J. Org. Chem. **1995**, *60*, 4893−4899

Crystal and Solution Structures of Novel Bulky Bis[2,6-di(acylamino)phenyl] Disulfides. Absence of Covalent NH---S Hydrogen Bond between Amide NH and Neighboring Disulfide in Bis[2,6-di(pivaloylamino)phenyl] Disulfide

Norikazu Ueyama,* Taka-aki Okamura, and Yusuke Yamada

Department of Macromolecular Science, Faculty of Science, Osaka University, Toyonaka, Osaka 560, Japan

Akira Nakamura*

Institute for Molecular Science, Okazaki 444, Japan

Received November 7, 1994 (Revised Manuscript Received April 4, 1995[⊗])

Novel bulky bis[2,6-di(acylamino)phenyl] disulfides, e.g. bis[2,6-di(pivaloylamino)phenyl] disulfide and bis[2,6-di(triphenylacetylamino)phenyl] disulfide, having two acylamino groups at the 2,6-positions of the benzene ring were synthesized and the crystal structures determined. The two bulky acylamino groups cover the disulfide group, and the two amide NH groups are directed toward the sulfur atom, but the IR NH bands observed in the solid state indicate the absence of covalent NH−S hydrogen bonds in bis[2,6-di(pivaloylamino)phenyl] disulfide.

Introduction

Many types of bisalkyl and bisaryl disulfides have been synthesized and characterized as mimics of various cysteine-containing proteins, especially to understand the biologically important thiol-disulfide interexchange reaction.[1,2] The introduction of bulky groups around the thiol or thiolate would also be useful for the investigation of specific cysteine thiol or thiolate groups in cysteine-containing proteins. For example, papain contains one active thiol that is protected from air oxidation during the catalytic reaction.[3]

Various bisphenyl disulfides having bulky alkyl groups at the 2,6-position have been synthesized to study the slow inversion process of S−S or S−C bonds in weakly polar solvents.[4,5] Recently, a new synthetic technique to introduce bulky substituents (e.g. triphenylsilyl) on benzenethiol has been developed to synthesize mononuclear Hg(II) thiolate complexes.[6] The restricted S−S rotation in a bulky disulfide, di-*tert*-adamantyl disulfide, has been proposed using theoretical calculations.[7] An extremely bulky disulfide, tris(trimethylsilyl)methane disulfide, has been synthesized[8] and is thought to have a large C−S−S−C torsion angle on the basis of the large angle in the crystal structure of the related diselenide.[9]

In this paper, we report the synthesis of novel bulky disulfides having bulky amide groups close to the sulfur atom at the 2,6-position of the aromatic ring. These compounds have the advantage of arbitrary introduction of bulky groups near the sulfur atom. In addition, this type of bulky disulfide has a conformationally restricted structure, for preventing π-conjugation between the amide plane and the benzene ring. This restriction allows the arenethiol to act as a model for bulky alkanethiols, such as cysteine thiol, in proteins. In addition, the amide NH groups of bis[2,6-di(acylamino)phenyl] disulfides preferentially point toward the sulfur atom because of steric and charge repulsions between the carbonyl and sulfur groups.

The effect of local electrostatic fields during the disulfide exchanges in thioredoxin has been discussed.[10] Actually, the X-ray structure of *Escherichia coli* thioredoxin shows the presence of a proximal amide NH near one cysteine residue, and the formation of a NH−S hydrogen bond has been proposed.[11] The disulfides designed in this paper have a similar directionality of the two amide dipoles toward the sulfur atom and should be relevant as models of redox proteins.

Experimental Section

All solvents were distilled before use. Bis(2,6-diaminophenyl) disulfide was prepared according to the reported method.[12] The synthesis of bis(2-pivaloylaminophenyl) disulfide was carried out according to the same procedure reported in the previous paper.[13]

Synthesis of Bis[2,6-di(acetylamino)phenyl] Disulfide (1). Bis(2,6-diaminophenyl) disulfide (0.4 g, 1.4 mmol) was dissolved in acetic anhydride (5 mL) at room temperature. After refluxing for 1 h, unreacted acetic anhydride was decomposed by the addition of water and heating. Then the solution was concentrated to give a yellow solid. The crude product was recrystallized from ethanol. The product includes one ethanol molecule as the crystal solvent: yield 70%; ^{1}H NMR (Me$_2$SO-d_6) δ 9.01 (s, 4H), 7.54 (d, 4H), 7.34 (t, 2H), 1.96 (s, 12H); ^{13}C NMR (Me$_2$SO-d_6) δ 168.75, 140.54, 130.73, 120.72, 119.97, 23.42. Anal. Calcd for $C_{20}H_{22}N_4O_4S_2(C_2H_6O)$: C, 53.64; H, 5.73; N, 11.32. Found: C, 53.51; H, 5.78; N, 11.38.

[⊗] Abstract published in *Advance ACS Abstracts*, June 15, 1995.

(1) Lees, W. J.; Whitesides, G. M. *J. Org. Chem.* **1993**, *58*, 642−647.

(2) Lamoureux, G. V.; Whitesides, G. M. *J. Org. Chem.* **1993**, *58*, 633−641.

(3) Drenth, J.; Jansonius, J. N.; Koekoek, R.; Swen, H. M.; Wolthers, B. G. *Nature* **1968**, *218*, 929−932.

(4) Kessler, H.; Rieker, A.; Rundel, W. *J. Chem. Soc., Chem. Commun.* **1968**, 475−476.

(5) Kessler, H.; Rundel, W. *Chem. Ber.* **1968**, *101*, 3350−3357.

(6) Block, E.; Brito, M.; Gernon, M.; McGowty, D.; Kang, H.; Zubieta, J. *Inorg. Chem.* **1990**, *29*, 3172−3181.

(7) Jørgensen, F. S.; Snyder, J. P. *J. Org. Chem.* **1980**, *45*, 1015−1020.

(8) Maher, D. C.; Harpp, D. N. *Sulfur Lett.* **1993**, *16*, 11−18.

(9) Wagner, I.; Mont, W.; Poul, S.; Saak, W. *Chem. Ber.* **1990**, *123*, 2325−2327.

(10) Snyder, G. H.; Cennerazzo, M. J.; Karalis, A. J.; Field, D. *Biochemistry* **1981**, *20*, 6509−6519.

(11) Katti, S. K.; LeMaster, D. M.; Eklund, H. *J. Mol. Biol.* **1990**, *212*, 167−184.

(12) Ward, E. R.; Heard, D. D. *J. Chem. Soc.* **1965**, 1023−1028.

(13) Ueyama, N.; Okamura, T.; Nakamura, A. *J. Am. Chem. Soc.* **1992**, *114*, 8129−8137.

0022-3263/95/1960-4893$09.00/0 © 1995 American Chemical Society

Synthesis of Bis[2,6-di(pivaloylamino)phenyl] Disulfide (2). To a THF solution (25 mL) of bis(2,6-diaminophenyl) disulfide (0.6 g, 2.2 mmol) was added dropwise NEt_3 (1.5 mL, 11 mmol) and *t*-BuCOCl (1.3 mL, 11 mmol) at 0 °C. The solution was stirred overnight and then concentrated under reduced pressure. The residue was extracted with 200 mL of ethyl acetate and washed with water, 2% HCl aqueous, saturated NaCl aqueous, 4% sodium hydrogen carbonate aqueous, and saturated NaCl aqueous solutions, successively. The organic layer was dried over sodium sulfate and concentrated under reduced pressure to give an orange-yellow oil which was recrystallized from diethyl ether, and yellow crystals containing one molecule of diethyl ether were formed. Yellow powder without ether was obtained by drying under reduced pressure: yield, 69%; ^{1}H NMR (acetonitrile-d_3) δ 8.37 (s, 4H, NH), 7.97 (d, 4H, *m*-ArH), 7.41 (t, 2H, *p*-ArH), 1.15 (s, 36H, *t*-Bu); (Me_2SO-d_6) δ 8.71 (s, 4H, NH), 7.70 (d, 4H, *m*-ArH), 7.41 (t, 2H, *p*-ArH), 1.11 (s, 36H, *t*-Bu); ^{13}C NMR (Me_2SO-d_6) δ 175.83, 140.52, 131.32, 119.59, 118.64, 26.89. Anal. Calcd for $C_{32}H_{46}N_4O_4S_2$: C, 62.51; H, 7.54; N, 9.11. Found: C, 62.56; H, 7.58; N, 9.13.

Synthesis of Bis[2,6-di(triphenylacetylamino)phenyl] Disulfide (3). To a THF solution (20 mL) of triphenylacetic acid (2.0 g, 6.9 mmol) was added thionyl chloride (2 mL) and refluxed for 2 h. The solution was concentrated under reduced pressure to give solid materials. Then a THF solution of the solid materials was dropped into a THF solution (10 mL) of bis(2,6-diamino)phenyl disulfide (0.4 g, 1.4 mmol) and triethylamine (0.8 mL, 5.8 mmol) and refluxed for 2 h. The solution was concentrated and mixed with 200 mL of ethyl acetate. The solution was washed with 4% sodium hydrogen carbonate aqueous solution, NaCl-saturated aqueous solution, 2% HCl aqueous solution, and NaCl-saturated aqueous solution, successively. The organic layer was dried over sodium sulfate and concentrated under reduced pressure to give crystalline materials which were recrystallized from THF/acetonitrile. The crystal for the X-ray analysis contains two acetonitrile molecules. Yellowish microcrystals were obtained in a 45% yield: mp 289−290 °C; mass (FAB), found 1359 (M^+, MH^+); ^{1}H NMR (chloroform-*d*) δ 8.08 (s, 4H, NH), 7.98 (d, 4H, *m*-ArH), 7.19 (m, 60H, Ph), 6.96 (t, 4H, *p*-ArH); ^{13}C NMR (chloroform-*d*) δ 171.75, 142.80, 140.22, 132.26, 130.33, 128.25, 127.13, 117.88, 114.95, 68.91. Anal. Calcd for $C_{90}H_{70}N_4O_4S_2 \cdot CH_3CN \cdot {}^3/_2H_2O$: C, 79.08; H, 5.37; N, 4.91. Found: C, 78.98; H, 5.37; N, 4.90. The acetonitrile and water molecules in crystal are readily removable under reduced pressure.

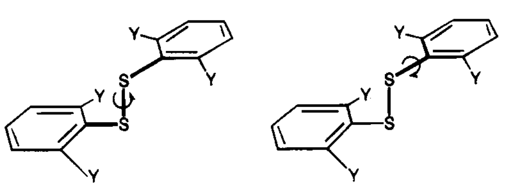
Physical Measurements. ^{1}H NMR spectra were recorded on a JEOL EX 270 or JEOL GSX-400 spectrometer. The temperatures were varied from −40 to 56 °C. IR spectra in the solid state were taken on a Jasco FT/IR-8300 spectrometer.

A complete line shape analysis of **2** and **3** was carried out by the measurements of the half-line width of *tert*-butyl or NH ^{1}H NMR signals and chemical shift difference. When the exchange between two separate signals for **2** is frozen at −40 °C, each rate was obtainable. The ln(*k*/T) was plotted against 1/*T*, and $\Delta Ho^{\ddagger}$ and $\Delta So^{\ddagger}$ values were estimated by the slope and intercept of the straight line.

X-ray Structure Determination. Crystal data for $\mathbf{2}\cdot Et_2O$:[31] $(C_{32}H_{46}N_4O_4S_2)\cdot(C_4H_{10}O)$, tetragonal crystal system, space group $I4_1/a$, $a = 14.418(3)$, $c = 42.792(6)$ Å, $V = 8896(4)$ Å^3, $Z = 8$, $\mu = 1.50$ cm^{-1}, $d_{calc} = 1.029$ g cm^{-3}, scan type = ω. X-ray diffraction experiments were carried out at 296 K on a Rigaku AFC5R diffractometer with graphite monochromated Mo Kα radiation and a 12 kW rotating anode generator. Data up to $2\theta_{max} = 60°$ on a total of 5855 reflections were collected, and the 1814 with $I > 3\sigma(I)$ were used in the calculations.

Crystal data for $\mathbf{3}\cdot 2CH_3CN$:[31] $(C_{92}H_{70}N_4O_4S_2)(C_4H_6N_2)$, space group $C2/c$, $a = 21.555(6)$, $b = 14.434(9)$, $c = 24.98(1)$ Å, $\beta = 101.65(3)°$, $V = 7610(5)$ Å^3, $Z = 4$, μ (Mo Kα) = 1.29 cm^{-1}, $d_{calc} = 1.258$ g cm^{-3}, scan type = ω. X-ray diffraction experiments were carried out at 296 K on a Rigaku AFC5R diffractometer with graphite monochromated Mo Kα radiation and a 12 kW rotating anode generator. Data were collected up to $2\theta_{max} = 45°$ on a total of 5404 reflections. The 1230 with $I > 3\sigma(I)$ were used in the calculations.

Chart 1



(Y = acylamino)

S-S inversion process **S-C inversion process**

The structures were solved by the direct method using a teXsan crystallographic software package. The non-hydrogen atoms except solvent molecules and phenyl groups in **3** were refined anisotropically. Hydrogen atoms were placed on the calculated positions. The final refinement was carried out using full-matrix least-squares techniques with non-hydrogen atoms. The refinement with anisotropic thermal parameters converged at $R = 0.083$ ($R_w = 0.110$) for **2** and at $R = 0.071$ ($R_w = 0.073$) for **3**. Atom scattering factors and dispersion corrections were taken from the *International Tables*.[14]

Energy Minimization Calculations. Energy minimization calculations were performed with a Dreiding force field[15] using BIOGRAF[16] on an IRIS R-4000 computer. Total energy was estimated by the grid charges of S−S and S−C torsional angles to theoretically evaluate the two inversion processes as shown in Chart 1. Each 400 step optimized geometry and its total energy was obtained at every 2.5° change of the C−S−S−C torsion angle from 0° to 180°. The torsional energy barrier for the S−S inversion process between the right-handed and left-handed helix S−S conformers was estimated from cis (C−S−S−C = 0°) and trans (C−S−S−C = 180°) barrier heights based on the lowest energy conformer that is similar to the crystallographically determined structure in the solid state.

Similar calculations were carried out to predict the possibility of the S−C inversion process. The S−C torsional energy barrier for the rotation of the 2,6-substituted aromatic ring was obtained by grid rotations of the C−S−S−C torsion angle on the corresponding half-side of the disulfide. The grid rotation of the S−C bond was performed from 90° to 270° at 1° intervals, and their energy-minimized structures were obtained after 500 steps. A further quenching search at each S−C torsional angle was carried out for 0.5 ps to obtain an energy minimum conformer, especially for the bulky disulfide (**3**). The charge of each atom was readjusted stepwise using a charge equilibration method[17] with two different dielectric constants, $\epsilon = 4.8$ for chloroform and $\epsilon = 48.7$ for dimethyl sulfoxide.

Results and Discussion

Bulky Bisaryl Disulfides with Two Amide Groups at the 2,6-Position. A novel type of bulky bis[2,6-di(acylamino)phenyl] disulfides is prepared by the acylation of bis(2,6-diaminophenyl) disulfide. Various bulky disulfides, e.g. $[S\text{-}2,4,6\text{-}(t\text{-}Bu)_3C_6H_2]_2$, have already been synthesized to study the sterically hindered rotation of the S−S bond.[5] The synthesis of these types of bulky thiols is limited by the difficulty of introducing bulky alkane groups at the 2,6-position of benzenethiol, even using a recently developed lithiation method.[6]

Bis[2,6-di(acylamino)phenyl] disulfides are a new type of bulky disulfide. The two amide NH groups at the 2,6-

---

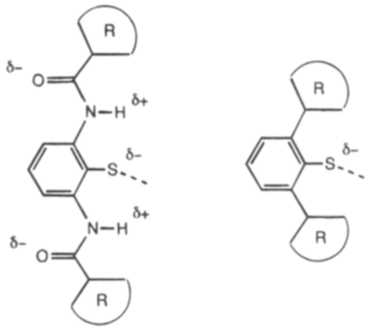
[14] Cromer, D. T.; Waber, J. T. *International Tables for X-ray Crystallography*; Kynoch Press: Birmingham, U.K., 1974; Vol. IV.

[15] Mayo, S. L.; Olafson, B. D.; Goddard, W. A., III. *J. Phys. Chem.* **1990**, *94*, 8897−8909.

[16] The BIOGRAF program was supplied by Molecular Simulation Inc.

[17] Rappe, A. K.; Goddard W. A., III. *J. Phys. Chem.* **1991**, *95*, 3358−3363.

Chart 2



1: R = Me
2: R = *t*-Bu
3: R = Ph $_3$C

R = Me, Et, *t*-Bu

positions are directed toward the sulfur atom because of steric interactions of the amide carbonyl groups. The bulky acyl groups shield the sulfur atom widely as shown in Chart 2.

Crystal Structures of Bis[2,6-di(pivaloylamino)phenyl] Disulfide and Bis[2,6-di(triphenylacetylamino)phenyl] Disulfide. Bis[2,6-di(pivaloylamino)phenyl] disulfide (**2**) crystallizes in a tetragonal system (space group $I4_1/a$) containing one diethyl ether molecule against each molecule of **2**. As shown in Figure 1, **2** has C_2 symmetry with the twofold axis in the crystalline form bisecting the center of the S–S bond. The dihedral angle of C–S–S–C in **2** is 98.9°, which is similar to that of reported disulfides, e.g. CH_3SSCH_3 (83.9°–84.7°),[18,19] bis(4-nitrophenyl) disulfide [72(2)°], and bis(2-nitrophenyl) disulfide [85.1(4)°]. Actually, recent *ab initio* calculations of the C–S–S–C dihedral angle for CH_3SSCH_3 show an energy minimum near 85° in a wide well of 60–120° within 2 kcal/mol.[20] The S–S and S–C distances for **2** are 2.079(4) and 1.778(8) Å, also similar to those of 2.038 or 2.022(3) and 1.806(3) Å, respectively, reported as experimental values for CH_3SSCH_3.[18-20] The slightly longer S–S distance in **2** can be ascribed to the large difference in the theoretically stable energy minimized C–S–S–C torsional angle (90°)[20] and to the prevention of a pπ–pπ interaction between the sulfur atom and the aromatic ring, since the aromatic plane is perpendicular to its C–S–S plane. Interestingly, two of the four amide planes overlap with each other, whereas the other two amide groups are far apart. All four amide NH groups of **2** and **3** are directed toward the sulfur atoms with short N–S distances (2.39–2.99 Å).

Bis[2,6-di(triphenylacetylamino)phenyl] disulfide (**3**) crystallizes in space group $C2/c$ and contains two acetonitrile molecules. Its crystalline form also has a twofold axis at the center of the S–S bond. Table I lists selected distances and angles for **2** and **3**. The structural parameters of **3** are similar to those of **2**. The relatively large C–S–S–C dihedral angle (104.3°) is due to the bulkiness of the triphenylacetyl group as shown in Figure 2. The S–S distance [2.099(8) Å] and S–C distance [1.74(1) Å] also reflect the large C–S–S–C dihedral angle in **3** as well as in **2**. Large C–S–S–C (115°) and C-Se-Se-C (180°) torsional angles have been reported for D-penicillamine disulfide[21] and bis[tris(trimethylsilyl)methyl] diselenide,[9] respectively. Sterically congested dialkyl disulfides have already been designed and have been predicted to exhibit unusually large C–S–S–C torsion angles.[7]

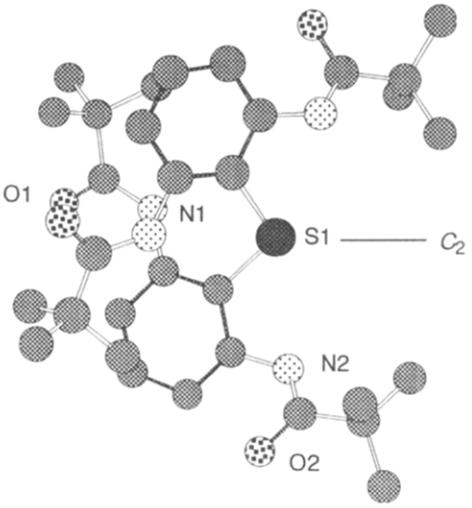


Figure 1. Molecular structure of bis[2,6-di(pivaloylamino)phenyl] disulfide (**2**) without hydrogen atoms.

Table 1. Selected Bond Distances and Angles for Bis(acylaminobenzene) Disulfides

atoms	bis[2,6-di(pivaloylamino)phenyl] disulfide (2)	bis[2,6-di(triphenylacetylamino)phenyl] disulfide (3)
	Bond Distances (Angstroms)	
S–S	2.079(4)	2.099(8)
S–C	1.778(8)	1.74(1)
	Bond Angles (Degrees)	
S–S–C	104.3(3)	103.2(5)
C–S–S–C	98.9	104.3
S–S–C11–C12	106.9(6)	−78(1)

IR Spectra in Solid State. The IR spectrum of bis[2,6-di(acetylamino)phenyl] disulfide in the solid state shows broad amide NH bands at 3469–3335 cm^{-1} due to the presence of free NH and intermolecular NH–O=C hydrogen bonds. The acetylamino group is known to readily form an intermolecular NH–O=C hydrogen bond.[22]

Parts a and b Figure 3 show the IR spectra of bis(2-pivaloylaminophenyl) disulfide and bis[2,6-di(pivaloylamino)phenyl] disulfide (**2**); respectively, in the solid state. Bis(2-pivaloylaminophenyl) disulfide shows two sets of NH stretchings at 3389 and 3251 cm^{-1} and CO stretchings at 1679 and 1644 cm^{-1}. the free amide NH stretching band is known to appear in the range 3400–3500 cm^{-1}.[23] A pair of bands at 3389 and 1679 cm^{-1} is assignable to those of free amide NH and CO groups, respectively, whereas another pair at 3251 and 1644 cm^{-1} is due to the hydrogen-bonded amide NH and CO groups. At least one of the two amide groups is responsible for the formation of the intermolecular NH–O=C hydrogen bonds. The shift of the NH stretching band depends on a change in the force constant of the N-H bond, since a change in the covalent, ionic, and van der Waals character of the NH–O hydrogen bond leads to an IR shift.[24,25]

---

[18] Sutter, D.; Dreizler, H.; Rudolph, H. D. *Z. Naturforsch.* **1965**, *20A*, 1676–1681.

[19] Beagley, B.; McAloon, K. T. *Trans. Faraday Soc.* **1971**, *67*, 3216–3222.

[20] Jiao, D.; Barfield, M.; Combariza, J. E.; Hruby, V. J. *J. Am. Chem. Soc.* **1992**, *114*, 3639–3643.

[21] Rosenfield, R. E. J.; Parthasarathy, R. *Acta Crystallogr., Sect. B* **1975**, *31*, 462–468.

[22] Bystrov, V. F.; Portnova, S. L.; Tseltin, V. I.; Ivanov, V. T.; Ovchinnikov, Y. A. *Tetrahedron* **1969**, *25*, 493.

[23] Silverstein, R. M.; Bassler, G. C.; Morrill, T. C. *Spectrometric Identification of Organic Compounds*; Wiley: New York, 1981.

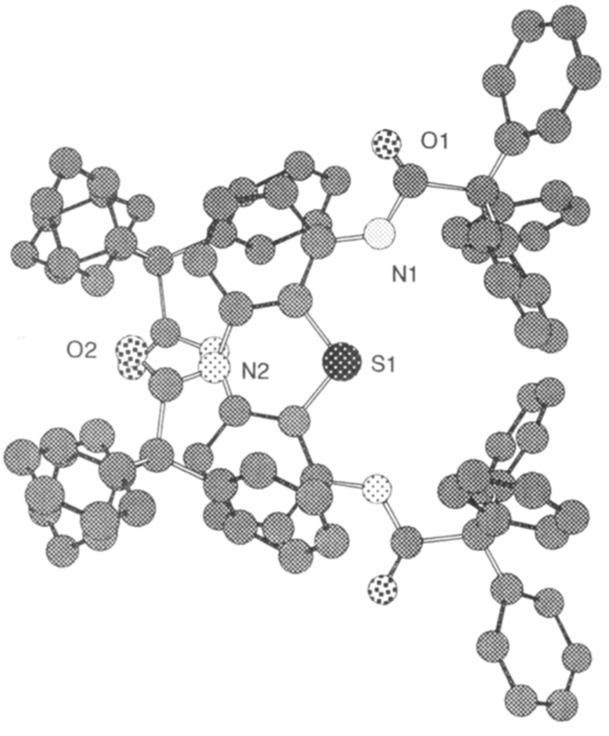


Figure 2. Molecular structure of bis[2,6-di(triphenylacetylamino)phenyl] disulfide (**3**) without hydrogen atoms.

Therefore, the observation of an almost free NH stretching band suggests that a covalent NH—S hydrogen bond is not involved in the disulfide, although a weak ionic interaction probably exists between the positively charged amide NH and the negatively charged sulfur atom since the NH and sulfur groups are in close proximity (Chart 2).

The observation of the NH band at 3398 cm^{-1} and the CO band at 1695 cm^{-1} in **2** clearly indicates the absence of a hydrogen bond between the NH and S or O=C (Figure 3b). The two amide NH groups are sterically disfavored from forming an intermolecular NH—O=C hydrogen bond. The lack of a NH—S hydrogen bond was also found as in the case of bis(2-pivaloylaminophenyl) disulfide. Disulfide **3** exhibits a slightly shifted NH band (shift 52 cm^{-1}) at 3346 cm^{-1} and a free C=O band at 1692 cm^{-1} in the solid state as shown in Figure 3c. The shifted NH band is presumably caused by the perturbation of a proximal phenyl ring since this type of shifted band was not observed for **2**. Thus, it is likely that a weak covalent NH—S hydrogen bond or a direct interaction between the aromatic ring and amide NH is involved in the triphenylacetyl derivative.[26] Further study will be required for an estimation of the effect of the aromatic ring. The IR results for **2** strongly suggest the absence of a covalent NH—S hydrogen bond in spite of the presence of the 2,6-amide NH groups directed toward the sulfur atom.

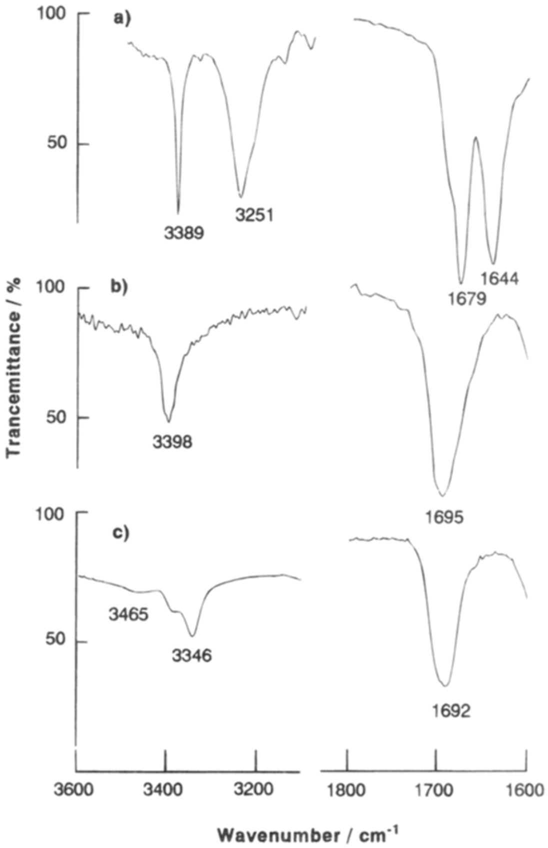


Figure 3. IR spectra of the amide regions of (a) bis(2-pivaloylaminophenyl) disulfide (**1**), (b) bis[2,6-di(pivaloylamino)phenyl] disulfide (**2**), and (c) bis[2,6-di(triphenylacetylamino)phenyl] disulfide (**3**) in the solid state (KBr disk).

A few papers have discussed the existence of an NH—S hydrogen bond in proteins. For example, the X-ray structure of α-chymotrypsin has predicted the existence of an NH—S hydrogen bond between the amide NH and methionine thioether sulfur.[27] Katti et al. have reported that the cystine sulfur in *E. coli* thioredoxin is involved in a hydrogen bond with the main-chain amide NH group.[11] Our IR results suggest that only a weakly ionic interaction occurs between the amide NH and sulfur in disulfides. Recent *ab initio* calculations of the H_2S—HF complex have pointed out the inadequency of simple charged models since a strong interaction accompanied by an IR shift of the H—F stretching band is observed.[28] If a similar covalent interaction exists between NH and S, the IR shift of the NH stretching is remarkable. Further detailed investigation will be necessary for the characterization of NH—S interactions in thioethers and thiols.

Solution Structures of 2 and 3. The ^1H NMR spectrum of bis(2-pivaloylaminophenyl) disulfide shows sharp signals at room temperature in $CDCl_3$, acetonitrile-d_3, or Me_2SO-d_6. On the contrary, broad signals except for 4-ArH were observed for bis[2,6-di(pivaloylamino)phenyl] disulfide (**2**) at room temperature in $CDCl_3$ as shown in Figure 4 although the disulfide exhibits only sharp signals in acetonitrile-d_3 and Me_2SO-d_6. The observation of sharp triplet 4-ArH signals in $CDCl_3$ is ascribed to sterically restricted rotation of the aromatic ring around the S—C bond. The broadening of the 3-ArH signals in **2** is due to a relatively high energy barrier for S—C rotation in the aromatic ring flipping process. It is supported by the fact that bis(2,6-diaminophenyl) disulfide exhibits only one sharp ^1H NMR signal for the 3- or

---

[24] Kollman, P.; McKelvey, J.; Johansson, A.; Rothenberg, S. *J. Am. Chem. Soc.* **1975**, *97*, 955–965.

[25] Maillard, D.; Schriver, A.; Perchard, J. P. *J. Chem. Phys.* **1979**, *71*, 517–529.

[26] Hg[*S*-2,6-(triphenylacetylamino)$_2C_6H_3]_2$ exhibits a shift (65 cm^{-1}) of NH stretching by a weak covalent NH—S hydrogen bond similar to that (69 cm^{-1}) of Hg[S-2,6-(*t*-BuCONH)$_2C_6H_3]_2$. In this case, the aromatic effect is not involved in the case of the Hg(II) complexes.

[27] Birktoft, J. J.; Blow, D. M. *J. Mol. Biol.* **1972**, *68*, 187–240.

[28] Viswanathan, R.; Dyke, T. R. *J. Chem. Phys.* **1982**, *77*, 1166–1174.

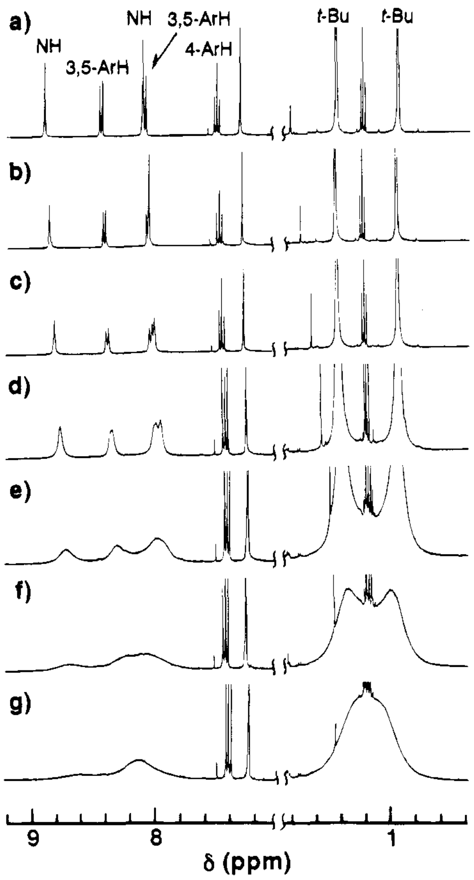


Figure 4. Temperature dependence of ^{1}H NMR spectra (400 MHz) of bis[2,6-di(pivaloylamino)phenyl] disulfide (**2**) in $CDCl_3$ at (a) −40, (b) −20, (c) 0, (d) 20, (e) 40, (f) 50, and (g) 56 °C.

5- and 4-ArH in $CDCl_3$ at ambient temperature. Low-temperature spectra (−40 °C) show two separate 3- or 5-ArH signals at 8.41 and 8.06 ppm with a 1:1 ratio as well as two kinds of amide NH signals at 8.86 and 8.07 ppm as shown in Figure 4. Two kinds of *t*-Bu signals were also observed at 1.45 and 0.96 ppm, and a coalescence temperature (T_c) was observed at 56 °C for **2** in $CDCl_3$. The difference in chemical shifts between these protons probably arises from the magnetically anisotropic influence of the amide or benzene plane as predicted by the crystal structure in Figure 1. Thus, two possibilities of conformational inversion in **2** can be considered for the coalescence of ^{1}H NMR signals. One proceeds from the rotation of the S−S bond and the other from the rotation of the S−C bond.

The S−S or S−C inversion process of **2** in $CDCl_3$ was evaluated by a complete line shape analysis. The rate constant was obtained by comparison between the observed and theoretical shapes. These results are also supported by analysis of the chemical shift difference and T_c in the dynamic NMR spectra. The obtained plot of $\ln(k/T)$ against $1/T$ in $CDCl_3$ gives $\Delta Ho^{\ddagger}$ (15 kcal/mol), $\Delta So^{\ddagger}$ (−2.1 cal/mol), and $\Delta Go^{\ddagger}$ *(15 kcal/mol) at 303 K for the S−S or S−C inversion process. This is similar to the value (*$\Delta Go^{\ddagger}$ = 16.3 kcal/mol) of bis[2,4,6-tri(*tert*-butyl)phenyl] disulfide (T_c = 54 °C) reported in the literature.[5]

The rotational barrier for the S−S inversion was reported to be 6.8 kcal/mol for CH_3SSCH_3 experimentally[29] and theoretically.[20] A similar value has been reported for $PhCH_2SSC(CH_3)_3$.[30] Both disulfides undergo a similar trans S−S torsional inversion process rather than a cis S−S inversion process, since a higher barrier exists for the cis S−S inversion with the bulky group. The steric congestion between the two adjacent *t*-Bu groups, as shown in the X-ray structure of **2** (Figure 1),[31] prevents a smooth S−S inversion with a high torsional barrier of the S−S bond also seen in bis[2,4,6-tri(*tert*-butyl)phenyl] disulfide.

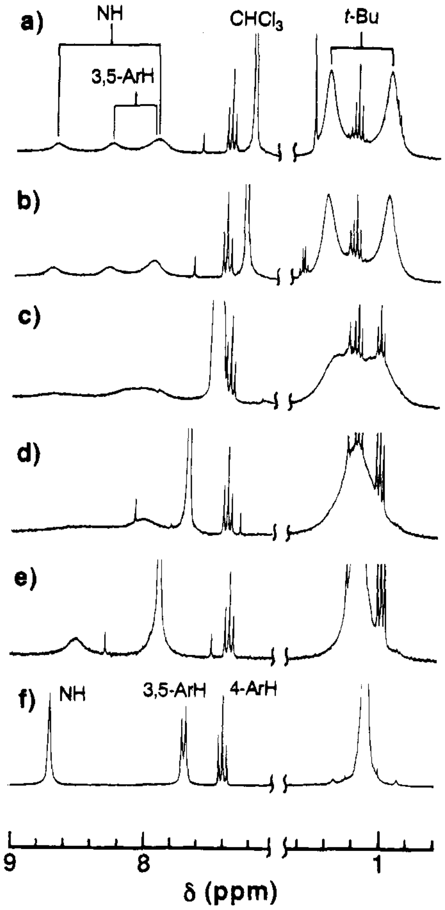


Figure 5. ^{1}H NMR spectra (400 MHz) of bis[2,6-di(pivaloylamino)phenyl] disulfide (**2**) in (a) $CDCl_3$, (b) Me_2SO-d_6/$CDCl_3$ (0.015:1), (c) Me_2SO-d_6/$CDCl_3$ (0.15:1), (d) Me_2SO-d_6/$CDCl_3$ (0.3:1), (e) Me_2SO-d_6/$CDCl_3$ (0.6:1), and (f) Me_2SO-d_6, at 30 °C

A fast inversion for **2** was observed in mixed solvents (Me_2SO-d_6/$CDCl_3$ = 0.015−0.6 v/v) as shown in Figure 5. Me_2SO is known to be a strongly solvating medium for the amide group. On the other hand, **2** in a polar solvent, e.g. Me_2SO-d_6 or acetonitrile-d_3, exhibits narrow signals for the amide and *m*-ArH and *t*-Bu signals even at room temperature. The ^{1}H NMR results indicate the presence of a fast S−C inversion on the NMR time scale. The polar solvents decrease the energy barrier for the S−C inversion process, since the weak charge interaction between the two amide NH groups and sulfur is disrupted by the strong solvation of the amide group.

The ^{1}H NMR spectrum of **3** shows one shielded NH signal at 8.08 ppm in $CDCl_3$ at room temperature. The

---

[29] Hubbard, W. N.; Douslin, D. R.; McCullough, J. P.; Scott, D. W.; Todd, S. S.; Messerly, J. F.; Hossenlopp, I. A.; George, A.; Waddington, G. *J. Am. Chem. Soc.* **1958**, *80*, 3547−3554.

[30] Fraser, R. R.; Boussard, G.; Saunders, J. K.; Lambert, J. B. *J. Am. Chem. Soc.* **1971**, *93*, 3822−3823.

[31] The author has deposited atomic coordinates for this structure with the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, U.K.

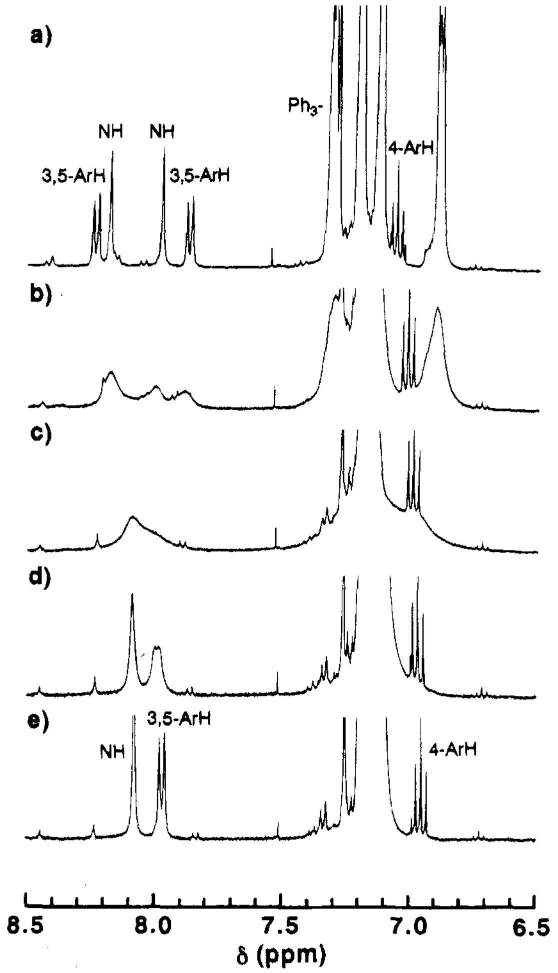


Figure 6. Temperature dependence of ^{1}H NMR spectra (400 MHz) of bis[2,6-di(triphenylacetylamino)phenyl] disulfide (**3**) in CDCl$_3$ at (a) −50, (b) −20, (c) 0, (d) 20, and (e) 40 °C. A coalescence point is observed at 0 °C.

temperature dependence of the amide NH signal gives a coalescence point at 0 °C as shown in Figure 6. The complete line shape analysis of the ^{1}H NMR signals in CDCl$_3$ gives $\Delta H^{\ddagger}$ (13.7 kcal/mol), $\Delta S^{\ddagger}$ (3.6 cal/mol), and $\Delta G^{\ddagger}$ (12.6 kcal/mol) at 303 K for the S−S or S−C inversion process. A relatively small S−S or S−C torsional energy barrier for **3** is obtained in spite of the presence of extremely bulky triphenylacetyl groups. The addition of a small amount (0.01 v/v) of Me$_2$SO-d_6 to a CDCl$_3$ solution at −50 °C results in the observation of coalesced signals.

Molecular Mechanics Calculations of Bis[2,6-di-(t-butyl)phenyl] Disulfide, 2 and 3. Molecular mechanics calculations by grid rotation of the S−S or S−C torsion angle were carried out to simulate both of the inversion processes. Parts a, b, and c of Figure 7 show the minimized total energy changes for **3**, bis[2,6-di(*tert*-butyl)phenyl] disulfide, and **2**, respectively, with the grid change of the C−S−S−C torsion angle (0−180°) at ϵ = 4.8 (chloroform). The inversion passes through the lowest barrier between the two conformers. The lowest barrier presumably corresponds to the observed energy barrier obtained by the ^{1}H NMR analysis. Energy minimization calculations for **2** show the presence of stable conformers in the range 50−130° for C−S−S−C torsion angles (Figure 7c). The trans S−S torsional energy barrier is $\Delta G^{\ddagger} = 16.3 \pm 0.8$ kcal/mol (300 K), which roughly corresponds to the experimental value ($\Delta G^{\ddagger}$ = 15 kcal/mol) obtained by the ^{1}H NMR method. Interestingly, the bulky amide *tert*-butyl groups in **2** provide a different type of steric congestion, but at a more remote position from the S−S bond than is observed for bis[2,6-di(*tert*-butyl)phenyl] disulfide.

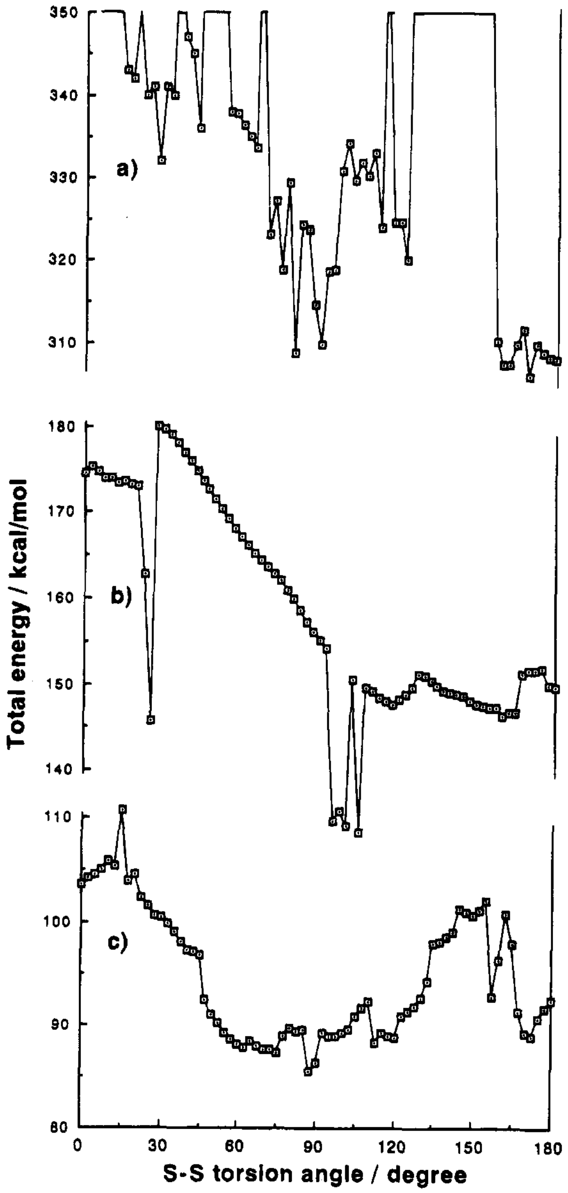


Figure 7. Minimized total energy against C−S−S−C torsion angle for (a) bis[2,6-di(triphenylacetylamino)phenyl] disulfide (**3**), (b) bis[2,6-di(*tert*-butyl)phenyl] disulfide, and (c) bis[2,6-di(pivaloylamino)phenyl] disulfide (**2**) in ϵ = 4.8 (chloroform).

Similar calculations were performed for the simulation of the S−S−C−C inversion process. The energy barriers are compared with those for the S−S inversion process in Table 2. The calculations (grid rotations for each 1° from 0° to 180°) indicate the presence of a slightly higher energy barrier ($\Delta G^{\ddagger} = 18.7 \pm 0.8$ kcal/mol at 300 K) in a low dielectric constant solvent (ϵ = 4.8). Comparison between the S−S and the S−C inversion processes suggests that the S−S process is predominant for **2**.

The strong solvation in **2** leads to a coalescence of peaks upon addition of Me$_2$SO-d_6 to a CDCl$_3$ solution. The calculated barrier for the inversion process in Me$_2$SO using a dielectric constant ϵ = 48.7 is 12 kcal/mol, which reflects fast exchange on the ^{1}H NMR time scale. In a high dielectric constant solvent, the S−C inversion

Table 2. Calculated Torsional Energy Barriers for S−S or S−C Inversion in 2, Bis[2,6-di(*tert*-butyl)phenyl] Disulfide, and 3 at 300 K (ϵ = 4.8)

	energy barrier (kcal/mol)	
disulfide	S−S inversion	S−C inversion
bis[2,6-di(pivaloylamino)phenyl] disulfide (**2**)	16.8 ± 0.8	18.7 ± 0.8
bis[2,6-di(*tert*-butyl)phenyl] disulfide	18.9 ± 0.2	15.2 ± 0.2
bis[2,6-di(triphenylacetylamino)phenyl] disulfide (**3**)	180 ± 8	14.8 ± 0.2

process presumably becomes dominant due to the lack of charge interaction between the amide NH and sulfur. For the simulation in Me_2SO, we could not succeed in obtaining any results by molecular mechanics, since over 100 Me_2SO molecules would be involved in the system.

Bis[2,6-di(*tert*-butyl)phenyl] disulfide has a stable conformer in the range 98−105° for the S−S torsion angle (Figure 7b). A preferable inversion process probably occurs over the trans S−S torsional barrier (calculated as 18.9 ± 0.2 kcal/mol at 300 K). The calculated energy barrier for the S−C inversion is 15.2 ± 0.2 kcal/mol at 300 K, close to the experimental value (16.3 kcal/mol at 327 K) reported for bis[2,4,6-tri(*tert*-butyl)phenyl] disulfide.[5]

In contrast, the energy minimization calculations for **3** with a grid change of the S−S torsional angle indicate the presence of two ranges, 80−90° and 160−180°, in which stable conformations exist, as shown in Figure7a. The most stable structure has an approximately trans C−S−S−C conformation, although in the crystal structure, a structure with a relatively large S−S torsional angle (104.3°) is observed as in Figure 2. However, the calculated S−S torsional energy barrier (180 ± 8 kcal/mol) is too high, as illustrated in Figure 7a. Therefore, another S−C inversion process is preferred since a relatively small inversion energy ($\Delta G^{\ddagger}$ = 12.6 kcal/mol) was experimentally obtained by the ^1H NMR analysis of **3** in $CDCl_3$.

We similarly examined the S−C inversion process theoretically. The S−C torsional energy barriers for **3** are listed in Table 2 together with the calculated S−S torsional energy barriers. A small energy barrier (14.8 ± 2.0 kcal/mol) was estimated for the S−C inversion process of **3** and corresponds to the value obtained by ^1H NMR analysis. The molecular mechanics results indicate that low temperature coalescence of ^1H NMR signals for **3** is predominantly subjected to the S−C torsional inversion process. A conformer with the highest energy barrier during the S−C torsional inversion in **3** adopts an approximately 180° C−S−S−C torsional angle.

In conclusion, those novel bulky disulfides with two amide NH groups at the 2,6-positions serve as a unique type of sterically congested organic disulfide. The charge interaction between the amide NH and sulfur makes it susceptible to solvation by polar donor atoms.

Acknowledgment. Support of this work by a Grant-in-Aid for Specially Promoted Research (06101004) from the Ministry of Education, Science and Culture of Japan as well as the financial assistance by Ogasawara Science Foundation is gratefully acknowledged.

Supporting Information Available: Figures for the complete line shape analysis (2 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.

JO941883D