cyclohexyl[c]	$(9.9 \pm 0.5) \times 10^1$
1f	*t*-Bu	*t*-Bu	*b*
1g	*t*-Bu	neopentyl	$(5.3 \pm 0.8) \times 10^2$
1h	*t*-Bu	$CH_2C_6H_4OCH_3$ (*p*)	$(3.9 \pm 0.8) \times 10^2$
1i	*t*-Bu	$CH_2C_6H_4CF_3$ (*p*)	$(2.2 \pm 0.3) \times 10^3$
1j	*t*-Bu	$CH_2C_6H_3F_2$ (3,5)	$(4.2 \pm 1.5) \times 10^3$
1k	*t*-Bu	$CH_2C_6F_5$	$(5.5 \pm 0.8) \times 10^3$
2	H	*n*-Bu	$(1.3 \pm 0.3) \times 10^3$
3	Br	*n*-Bu	$(2.7 \pm 0.7) \times 10^3$
4	CF_3	*n*-Bu	$(2.7 \pm 0.4) \times 10^3$

[a] Measured in $CDCl_3$ at 50 °C by following the change of the chemical shift of $N(H_b)-CH_2$ methylene protons upon dilution. The K_a values within the experimental errors were also obtained by observing the chemical shift change of $N(H_a)-CH_2$ benzyl protons or aromatic protons. [b] Self-association was not observed. [c] Determined from the chemical shift change of the NH_a proton.

association process. The energy barrier for this inversion was estimated roughly from the coalescence temperature (T_c = 20 °C) and the $\Delta\nu$ values (376 Hz) to be about 13 kcal/mol in $CDCl_3$.[18] A similar value was obtained in toluene-d_8.

Dimerization Constants of Dithioureas 1a−k and 2−4 in $CDCl_3$. The dimerization constants (K_a) of dithioureas **1a−k** and **2−4** were measured in $CDCl_3$ at 50 °C by dilution experiments using ^{1}H NMR spectroscopy, and the results are summarized in Table 2. The data show that the dimerization constants of the various dithioureas are strongly dependent on the nature of the side-chain substituent. As expected from the dimer structure **24**, the bulky groups on the side chains hindered the dimerization process in solution. A downfield shift of the NH resonances was not observed in the ^{1}H NMR spectra of **1c** and **1f**, wherein the bulky phenyl or *tert*-butyl group is directly attached to the NH. The dimerization constants were, therefore, not measured in these cases. The small K_a value of cyclohexyl derivative **1e** can be ascribed to the steric hindrance of the tertiary carbon atom adjacent to NH. In the case of benzyl derivative **1d** and neopentyl derivative **1g**, the K_a values are nearly half of that of **1a**, indicating that even benzyl and neopentyl groups sterically suppressed the association phenomena. On the other hand, the K_a value of ethyl derivative **1b** is almost the same as that of **1a**.

The substituent on the aromatic spacer has a moderate effect on the self-association process. Thus, thioureas **1a** and **2−4**, which have the same butyl groups on the side chain and a different substituent (X) on the aromatic spacer, showed the K_a values in the order of $CF_3 \approx Br >$ $H \approx$ *tert*-butyl. Although the differences in K_a are small, electron-withdrawing groups such as CF_3 and Br may enhance the self-aggregation process by indirectly increasing the acidity of the nearby hydrogen (H_a), which is close to the spacer aromatic ring.

The benzene ring substituent of the appended side chain also exhibited a significant effect on the dimerization constants found for **1d** and **1h−k**. *p*-Methoxy compound **1h** showed the K_a value which was of the same magnitude as that of the parent benzyl compound **1d**. On the other hand, the dimerization constants of thioureas **1i−k**, possessing electron-withdrawing groups on the side-chain aromatic rings, are larger than that of **1d**. The increase of the self-association ability is ascribed to the increased acidity of the hydrogen (H_b) of the thiourea group which is close to the side-chain aromatic ring. However, it seems likely that a weak interaction between the spacer aromatic ring and the aromatic substituents at the side chains may also contribute to the association, as shown from the crystal structure of the dimer of **1j**.

IR and VPO Studies for Self-Association of Dithiourea 1a. The role of hydrogen bonds in the self-association of **1a** in solution is also evidenced by the infrared spectra.[19] Namely, the IR band of **1a** was observed at 3254 cm^{-1} in $CHCl_3$ solution (0.05 M) at room temperature, which is typical of hydrogen-bonded NH stretching. On the other hand, the corresponding band of monothiourea **9** appeared at 3422 cm^{-1}, which is attributed to the non-hydrogen-bonded NH stretching; the difference between **1a** and **9** is 168 cm^{-1}.

To estimate the molecular weight (MW) of the aggregate of dithiourea **1a**, vapor pressure osmometric (VPO) measurements were undertaken in toluene at 60 °C against a benzil standard. The apparent molecular weight in the concentration range of 7−46 mM varied within a range of 832−861, which is consistent with a dimer (MW(calcd) = 845). Below these concentrations the dimer appears to gradually dissociate. For example, the observed MW (707) at 0.9 mM was smaller than that of a dimer presumably due to a mixed population of monomer and dimer units.

X-ray Crystallographic Study of Dithioureas 1a,b,j. To elucidate the structure in the solid state, X-ray crystallographic analyses were undertaken for dithioureas **1a,b,j**. Single crystals of **1a,b,j** suitable for X-ray diffraction were obtained from ethanol, ethanol, and benzene solutions, respectively.

The structure analysis (Figure 4) shows that **1a** self-assembles to form an orthogonal dimer structure, in which the four thiourea groups of the dimer constitute a novel closed network of hydrogen bonds. The observed intermolecular S···N distances within the dimer structure are S**···N(1) = 3.41 Å and S**···N(2) = 3.49 Å, which are in accord with the presence of hydrogen bonding. The plane of one thiourea group is orthogonal to the planes of the two thiourea groups of the counterpart molecule. The benzene rings are also perpendicular to each other. Such orthogonal geometry between hydrogen-bonded

(18) For calculation of the $\Delta G^{\ddagger}$ value, we did not take into account the participation of monomer **1a** in the equilibrium between **24** and **24′**, because even at 90 °C the monomer−dimer equiliblium shifted almost exclusively to the dimer at this concentration. The apparent upfield shift of the chemical shift of the NH protons with increasing temperatures is ascribed to the distortion of the hydrogen bond rather than dissociation of **24**. See, for the temperature effects on the chemical shift of hydrogen-bonded protons: Adrian, J. C., Jr.; Wilcox, C. S. *J. Am. Chem. Soc.* **1991**, *113*, 678−680.

(19) For IR studies of hydrogen bonds, see: (a) Pimentel, G. C.; McClellan, A. L. *The Hydrogen Bond*: Freeman: San Francisco, CA, 1960. (b) Klotz, I. M.; Franzen, J. S. *J. Am. Chem. Soc.* **1962**, *84*, 3461−3466. (c) Néel, J. *Pure Appl. Chem.* **1972**, *31*, 201−225. (d) Dado, G. P.; Gellman, S. H. *J. Am. Chem. Soc.* **1994**, *116*, 1054−1062.

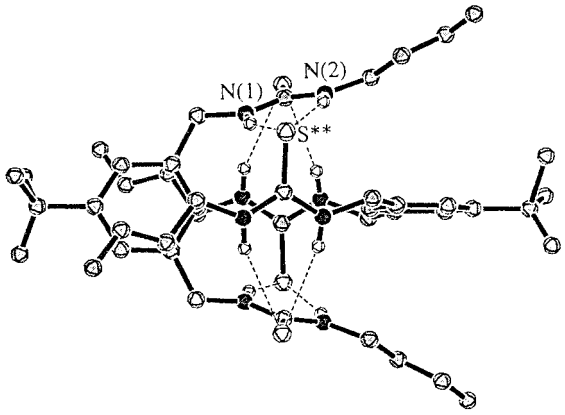


Figure 4. Crystal structure of dimeric unit **24** (four crystallographically independent units of **1a**) showing the hydrogen-bonding pattern. Hydrogens except for N−*H* and the disordered methyl carbons of the *tert*-butyl group having equal occupancies are omitted for clarity. The observed intermolecular S···N distances are S**···N(1) = 3.41 and S**···N(2) = 3.49 Å.

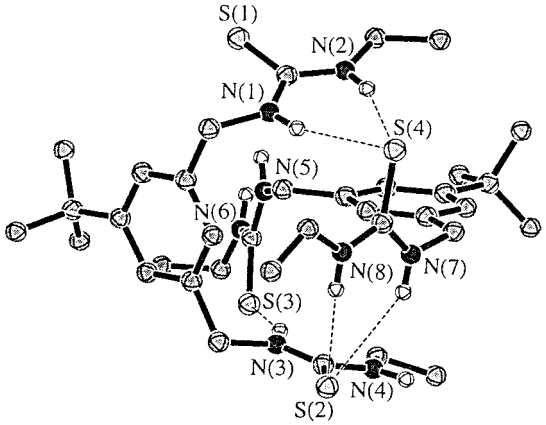


Figure 5. Crystal structure of **1b** showing the hydrogen-bonding pattern. Hydrogens except for N−*H* are omitted for clarity. The observed intermolecular S···N distances are S(2)···N(7) = 3.56, S(2)···N(8) = 3.41, S(3)···N(3) = 3.50, S(4)···N(1) = 3.39, and S(4)···N(2) = 3.50 Å.

thiourea groups has been reported by Lauher for the crystal structure of 4,4′-(thioureylene)dibutyric acid.[3e] It should be pointed out that the hydrogen-bonding pattern of **1a** is different from the well-documented pattern of ureas in the solid state,[3e−g,20] in which the urea groups are linearly aligned in a head-to-tail manner.

Figure 5 shows that ethyl derivative **1b** self-assembles to form a dimer structure through intermolecular hydrogen bonding. However, in contrast to the highly symmetrical structure of **1a**, the crystal structure of **1b** adopts an asymmetric dimer structure and the hydrogen bond network is partially broken. Hydrogen bonding is observed between S(2)···N(7), S(2)···N(8), S(3)···N(3), S(4)···N(1), and S(4)···N(2), whose distances are 3.56, 3.41, 3.50, 3.39, and 3.46 Å, respectively. S(1), N(4), N(5), and N(6) do not participate in hydrogen bonding. Because the dimerization constant of **1b** in solution is

(20) Nonlinear alignment of urea groups in the solid state was found in the structure of hydrogen-bonded dimer of a calix[4]arene derivative. However, it seems likely that the exceptional hydrogen bonding pattern is due to the restricted geometry of urea functions anchored to the rigid calixarene backbone: Mogck, O.; Paulus, E. F.; Böhmer, V.; Thondorf, I.; Vogt, W. *Chem. Commun.* **1996**, 2533−2534.

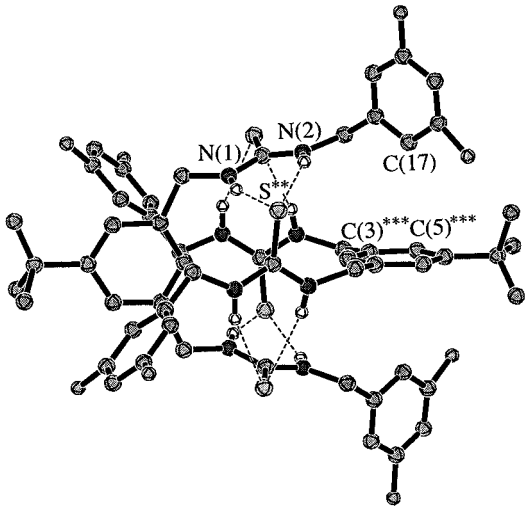


Figure 6. Crystal structure of dimer of **1j** (four crystallographically independent units) showing the hydrogen-bonding pattern. Hydrogens except for N−*H* and the disordered methyl carbons of the *tert*-butyl group having equal occupancies are omitted for clarity. The observed intermolecular S···N distances are S**···N(1) = 3.41 and S**···N(2) = 3.51 Å. The observed intermolecular C···C distances are C(17)···C(3)*** = 3.78 and C(17)···C(5)*** = 3.70 Å.

similar to that of **1a**, suggesting that in solution **1b** forms an orthogonal dimer structure like **24**, the formation of unsymmetrical structure in the solid state must be due to the crystal packing force.

On the other hand, difluorobenzyl derivative **1j** forms an orthogonal dimer through the closed network of hydrogen bonds in the solid state as shown in Figure 6, which resembles the dimer structure of **1a**. The intermolecular S**···N(1) and S**···N(2) distances within the dimer are 3.41 and 3.51 Å, respectively. Moreover, the crystal structure of **1j** suggests the presence of an intermolecular C−H···π interaction. The nonbonded distances between the aromatic rings are relatively short, C(17)···C(3)*** = 3.78 Å and C(17)···C(5)*** = 3.70 Å, which are below the sum of van der Waals distances.

Conclusions

In summary, we have demonstrated that *m*-xylylene type dithioureas self-assemble to form a novel orthogonal dimer structure in which four thiourea groups constitute a cyclic array involving a closed network of hydrogen bonds. The magnitudes of the K_a values in $CDCl_3$ are dependent on the steric hindrance of the substituent at the side chains and the acidity of the thiourea groups. It is worth noting that this orthogonal self-assembly will lend itself to the construction of a variety of supramolecular structures.

Experimental Section

General Methods. Melting points are uncorrected. Vapor pressure osmometry was carried out on a Hitachi 117 vapor pressure osmometer with benzil as the calibration standard in toluene at 60 °C.

Materials. THF was dried and distilled under nitrogen from sodium benzophenone ketyl immediately before use. Diethyl ether was dried with $LiAlH_4$ followed by distillation. DMF and HMPA were dried and distilled from CaH_2. 1,3-Bis(bromomethyl)-5-*tert*-butylbenzene (**12**),[10] 3,3′-bis(hydroxymethyl)biphenyl (**20**),[11] 5-bromo-1,3-bis(bromomethyl)benzene

(**15**),[10] and 1,1′-thiocarbonyldiimidazole[21] were prepared according to literature procedures. Other solvents and reagents used were of reagent grade and were employed as purchased without further purification.

Typical Procedure for the Synthesis of Dithioureas. Preparation of 5-*tert*-Butyl-1,3-bis[(*N*′-ethylthioureido)-methyl]benzene (1b). Into a nitrogen-purged flask a solution of 962 mg (5.0 mmol) of diamine **13** in 20 mL of THF was added followed by a solution of 0.88 mL (10 mmol) of ethyl isothiocyanate in 10 mL of THF. The mixture was refluxed for 1 h and concentrated to remove the solvent. The product was purified by column chromatography (silica gel, 49:1 $CHCl_3$−MeOH) to afford 1.42 g (77%) of **1b** as a white solid, which was recrystallized from ethanol to give colorless crystals: mp 157−159 °C; IR (KBr) 3239, 876, 795, 705 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$, 50 °C, 0.02 M) δ 0.83 (t, J = 7.0 Hz, 6H), 1.31 (s, 9H), 2.92 (br s, 4H), 4.92 (br s, 4H), 6.97 (s, 1H), 7.1−7.3 (br s containing s at 7.14, 6H); MS (FAB) m/z 367 ($M^+ + 1$). Anal. Calcd for $C_{18}H_{30}N_4S_2$: C, 58.97; H, 8.25; N, 15.28. Found: C, 59.29; H, 8.51; N, 15.46. The following compounds were similarly prepared.

5-*tert*-Butyl-1,3-bis[(*N*′-butylthioureido)methyl]benzene (1a). Obtained as colorless crystals after recrystallization from ethanol: yield 77%; mp 162−164 °C; IR (KBr) 3246, 1569, 898, 852, 702 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$, 50 °C, 0.01 M) δ 0.77 (t, J = 6.9 Hz, 6H), 1.17 (m, 8H), 1.31 (s, 9H), 2.86 (br s, 4H), 4.93 (br s, 4H), 6.96 (s, 1H), 7.1−7.3 (br s containing s at 7.14, 6H); MS (FAB) m/z 845 ($2M^+$, 3% relative to $M^+ + 1$), 423 ($M^+ + 1$). Anal. Calcd for $C_{22}H_{38}N_4S_2$: C, 62.51; H, 9.06; N, 13.25. Found: C, 62.45; H, 9.06; N, 13.25.

5-*tert*-Butyl-1,3-bis[(*N*′-phenylthioureido)methyl]benzene (1c). Obtained as a white solid after recrystallization from methanol: yield 89%; mp 158−160 °C; IR (KBr) 3240, 3206, 1533, 748, 694 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$, 0.05 M, 50 °C) δ 1.59 (s, 9H), 4.84 (d, J = 5.4 Hz, 4H), 6.27 (br s, 2H), 7.00−7.60 (m, 13H), 7.87 (br s, 2H); MS (FAB) m/z 463 ($M^+ + 1$). Anal. Calcd for $C_{26}H_{30}N_4S_2$: C, 67.49; H, 6.54; N, 12.11. Found: C, 67.29; H, 6.79; N, 12.27.

5-*tert*-Butyl-1,3-bis[(*N*′-benzylthioureido)methyl]benzene (1d). Obtained as a white solid after recrystallization from ethanol: yield 68%; mp 177−179 °C; IR (KBr) 3242, 1554, 867, 766, 733, 697 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$, 0.05 M, 50 °C) δ 1.35 (s, 9H), 4.00 (br s, 4H), 4.84 (br s, 4H), 6.95−7.21 (m, 13H), 7.49 (br s, 4H); MS (FAB) m/z 491 ($M^+ + 1$). Anal. Calcd for $C_{28}H_{34}N_4S_2$: C, 68.53; H, 6.98; N, 11.42. Found: C, 68.81; H, 7.18; N, 11.53.

5-*tert*-Butyl-1,3-bis[(cyclohexylthioureido)methyl]-benzene (1e). Obtained as a white solid after recrystallization from methanol: yield 77%; mp 143−145 °C; IR (KBr) 3252, 1546, 892 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$, 0.05 M, 50 °C) δ 0.80−1.80 (m, 20H), 1.29 (s, 9H), 3.80 (br s, 2H), 4.71 (br s, 2H), 6.48 (br s, 2H), 6.88 (br s, 2H), 7.03 (s, 1H), 7.18 (s, 2H); MS (FAB) m/z 949 ($2M^+$, 2% relative to $M^+ + 1$), 475 ($M^+ + 1$). Anal. Calcd for $C_{26}H_{42}N_4S_2$: C, 65.78; H, 8.92; N, 11.80. Found: C, 65.78; H, 9.08; N, 12.12.

5-*tert*-Butyl-1,3-bis[(*N*′-*tert*-butylthioureido)methyl]-benzene (1f). Obtained as a white solid after column chromatography (silica gel, 7:3 hexanes−EtOAc): yield 94%; mp 157−159 °C; IR (KBr) 3287, 1542, 787, 700 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$, 0.05 M, 50 °C) δ 1.30 (s, 9H), 1.36 (s, 18H), 4.77 (d, J = 5.2 Hz, 4H), 6.21 (br s, 4H), 7.09 (s, 1H), 7.25 (s, 2H); MS (FAB) m/z 844 ($2M^+ - 1$, 2% relative to $M^+ + 1$), 423 ($M^+ + 1$). Anal. Calcd for $C_{22}H_{38}N_4S_2$: C, 62.51; H, 9.06; N, 13.25. Found: C, 62.49; H, 9.28; N, 13.06.

5-*tert*-Butyl-1,3-bis[(*N*′-neopentylthioureido)methyl]-benzene (1g). Obtained as a white solid after column chromatography (silica gel, 8:2 hexanes−EtOAc): yield 74%; mp 170−173 °C; IR (KBr) 3267, 1559, 703 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$, 0.05 M, 50 °C) δ 0.73 (s, 18H), 1.32 (s, 9H), 2.66 (br s, 4H), 4.98 (br s, 4H), 6.97 (s, 1H), 7.0−7.3 (br s containing s at 7.14, 4H), 7.70 (br s, 2H); MS (FAB) m/z 900 ($2M^+ - 1$, 2% relative to $M^+ + 1$), 451 ($M^+ + 1$). Anal. Calcd for $C_{24}H_{42}N_4S_2$: C, 63.95; H, 9.39; N, 12.43. Found: C, 63.98; H, 9.58; N, 12.64.

5-*tert*-Butyl-1,3-bis[(*N*′-4-methoxybenzylthioureido)-methyl]benzene (1h). Obtained as a white solid after recrystallization from ethanol: yield 88%; mp 174−175 °C; IR (KBr) 3245, 1550, 821, 701 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$, 0.05 M, 30 °C) δ 1.35 (s, 9H), 3.75 (s, 6H), 3.90 (br s, 4H), 4.83 (br s, 4H), 6.73 and 6.85 (AA′BB′, J = 8.6 Hz, 8H), 7.00 (s, 1H), 7.19 (s, 2H), 7.60 (br s, 4H); MS (FAB) m/z 550 (M^+). Anal. Calcd for $C_{30}H_{38}N_4O_2S_2$: C, 65.42; H, 6.95; N, 10.17. Found: C, 65.04; H, 6.96; N, 9.94.

5-*tert*-Butyl-1,3-bis[[*N*′-(4-(trifluoromethyl)benzyl)-thioureido]methyl]benzene (1i). Obtained as colorless crystals after column chromatography (silica gel, 1:1 hexanes−EtOAc) followed by recrystallization from methanol: yield 84%; mp 178−179 °C; IR (KBr) 3224, 1552, 854, 824, 703 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$, 0.05 M, 50 °C) δ 1.35 (s, 9H), 4.02 (br s, 4H), 4.88 (br s, 4H), 7.02 (s, 1H), 7.08 and 7.47 (AA′BB′, J = 8.0 Hz, 8H), 7.26 (s, 2H), 7.68 (br s, 2H), 7.80 (br s, 2H); MS (FAB) m/z 627 ($M^+ + 1$). Anal. Calcd for $C_{30}H_{32}F_6N_4S_2$: C, 57.49; H, 5.15; N, 8.94. Found: C, 57.40; H, 5.31; N, 8.70.

5-*tert*-Butyl-1,3-bis[(*N*′-(3,5-difluorobenzyl)thioureido)-methyl]benzene (1j). Obtained as colorless crystals after column chromatography (silica gel, 1:1 hexanes−EtOAc) followed by recrystallization from benzene: yield 84%; mp 156−158 °C; IR (KBr) 3249, 1549, 855, 702 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$, 0.05 M, 30 °C) δ 1.36 (s, 9H), 3.96 (br s, 4H), 4.90 (d, J = 4.5 Hz, 4H), 6.48−6.53 (m, 4H), 6.64 (tt, J = 8.9, 2.3 Hz, 2H), 6.96 (s, 1H), 7.24 (s, 2H), 7.63 (br s, 2H), 7.72 (br s, 2H); MS (FAB) m/z 1124 ($2M^+$, 2% relative to $M^+ + 1$), 563 ($M^+ + 1$). Anal. Calcd for $C_{28}H_{30}F_4N_4S_2$: C, 59.77; H, 5.37; N, 9.96. Found: C, 59.39; H, 5.41; N, 9.81.

5-*tert*-Butyl-1,3-bis[(*N*′-(2,3,4,5,6-pentafluorobenzyl)-thioureido)methyl]benzene (1k). Obtained as colorless crystals after recrystallization from benzene: yield 90%; mp 161−163 °C; IR (KBr) 3259, 1558, 703 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$, 0.05 M, 30 °C) δ 1.24 (s, 9H), 4.07 (br s, 4H), 4.86 (br s, 4H), 6.76 (s, 1H), 7.16 (s, 2H), 7.62 (br s, 2H), 7.93 (br s, 2H); MS (FAB) m/z 671 ($M^+ + 1$). Anal. Calcd for $C_{28}H_{24}F_{10}N_4S_2$: C, 50.15; H, 3.61; N, 8.35. Found: C, 50.38; H, 3.41; N, 8.38.

5-Bromo-1,3-bis[(*N*′-butylthioureido)methyl]benzene (3). Obtained as colorless crystals after recrystallization from methanol: yield 72%; mp 155−156 °C; IR (KBr) 3336, 857, 706 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$, 50 °C, 0.03 M) δ 0.82 (t, J = 7.2 Hz, 6H), 1.20 (m, 8H), 2.90 (br s, 4H), 4.91 (d, J = 4.7 Hz, 4H), 7.05 (s, 1H), 7.11 (br s, 2H), 7.30 (s, 2H), 7.54 (br s, 2H); MS (FAB) m/z 447 ($M^+ + 3$), 445 ($M^+ + 1$). Anal. Calcd for $C_{18}H_{29}Br\ N_4S_2$: C, 48.53; H, 6.56; N, 12.58. Found: C, 48.43; H, 6.53; N, 12.57.

1,3-Bis[(*N*′-butylthioureido)methyl]-5-(trifluoromethyl)benzene (4). Obtained as a white solid after column chromatography (silica gel, 1:1 hexanes−EtOAc): yield 51%; mp 154−156 °C; IR (KBr) 3254, 1567, 860, 701 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$, 50 °C, 0.025 M) δ 0.77 (t, J = 7.0 Hz, 6H), 1.13 (m, 8H), 2.83 (br s, 4H), 5.03 (br s, 4H), 7.20 (br s, 2H), 7.34 (s, 1H), 7.41 (s, 2H), 7.54 (br s, 2H); MS (FAB) m/z 435 ($M^+ + 1$). Anal. Calcd for $C_{19}H_{29}F_3N_4S_2$: C, 52.51; H, 6.73; N, 12.89. Found: C, 52.82; H, 6.88; N, 12.80.

5-*tert*-Butyl-1,3-bis[(*N*′-butylureido)methyl]benzene (5). Obtained as a white solid after recrystallization from methanol: yield 73%; mp 195−197 °C; IR (KBr) 3333, 1631 cm^{-1}; ^1H NMR (270 MHz, DMSO-d_6, 30 °C) δ 0.87 (t, J = 7.2 Hz, 6H), 1.25 (s, 9H), 1.20−1.41 (m, 8H), 3.01 (m, 4H), 4.16 (d, J = 5.9 Hz, 4H), 5.85 (t, J = 5.6 Hz, 2H), 6.18 (t, J = 5.9 Hz, 2H), 6.91 (s, 1H), 7.13 (s, 2H); MS (FAB) m/z 782 ($2M^+ + 1$, 22% relative to M^+), 391 (M^+). Anal. Calcd for $C_{22}H_{38}N_4O_2$: C, 67.66; H, 9.81; N, 14.34. Found: C, 67.60; H, 9.76; N, 14.43.

3,3′-Bis[(*N*′-butylthioureido)methyl]biphenyl (6). To a stirred solution of diamine **22** (641 mg, 3.0 mmol) in 20 mL of $CHCl_3$ was added dropwise a solution of butyl isothiocyanate (0.73 mL, 6.0 mmol) in 10 mL of $CHCl_3$ under nitrogen. The reaction mixture was refluxed for 6 h, and then the solvent was removed to dryness. Recrystallization from ethanol gave 755 mg (57%) of analytically pure sample **6** as a white solid:

(21) Pullukat, T. J.; Urry, G. *Tetrahedron Lett.* **1967**, 1953−1954.

mp 160−162 °C; IR (KBr) 3243, 1561, 774, 698 cm^{-1}; ^1H NMR (270 MHz, DMSO-d_6, 30 °C) δ 0.87 (t, J = 7.2 Hz, 6H), 1.29 (m, 4H), 1.47 (m, 4H), 3.37 (m, 4H), 4.71 (d, J = 5.0 Hz, 4H), 7.28 (d, J = 7.5 Hz, 2H), 7.4−7.6 (br s containing dd at 7.42, J = 7.5, 7.5 Hz, d at 7.50, J = 7.5 Hz, and s at 7.56, 8H), 7.81 (br s, 2H); MS (FAB) m/z 443 (M^+ + 1). Anal. Calcd for $C_{24}H_{34}N_4S_2$: C, 65.12; H, 7.74; N, 12.66. Found: C, 64.90; H, 7.55; N, 12.40.

3,3′-Bis[(*N*′-butylureido)methyl]biphenyl (7). Diurea **7** was prepared by the same procedure as described above for **6** except for the use of butyl isocyanate in 56% yield as a white solid: mp 202−203 °C; IR (KBr) 3337, 1620, 774, 700 cm^{-1}; ^1H NMR (270 MHz, DMSO-d_6, 30 °C) δ 0.86 (t, J = 7.2 Hz, 6H), 1.20−1.42 (m, 8H), 3.01 (m, 4H), 4.26 (d, J = 5.9 Hz, 4H), 5.90 (t, J = 5.9 Hz, 2H), 6.30 (t, J = 5.9 Hz, 2H), 7.24 (d, J = 7.5 Hz, 2H), 7.40 (dd, J = 7.5, 7.5 Hz, 2H), 7.47 (d, J = 7.5 Hz, 2H), 7.49 (s, 2H); MS (FAB) m/z 821 ($2M^+$, 2% relative to M^+ + 1), 411 (M^+ + 1). Anal. Calcd for $C_{24}H_{34}N_4O_2$: C, 70.21; H, 8.35; N, 13.65. Found: C, 70.21; H, 8.28; N, 13.75.

1,3-Bis[(butylthiocarbamoyl)methyl]benzene (8). To a solution of butylmagnesium bromide prepared from 1-bromobutane (400 mg, 2.9 mmol) and magnesium (71 mg, 2.9 mmol) in 5 mL of ether was added *m*-xylylene diisothiocyanate (**23**) (212 mg, 0.98 mmol), and the mixture was stirred for 3 h. Aqueous HCl (10% by weight) was added, and the mixture was extracted three times with $CHCl_3$. The combined organic phase was washed with saturated aqueous $NaHCO_3$ and brine, dried over anhydrous $MgSO_4$, filtered, and concentrated. The product was purified by column chromatography (silica gel, 8:2 hexanes−EtOAc) to afford 228 mg (70%) of **8** as a white solid: mp 79−81 °C; IR (KBr) 3220, 1549, 772, 729 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$, 0.05 M, 30 °C) δ 0.93 (t, J = 7.3 Hz, 6H), 1.31−1.44 (m, 4H), 1.72−1.83 (m, 4H), 2.68 (t, J = 7.7 Hz, 4H), 4.84 (d, J = 5.0 Hz, 4H), 7.26−7.39 (m, 4H), 7.45 (br s, 2H); MS (FAB) m/z 337 (M^+ + 1). Anal. Calcd for $C_{18}H_{28}N_2S_2$: C, 64.24; H, 8.39; N, 8.32. Found: C, 64.18; H, 8.13; N, 8.70.

1,3-Bis(aminomethyl)-5-*tert*-butylbenzene (13). Potassium phthalimide (133.0 g, 0.719 mol) was added to a solution of 100.0 g (0.312 mol) of 1,3-bis(bromomethyl)-5-*tert*-butylbenzene (**12**) in 400 mL of DMF. The reaction mixture was stirred at 90 °C for 4 h and then cooled to room temperature. A 500 mL volume of water was added, and the mixture was extracted three times with $CHCl_3$. The combined extract was washed with 400 mL of 0.2 N aqueous NaOH to remove unreacted phthalimide followed by 400 mL of water. After being dried over anhydrous $MgSO_4$, the suspension was filtered and the filtrate concentrated under reduced pressure. The solid residue was washed with ether to afford 104.2 g (74%) of 5-*tert*-butyl-1,3-bis(phthalimidomethyl)benzene as a white solid: mp 184−185 °C; IR (KBr) 1714, 733, 712 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 1.27 (s, 9H), 4.80 (s, 4H), 7.32 (s, 1H), 7.37 (s, 2H), 7.67−7.84 (m, 8H); MS (EI) m/z (rel intensity) 452 (M^+ + 1, 100).

To a refluxing suspension of 102.0 g (0.225 mol) of the above imide in 500 mL of EtOH was added 68.5 mL (1.13 mol) of hydrazine monohydrate (80%), and the mixture was refluxed for 1 h. After cooling, 6 N aqueous HCl was added to acidify the mixture and it was refluxed for 1 h. After the mixture was cooled to 0 °C, phthalhydrazide was removed by filtration and the filtrate was made alkaline with aqueous KOH. The filtrate was extracted three times with $CHCl_3$, and the organic phase was washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated to give a yellow oil. The crude product was distilled under reduced pressure to afford 39.0 g (90%) of pure **12** as an air-sensitive colorless oil, which was stored under nitrogen: bp 137−138 °C (3 mmHg); IR (neat) 3361, 3293, 865, 713 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 1.33 (s, 9H), 1.44 (s, 4H), 3.87 (s, 4H), 7.11 (s, 1H), 7.21 (s, 2H); MS (EI) m/z (rel intensity) 192 (M^+, 23), 162 (100). HRMS: calcd for $C_{12}H_{20}N_2$ 192.1626, found 192.1600.

5-*tert*-Butyl-1,3-bis(isothiocyanatomethyl)benzene (14). To a solution of 9.72 g (52.0 mmol) of 1,1′-thiocarbonyldiimidazole in 45 mL of THF was added a solution of diamine **13** (5.00 g, 26.0 mmol) in 20 mL of THF under nitrogen. The reaction mixture was stirred for 3.5 h at room temperature and concentrated to give a brown oil. The product was purified by column chromatography (silica gel, 8:2 hexanes−EtOAc) to afford 2.28 g (32%) of **14** as a colorless oil: IR (neat) 2178, 2085, 856, 715 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.34 (s, 9H), 4.72 (s, 4H), 7.08 (s, 1H), 7.29 (s, 2H); MS (EI) m/z (rel intensity) 276 (M^+, 38), 218 (100). HRMS: calcd for $C_{14}H_{16}N_2S_2$ 276.0755, found 276.0740.

1,3-Bis(aminomethyl)-5-bromobenzene (16). Diamine **16** was prepared by the same procedure as described for **13** in 64% yield (two steps) from bromide **15**. 5-Bromo-1,3-bis(phthalimidomethyl)benzene: mp 233−234 °C; IR (KBr) 1709, 726, 710 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 4.87 (s, 4H), 7.44 (s), 7.70−7.85 (m, 8H); MS (EI) m/z (rel intensity) 476 (M^+ + 2, 80), 474 (M^+, 79), 329 (100). Diamine **16**: IR (neat) 3362, 3284, 855, 797, 699 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 1.50 (br s, 4H), 3.85 (s, 4H), 7.20 (s, 1H), 7.35 (s, 2H); MS (EI) m/z (rel intensity) 216 (M^+ + 2, 23), 214 (M^+, 22), 186 (100). HRMS: calcd for $C_8H_{11}Br\ N_2$ 214.0106, found 214.0079.

1,3-Diiodo-5-(trifluoromethyl)benzene (18). To a solution of 4-(trifluoromethyl)aniline (**17**) (16.1 g, 0.10 mol) in 100 mL of acetic acid was added dropwise a solution of iodine monochloride (36 g, 0.22 mol) in 120 mL of acetic acid, and then 400 mL distilled water was added at once. The resulting suspension was gradually heated to 80 °C and stirred at this temperature for 3 h. The reaction mixture was cooled, treated carefully with an aqueous solution of NaOH to pH = 11, and extracted with ethyl acetate. The extract was washed with sodium thiosulfate solution and brine and concentrated to leave 38.7 g of crude product as a brown solid. Recrystallization from hexane gave 29.8 g (72%) of pure 2,6-diiodo-4-(trifluoromethyl)aniline as a crystalline solid: mp 95−96 °C; IR (KBr) 3410, 891, 716, 705 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 4.96 (br s, 2H), 7.85 (s, 2H); MS (EI) m/z (rel intensity) 413 (M^+, 100). Anal. Calcd for $C_7H_4F_3I_2N$: C, 20.36; H, 0.98; N, 3.39. Found: C, 20.45; H, 0.88; N, 3.35.

A mixture of 300 mL of concentrated sulfuric acid and 150 mL of water was cooled to −10 °C by an ice−salt bath, and 15 g (0.22 mol) of sodium nitrite was added in small portions over a period of 15 min. Cold 50% hypophosphorous acid (102 mL, 0.98 mol) was then added over a period of 30 min keeping the temperature below −5 °C. A 26.0 g (63.0 mmol) amount of 2,6-diiodo-4-(trifluoromethyl)aniline dissolved in 300 mL of acetic acid (containing a few drops of concentrated sulfuric acid) was added to the stirred diazotizing solution over a period of 2 h maintaining the temperature below −10 °C. The resulting mixture was stirred for 7 h. The mixture was diluted with water and extracted several times with $CHCl_3$. The combined organic phase was washed with saturated aqueous $NaHCO_3$ and brine, dried over anhydrous $MgSO_4$, filtered, and concentrated to leave a brown solid. The product was purified by column chromatography (silica gel, hexane) followed by recrystallization from hexane gave 11.44 g (46%) of **18** as a white solid: mp 40−41 °C; IR (KBr) 901, 867, 712 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 7.91 (q, J = 0.7 Hz, 2H), 8.24 (s, 1H); MS (EI) m/z (rel intensity) 398 (M^+, 100). Anal. Calcd for $C_7H_3F_3I_2$: C, 21.13; H, 0.76. Found: C, 21.24; H, 0.58.

1,3-Bis(aminomethyl)-5-(trifluoromethyl)benzene (19). A mixture of **18** (10.3 g, 25.9 mmol) and CuCN (11.6 g, 130 mmol) in 150 mL of HMPA was stirred at 90 °C for 5 h. The mixture was poured into excess 0.2 M aqueous $FeCl_3$ solution and was extracted several times with ether. The extract was washed with aqueous $NaHSO_3$ and brine, dried over anhydrous $MgSO_4$, filtered, and concentrated. The product was purified by column chromatography (silica gel, 9:1 hexanes−EtOAc) to afford 3.12 g (61%) of 1,3-dicyano-5-(trifluoromethyl)benzene as a white solid: mp 95−97 °C; IR (KBr) 2245, 869, 710, 693 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 8.15 (s); MS (EI) m/z (rel intensity) 196 (M^+, 100). Anal. Calcd for $C_9H_3F_3N_2$: C, 55.12; H, 1.54; N, 14.28. Found: C, 55.09; H, 1.34; N, 14.67.

To a suspension of $LiAlH_4$ (1.43 g, 37.6 mmol) in 30 mL of ether was added dropwise a solution of 1,3-dicyano-5-(trifluoromethyl)benzene (2.83 g, 14.4 mmol) in 20 mL of ether at such rate as to produce a gentle reflux. After the mixture was stirred for 2 h at room temperature, water was added dropwise

followed by addition of 200 mL of 20% solution of sodium potassium tartrate. The mixture was extracted four times with $CHCl_3$, and the organic extract was washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated to yield 1.66 g of a slightly colored oil. The crude product was distilled under reduced pressure to afford 0.64 g (22%) of diamine **19** as an air-sensitive colorless oil, which was stored under nitrogen: bp 83−85 °C (0.5 mmHg); IR (neat) 3336, 857, 706 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 1.48 (br s, 4H), 3.94 (s, 4H), 7.47 (s, 2H), 7.49 (s, 1H); MS (EI) *m*/*z* (rel intensity) 203 ($M^+ - 1$, 18), 174 (100). HRMS: calcd for $C_9H_{11}N_2F_3$ 204.0874, found 204.0848.

3,3′-Bis(bromomethyl)biphenyl (21). To a suspension of 6.28 g (29.3 mmol) of 3,3′-bis(hydroxymethyl)biphenyl (**20**) in 300 mL of $CHCl_3$ was added dropwise a solution of 8.27 g (30.5 mmol) of phosphorus tribromide in 30 mL of $CHCl_3$ over a period of 30 min at room temperature. The solution was allowed to stir for 2 h. TLC showed the reaction to be complete. The mixture was cooled to 0 °C, and 300 mL of water was added. The organic layer was separated, and the aqueous layer was extracted twice with 100 mL portions of $CHCl_3$. The combined organic phase was washed with saturated aqueous $NaHCO_3$ and brine, dried over anhydrous $MgSO_4$, filtered, and concentrated. The resulting crude product was recrystallized from benzene to afford 6.40 g (64%) of **21** as colorless crystals: mp 119−120 °C (lit.[22] mp 103−104 °C); IR (KBr) 886, 786, 703 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 4.55 (s, 4H), 7.38 (ddd, J = 6.8, 1.8, 1.8 Hz, 2H), 7.42 (dd, J = 6.8, 6.8 Hz, 2H), 7.51 (ddd, J = 6.8, 1.8, 1.8 Hz, 2H), 7.60 (dd, J = 1.8, 1.8 Hz, 2H).

3,3′-Bis(aminomethyl)biphenyl (22). Diamine **22** was prepared by the same procedure as described for **13** in 63% yield (two steps) from bromide **21**. 3,3′-Bis(phthalimidomethyl)biphenyl: mp 223−224 °C; IR (KBr) 1708, 774, 732, 715 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 4.89 (s, 4H), 7.33−7.48 (m, 6H), 7.62 (s, 2H), 7.67−7.85 (m, 8H); MS (EI) *m*/*z* (rel intensity) 472 (M^+, 100). Diamine **22**: IR (neat) 3364, 3288, 892, 776, 697 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 1.58 (s, 4H), 3.93 (s, 4H), 7.29 (d, J = 7.5 Hz, 2H), 7.40 (dd, J = 7.5, 7.5 Hz, 2H), 7.46 (d, J = 7.5 Hz, 2H), 7.55 (s, 2H); MS (EI) *m*/*z* (rel intensity) 212 (M^+, 70), 83 (100). HRMS: calcd for $C_{14}H_{16}N_2$ 212.1313, found 212.1301.

***m*-Xylylene Diisothiocyanate (23).** Reaction of *m*-xylylenediamine (5.35 g, 39.3 mmol) and 1,1′-thiocarbonyldiimidazole (14.0 g, 78.6 mmol) was carried out as described for the preparation of **14** to give 5.84 g (67%) of **23** as a colorless oil: IR (neat) 2178, 2096, 743, 706 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 4.74 (s, 4H), 7.26 (s, 1H), 7.31 (d, J = 7.5 Hz, 2H), 7.43 (t, J = 7.5 Hz, 1H); MS (CI) *m*/*z* (rel intensity) 382 (100), 220 (M^+, 28). HRMS: calcd for $C_{10}H_9N_2S_2$ 221.0207, found 221.0212.

General Procedure for Determination of Association Constants (K_a) by ^1H NMR Dilution Method. $CDCl_3$ was dried over P_2O_5, distilled, and passed through a column of activated alumina prior to use. A 0.1 M solution of dithiourea was prepared in a 3-mL volumetric flask. An initial NMR spectrum of this solution was recorded. This solution was diluted in a volumetric flask to give another stock solution. Other samples were made by diluting stock solutions with $CDCl_3$ in NMR tubes. Typically, spectra of 10−14 different solutions with concentration range from 0.1 M to 0.2 mM (lower limit of NMR sensitivity) were recorded. The dimerization constant was obtained from these data by applying the method developed by Horman and Dreux.[14] The calculation was performed on a Macintosh personal computer using Excel version 5.0[23] and IGOR Pro 3.03[24] software.

X-ray Crystallography. Data collection was done at 20 °C on a Rigaku AFC7R diffractometer with graphite-monochromated Mo Kα radiation (λ = 0.710 69 Å). The structures were solved by direct methods (SHELXS-86[25] for **1a**, SAPI91[26] for **1b**, and SIR88[27] for **1j**) and refined by full-matrix least-squares techniques. The non-hydrogen atoms were refined anisotropically. Hydrogen atoms of the *tert*-butyl group of **1a,j** were not included in the refinement. Other hydrogen atoms were included but not refined.

Crystal Data for 1a: $C_{11}H_{19}N_2S$, f_w = 211.34, tetragonal, space group $I4_1/a$, a = 16.707(5) Å, c = 18.982(5) Å, V = 5298.3(22) Å^3, Z = 16, D_c = 1.060 g cm^{-3}, μ(Mo Kα) = 2.14 cm^{-1}. Single crystals were obtained from an ethanol solution. A colorless crystal with dimensions of 0.30 × 0.43 × 0.56 mm was used for data collection. A total of 1730 unique reflections were obtained, and 977 observed reflections ($I > 2\sigma(I)$) were used for refinement to give R = 0.070 and R_w = 0.206.

Crystal Data for 1b: $C_{18}H_{30}N_4S_2$, f_w = 366.58, triclinic, space group $P\bar{1}$, a = 13.104(4) Å, b = 14.700(4) Å, c = 12.678(4) Å, α = 111.93(2)°, β = 108.28(2)°, γ = 81.13(2)°, V = 2149(1) Å^3, Z = 4, D_c = 1.133 g cm^{-3}, μ(Mo Kα) = 2.55 cm^{-1}. Single crystals were obtained from an ethanol solution. A colorless crystal with dimensions of 0.15 × 0.30 × 0.60 mm was used for data collection. A total of 9856 unique reflections were obtained, and 3920 observed reflections ($I > 3\sigma(I)$) were used for refinement to give R = 0.093 and R_w = 0.079.

Crystal Data for 1j: $C_{14}H_{15}F_2N_2S$, f_w = 281.34, tetragonal, space group $I4_1/a$, a = 17.256(2) Å, c = 19.159(3) Å, V = 5704(1) Å^3, Z = 16, D_c = 1.310 g cm^{-3}, μ(Mo Kα) = 2.37 cm^{-1}. Single crystals were obtained from a benzene solution. A colorless crystal with dimensions of 0.30 × 0.36 × 0.45 mm was used for data collection. A total of 3388 unique reflections were obtained, and 1164 observed reflections ($I > 3\sigma(I)$) were used for refinement to R = 0.091 and R_w = 0.069.

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Supporting Information Available: Copies of ^1H NMR spectra (diamines **13**, **16**, and **22** and their precursors, **14**, **19**, and **23**) and X-ray crystallographic data (tables of atomic coordinates, thermal parameters, and bond lengths and angles and ORTEP diagrams) for **1a**,**b**,**j** (37 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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