Available online at www.sciencedirect.com
SCIENCE DIRECT
Tetrahedron
Tetrahedron 62 (2006) 8458–8462

# Four different types of hydrogen bonds observed in 1,2-bis(*N*-benzenesulfonylamino)benzenes due to conformational properties of the sulfonamide moiety

Takako Kato,[a] Hyuma Masu,[a] Hiroaki Takayanagi,[b] Eisuke Kaji,[b] Kosuke Katagiri,[a] Masahide Tominaga[a] and Isao Azumaya[a,*]

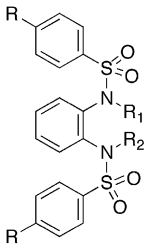
[a]*Faculty of Pharmaceutical Sciences at Kagawa Campus, Tokushima Bunri University, 1314-1 Shido, Sanuki, Kagawa 769-2193, Japan*
[b]*School of Pharmaceutical Sciences, Kitasato University, 5-9-1 Minato-ku, Shirokane, Tokyo 108-8641, Japan*

Received 31 May 2006; revised 21 June 2006; accepted 23 June 2006
Available online 18 July 2006

**Abstract**—The crystal structures of 1,2-bis(*N*-benzenesulfonylamino)benzenes with secondary and/or tertiary sulfonamide groups were determined by X-ray crystallographic analysis. Every Ar-sulfonamide group existed in synclinal conformation in the crystals even though it was secondary or tertiary. Each compound showed different types of hydrogen bonds in the crystal structure. 1,2-Bis(*N*-benzenesulfonylamino)-benzene (**1**) formed two double hydrogen bonds connected to the next molecules, 1-(*N*-benzenesulfonylamino)-2-(*N*-benzenesulfonyl-*N*-methylamino)benzene (**2**) contained double hydrogen bond involved by both the sulfonamide moieties, 1,2-bis(*N*-4-toluenesulfonylamino)-benzene (**3**) had both intra- and intermolecular hydrogen bonds, and 1-(*N*-methyl-*N*-4-toluenesulfonylamino)-2-(*N*-4-toluenesulfonylamino)-benzene (**4**) had one double hydrogen bond involved by only one sulfonamide moiety. Sulfonamides **1** and **3** formed infinite arrays of the molecules, and sulfonamides **2** and **4** formed racemic dimer of their conformational enantiomers via the hydrogen bonds.


## 1. Introduction

An aromatic sulfonamide moiety is one of the important structural fragments that is commonly seen in biologically active compounds.[1] Recently, several groups have used the aromatic sulfonamide structure to construct molecular recognition molecules,[2] or nanoporous networks in crystalline states.[3] Although Adsmond and Grant[4] discussed hydrogen bonding topology and Näther et al. reported on effects of the crystal solvent on the conformation of *p*-phenylenediamine derivatives with secondary sulfonamides,[5] the conformational properties of aromatic sulfonamides have not been well studied compared to the stereochemistry of the aromatic amides.[6,7] We investigated *o*-phenylenediamine derivatives showing interesting optical properties in the crystalline state,[8] and confirmed that the sulfonamide moiety of *o*-phenylenediamine derivatives existed in synclinal conformation[8d] even though the sulfonamide was secondary or tertiary. Due to this synclinal conformation, that is, by directing the amide hydrogen and the sulfonyl oxygen to the same side, secondary sulfonamides of *o*-phenylenediamine can form double hydrogen bonds intermolecularly.




| | R | $R_1$ | $R_2$ |
|---|---|---|---|
| **1** | H | H | H |
| **2** | H | $CH_3$ | H |
| **3** | $CH_3$ | H | H |
| **4** | $CH_3$ | $CH_3$ | H |

In this study, we demonstrated that four different types of hydrogen bonds resulting from a combination of inter- and/or intramolecular and single or self-complementary double hydrogen bonds formed in the crystals of aromatic sulfonamides of *o*-phenylenediamine.

## 2. Results and discussion

The crystal structure of 1,2-bis(*N*-benzenesulfonylamino)-benzene (**1**) was very recently reported by Bryan et al.[9]

*Keywords*: Aromatic sulfonamide; Synclinal conformation; Hydrogen bond; X-ray structure.
* Corresponding author. Tel.: +81 87 894 5111x6308; fax: +81 87 894 0181; e-mail: azumayai@kph.bunri-u.ac.jp

0040–4020/$ - see front matter © 2006 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2006.06.087

**Table 1**. Crystal data for compounds **2**–**4**

| Crystal | **2** | **3** | **4** |
|---|---|---|---|
| Formula | $C_{19}H_{18}N_2O_4S_2$ | $C_{20}H_{20}N_2O_4S_2$ | $C_{21}H_{22}N_2O_4S_2$ |
| Mol wt | 402.47 | 416.09 | 430.53 |
| Crystal system | Monoclinic | Orthorhombic | Triclinic |
| Space group | $P2_1/n$ | $Pccn$ | $P$-1 |
| $a$ (Å), $\alpha$ (°) | 12.9598 (7) | 37.065 (8) | 10.0135 (7), 90.9480 (10) |
| $b$ (Å), $\beta$ (°) | 11.2294 (6), 93.0170 (10) | 8.4075 (18) | 10.2644 (8), 92.9720 (10) |
| $c$ (Å), $\gamma$ (°) | 13.4081 (7) | 13.006 (3) | 10.7915 (8), 108.3800 (10) |
| $V$ (Å$^3$) | 1948.59 (18) | 4053.0 (15) | 1050.55 (13) |
| $D_c$ (Mg m$^{-3}$) | 1.372 | 1.365 | 1.361 |
| $Z$ | 4 | 8 | 2 |
| $R_1$ [$I>2\sigma(I)$] | 0.0378 | 0.0560 | 0.0420 |
| $wR_2$ [$I>2\sigma(I)$] | 0.0920 | 0.1383 | 0.1026 |
| CCDC no. | 607420 | 607418 | 607419 |

The other 1,2-bis(*N*-benzenesulfonylamino)benzenes (**2**–**4**) were prepared from *o*-phenylenediamine or *N*-methyl-1,2-phenylenediamine and corresponding sulfonyl chlorides. For each compound, recrystallization from ethyl acetate produced colorless prisms, which were suitable for X-ray crystallographic analysis. Crystal data are summarized in Table 1.

The crystal of 1,2-bis(*N*-benzenesulfonylamino)benzene (**1**) belonged to the space group $P2_1/c$.[9] This compound has two secondary sulfonamide bonds that form S═O···H–N hydrogen bonds. In the crystal, a complementary double hydrogen bond between adjacent molecules was observed, and both enantiomeric conformers were alternately arranged by double hydrogen bonds, forming an infinite chain of molecules (Table 2, Fig. 1a) as reported in Ref. 9. The crystal of 1-(*N*-benzenesulfonylamino)-2-(*N*-benzenesulfonyl-*N*-methylamino)benzene (**2**) belonged to the space group $P2_1/n$. In this compound, one of the two sulfonamide bonds is secondary, and the other is tertiary. In the crystal, both enantiomers formed dimer through a self-complementary double hydrogen bond between the amide proton of the secondary sulfonamide group and the oxygen of the tertiary sulfonamide group, but not the oxygen of the secondary sulfonamide group (Table 2, Fig. 1b). The crystal of 1,2-bis(*N*-4-toluenesulfonylamino)-benzene (**3**), which has two same secondary sulfonamide groups as compound **1**, belonged to the space group *Pccn*. In the crystal, two sulfonamide bonds were involved in both intra- and intermolecular hydrogen bonds (Table 2, Fig. 1c). Both enantiomers were alternately arranged, and formed an infinite chain structure through single intermolecular hydrogen bond. The crystal of 1-(*N*-methyl-*N*-4-toluenesulfonylamino)-2-(*N*-4-toluenesulfonylamino)-benzene (**4**), which contains secondary and tertiary sulfonamide bonds, as well as compound **2**, does belong to the space group *P*-1. In the crystal, both enantiomers formed dimer through a self-complementary double hydrogen bond between the two secondary sulfonamide moieties (Table 2, Fig. 1d). Although this double hydrogen bond was intrinsically the same as that of compound **1**, the infinite hydrogen bonding array was not observed because the tertiary sulfonamide group terminated the intermolecular hydrogen bonds.

Each crystal contained pairs of both conformational enantiomers in the unit cell in contrast to the crystal of 1,2-bis(*N*-benzenesulfonyl-*N*-methylamino)benzene, which had single enantiomers in the unit cell.[8d] In addition, each sulfonamide moiety of all compounds existed in the synclinal conformation in crystals even though the sulfonamide group was secondary or tertiary (Fig. 2, Table 3). Therefore, the S═O and the N–H bonds of the secondary sulfonamide groups were located in the same directions on the sulfonamide bond, the sulfur atom of which had a tetrahedral geometry, and the nitrogen atom of which had a trigonal geometry, providing an intermolecular hydrogen bonding network.

**Table 2**. Hydrogen bond geometry (Å, °) in compounds **1**–**4**

| | D–H···A | $d$(D–H) | $d$(H···A) | $d$(D···A) | D–H···A |
|---|---|---|---|---|---|
| **1**[a] | N1–H1···O2[b] | 0.79(2) | 2.15(2) | 2.9310(19) | 169(2) |
| | N2–H2···O3[c] | 0.814(19) | 2.275(19) | 3.0318(18) | 154.8(19) |
| **2** | N1–H1···O4[d] | 0.73(2) | 2.38(2) | 3.068(2) | 157(2) |
| **3** | N1–H1···O3[e] | 0.75(4) | 2.24(4) | 2.992(4) | 176(4) |
| | N2–H2···O1 | 0.75(3) | 2.31(3) | 2.885(4) | 135(3) |
| **4** | N1–H1···O1[f] | 0.82(2) | 2.34(2) | 3.084(2) | 151(2) |

[a] Ref. 9.
[b] Symmetry code: $-x+1, -y+1, -z$.
[c] Symmetry code: $-x+2, -y+1, -z$.
[d] Symmetry code: $-x+1, -y+2, -z$.
[e] Symmetry code: $x, -y+3/2, z+1/2$.
[f] Symmetry code: $-x+2, -y+1, -z+1$.

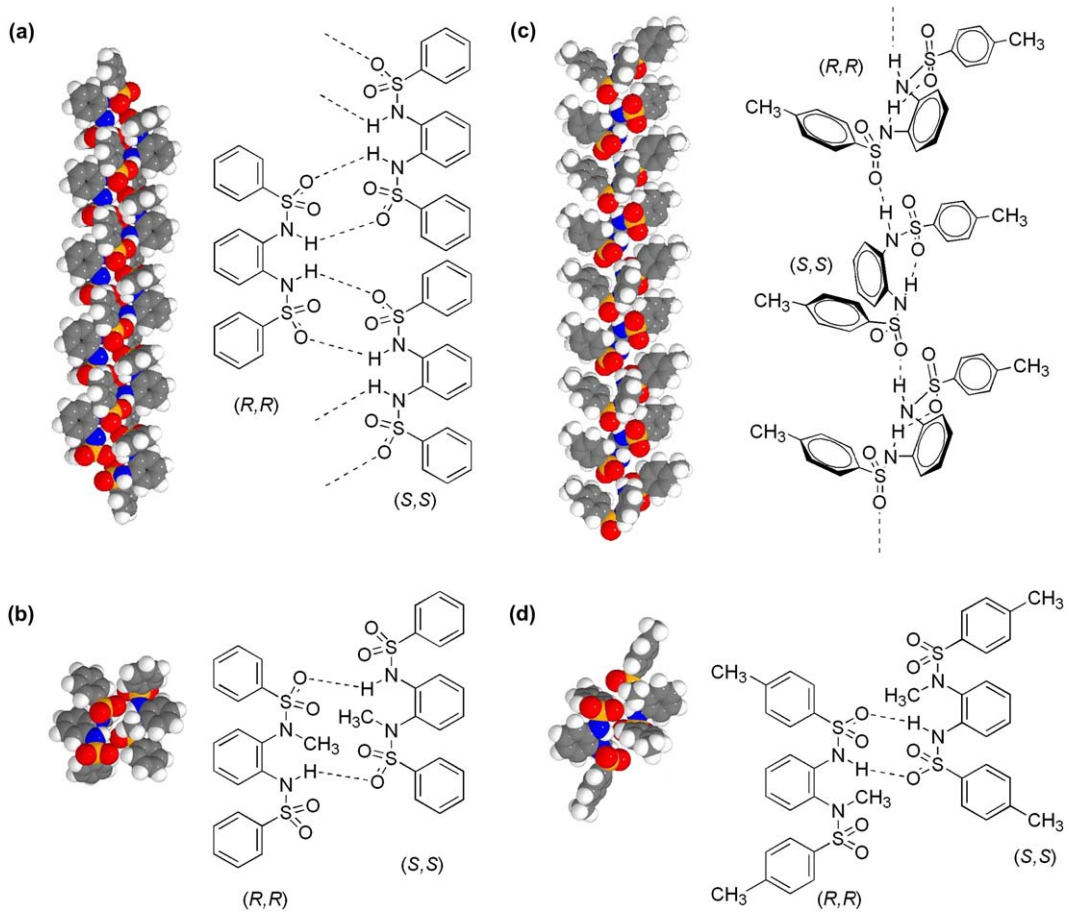



**Figure 1**. Spacefilling models of molecules, which formed hydrogen bonds in the crystal, their schematic representations of compounds (a) **1**,[9] (b) **2**, (c) **3**, and (d) **4**.

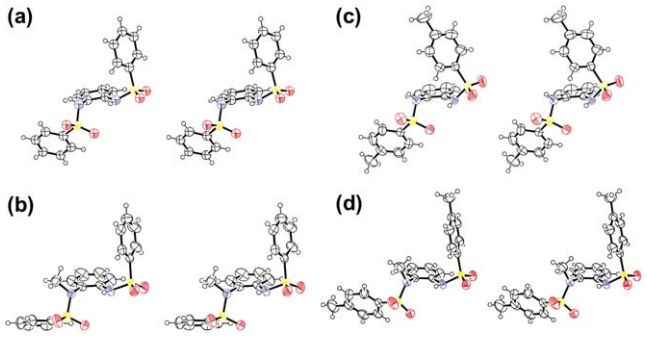



**Figure 2**. ORTEP stereoviews of compounds (a) **1**,[9] (b) **2**, (c) **3**, and (d) **4**. The thermal ellipsoids are drawn at the 50% probability level.

**Table 3**. Torsion angle (°) of sulfonamides in compounds **1–4**

| | **1**[a] | **2** | **3** | **4** |
|---|---|---|---|---|
| Ar–N($R^1$)–S–Ar | −65.23 | −68.20 | −63.98 | −72.88 |
| Ar–N($R^2$)–S–Ar | 61.36 | 59.87 | 60.31 | 60.51 |

[a] Ref. 9.

## 3. Conclusion

In conclusion, we demonstrated the existence of four different types of hydrogen bonds resulting from a combination of inter- and/or intramolecular and single or complementary double hydrogen bonds in crystals of aromatic sulfonamides of *o*-phenylenediamine. The sulfonamide moieties existed in synclinal conformations even though the sulfonamide was secondary or tertiary, producing various types of hydrogen bonds. A sulfonamide has the potential to construct 2-D or 3-D networks through intermolecular hydrogen bonds especially because of the synclinal conformation of secondary sulfonamides, which allows the arrangement of the amide hydrogen and sulfonyl oxygen in the same directions. We are currently exploring the supramolecular chemistry of macrocycles containing aromatic sulfonamide moieties, and the unique molecular array of aromatic sulfonamides resulting from intra- or intermolecular interactions such as hydrogen bonds, CH–π interactions, and π–π interactions in crystals.

## 4. Experimental

### 4.1. 1-(*N*-Benzenesulfonylamino)-2-(*N*-benzenesulfonyl-*N*-methylamino)benzene (2)

Benzenesulfonyl chloride (0.64 mL, 5.0 mmol) was added dropwise to a solution of *N*-methyl-1,2-phenylenediamine (0.23 mL, 2.0 mmol) in dry $CH_2Cl_2$ (20 mL) and pyridine (0.81 mL) at 0 °C, with stirring under Ar atmosphere. After stirring at room temperature for 2 h, benzenesulfonyl chloride (0.26 mL, 2.0 mmol) was added once again to the

reaction mixture. After 2.5 h, the reaction mixture was poured into ice, and was extracted with $CH_2Cl_2$ (50 mL). The organic layer was successively washed with 2 M HCl (10 mL), brine (15 mL), and dried over $Na_2SO_4$. The solvent was evaporated. The crude product was recrystallized from $CH_2Cl_2$ and methanol to produce pure 1-(*N*-benzenesulfonylamino)-2-(*N*-benzenesulfonyl-*N*-methylamino)benzene (0.78 g, 96%). Mp 156 °C. IR (KBr) $\nu$ 1180, 1350, 3280 $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ 2.50 (s, 3H), 6.17 (dd, $J$=8.0, 1.6 Hz, 1H), 6.89–6.95 (m, 1H), 7.24–7.31 (m, 1H), 7.40–7.56 (m, 7H), 7.58–7.64 (m, 1H), 7.71 (dd, $J$=8.0, 2.0 Hz, 1H), 7.79–7.84 (m, 2H), 7.98 (s, 1H). $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$ 38.9, 125.1, 125.8, 126.1, 127.4, 128.2, 128.9, 129.2, 132.8, 133.5, 133.6, 134.7, 135.2, 139.9. MS (FAB): $m/z$=403 $[M+H]^+$. HRMS Calcd for $C_{19}H_{18}N_2O_4S_2Na$ $[M+Na]^+$: 425.0605. Found 425.0616. Anal. Calcd for $C_{19}H_{18}N_2O_4S_2$: C, 56.70; H, 4.51; N, 6.96. Found: C, 56.70; H, 4.52; N, 6.90.

### 4.2. 1,2-Bis(*N*-4-toluenesulfonylamino)benzene (3)

4-Toluenesulfonyl chloride (0.95 g, 5.0 mmol) was added to a solution of *o*-phenylenediamine (0.22 g, 2.0 mmol) in pyridine (20 mL) at 0 °C, with stirring under Ar atmosphere. After stirring at room temperature for 3 h, 4-toluenesulfonyl chloride (0.19 g, 1.0 mmol) was added once again to the reaction mixture. After 5.5 h, the reaction mixture was poured into ice, and was extracted with AcOEt (50 mL). The organic layer was washed with 2 M HCl (10 mL), brine (10 mL), saturated $NaHCO_3$ aq (10 mL), brine (10 mL×2), and dried over $Na_2SO_4$. The solvent was evaporated. The crude product was recrystallized from $CH_2Cl_2$ and *n*-hexane to give pure 1,2-bis(*N*-4-toluenesulfonylamino)benzene (0.67 g, 81%). Mp 206 °C (lit.[10] 204–205 °C). IR (KBr) $\nu$ 1150, 1320, 3210 $cm^{-1}$. $^1H$ NMR (400 MHz, DMSO): $\delta$ 2.33 (s, 6H), 6.87–6.93 (m, 2H), 6.93–6.99 (m, 2H), 7.30 (d, $J$=8.0 Hz, 4H), 7.56 (d, $J$=8.0 Hz, 4H), 9.23 (br s, 2H). $^{13}C$ NMR (100 MHz, DMSO): $\delta$ 21.0, 122.6, 125.1, 126.9, 129.6, 130.2, 136.5, 143.3. MS (FAB): $m/z$=417 $[M+H]^+$. HRMS Calcd for $C_{20}H_{20}N_2O_4S_2Na$ $[M+Na]^+$: 439.0762. Found 439.0775. Anal. Calcd for $C_{20}H_{20}N_2O_4S_2$: C, 57.67; H, 4.84; N, 6.73. Found: C, 57.60; H, 4.90; N, 6.72.

### 4.3. 1-(*N*-Methyl-*N*-4-toluenesulfonylamino)-2-(*N*-4-toluenesulfonylamino)benzene (4)

4-Toluenesulfonyl chloride (0.95 g, 5.0 mmol) was added dropwise to a solution of *N*-methyl-1,2-phenylenediamine (0.23 mL, 2.0 mmol) in dry $CH_2Cl_2$ (20 mL) and pyridine (0.81 mL) at 0 °C, with stirring under Ar atmosphere. After stirring at room temperature for 3.3 h, 4-toluenesulfonyl chloride (0.38 g, 2.0 mmol) was added once again to the reaction mixture. After 2 h, the reaction mixture was poured into ice, and was extracted with $CH_2Cl_2$ (50 mL). The organic layer was successively washed with 2 M HCl (10 mL), brine (10 mL), and dried over $Na_2SO_4$. The solvent was evaporated. The crude product was recrystallized from $CH_2Cl_2$ and methanol to give pure 1-(*N*-methyl-*N*-4-toluenesulfonylamino)-2-(*N*-4-toluenesulfonylamino)benzene (0.66 g, 77%). Mp 138–140 °C. IR (KBr) $\nu$ 1173, 1347, 3247 $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ 2.36 (s, 3H), 2.43 (s, 3H), 2.56 (s, 3H), 6.91 (ddd, $J$=7.8, 7.8, 1.4 Hz, 1H), 7.21–7.29 (m, 5H), 7.39 (ddd, $J$=8.3, 1.8, 1.8 Hz, 2H), 7.65–7.73 (m, 3H), 7.93 (s, 1H). $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$ 21.5, 21.6, 38.9, 124.5, 125.4, 126.2, 127.5, 128.3, 129.1, 129.5, 129.6, 132.0, 133.5, 135.5, 137.0, 143.6, 144.5. MS (FAB): $m/z$=431.2 $[M+H]^+$. Anal. Calcd for $C_{21}H_{22}N_2O_4S_2$: C, 58.58; H, 5.15; N, 6.51. Found: C, 58.84; H, 4.97; N, 6.55.

### 4.4. X-ray crystallographic study

X-ray data were collected on Bruker ApexII CCD detector (for compounds **2** and **4**) and Bruker Smart1000 CCD detector (for compound **3**) with graphite monochromated Mo $K_\alpha$ ($\lambda$=0.71073 Å) radiation at room temperature. The crystal structures were solved by direct methods SHELXS-97 (Sheldrick, 1997) and refined by full-matrix least-squares SHELXL-97 (Sheldrick, 1997). All non-hydrogen atoms were refined anisotropically. The sulfonamide hydrogen atoms were located in a difference map and their coordinates were refined. Other hydrogen atoms were included as their calculated positions.

## Acknowledgements

This work was supported by Grant-in-aid for Scientific Research (C) (No. 16590011) from the Japan Society for the Promotion of Science and the Sasakawa Scientific Research Grant from The Japan Science Society.

## References and notes

1. (a) Maren, T. H. *Annu. Rev. Pharmacol. Toxicol.* **1976**, *16*, 309–327; (b) Scozzafava, A.; Owa, T.; Mastrolorenzo, A.; Supuran, C. T. *Curr. Med. Chem.* **2003**, *10*, 925–953; (c) Supuran, C. T.; Scozzafava, A.; Casini, A. *Carbonic Anhydrase—Its Inhibitors and Activators*; Supuran, C. T., Scozzafava, A., Conway, J., Eds.; CRC: Boca Raton, FL, 2004; pp 67–147.
2. (a) Morzherin, Y.; Rudkevich, D. M.; Verboom, W.; Reinhoudt, D. N. *J. Org. Chem.* **1993**, *58*, 7602–7605; (b) Kondo, S.; Suzuki, T.; Yano, Y. *Tetrahedron Lett.* **2002**, *43*, 7059–7061; (c) Kavallieratos, K.; Rosenberg, J. M.; Chen, W.-Z.; Ren, T. *J. Am. Chem. Soc.* **2005**, *127*, 6514–6515; (d) He, L.; An, Y.; Yuan, L.; Yamato, K.; Feng, W.; Gerlitz, O.; Zheng, C.; Gong, B. *Chem. Commun.* **2005**, 3788–3790.
3. (a) Hu, Z.-Q.; Chen, C.-F. *Chem. Commun.* **2005**, 2445–2447; (b) Hu, Z.-Q.; Chen, C.-F. *Tetrahedron* **2006**, *62*, 3446–3454.
4. Adsmond, D. A.; Grant, D. J. W. *J. Pharm. Sci.* **2001**, *90*, 2058–2077.
5. Bock, H.; Nagel, N.; Näther, C. *Chem.—Eur. J.* **1999**, *5*, 2233–2236.
6. (a) Pedersen, B. F.; Pedersen, B. *Tetrahedron Lett.* **1965**, 2995–3001; (b) Bourn, A. J. R.; Gillies, D. G.; Randall, E. W. *Tetrahedron* **1966**, *22*, 1825–1829; (c) Stewart, W. E.; Siddall, T. H., III. *Chem. Rev.* **1970**, *70*, 517–551; (d) Nanjan, M. J.; Kannappan, V.; Genesan, R. *Indian J. Chem.* **1979**, *18B*, 461–463.
7. (a) Itai, A.; Toriumi, Y.; Tomioka, N.; Kagechika, H.; Azumaya, I.; Shudo, K. *Tetrahedron Lett.* **1989**, *30*, 6177–6180; (b) Azumaya, I.; Kagechika, H.; Fujiwara, Y.; Itoh, M.; Yamaguchi, K.; Shudo, K. *J. Am. Chem. Soc.* **1991**, *113*, 2833–2838; (c) Yamaguchi, K.; Matsumura, G.; Kagechika, H.; Azumaya, I.; Ito, Y.; Itai, A.; Shudo, K. *J. Am. Chem.*

*Soc.* **1991**, *113*, 5474–5475; (d) Itai, A.; Toriumi, Y.; Saito, S.; Kagechika, H.; Shudo, K. *J. Am. Chem. Soc.* **1992**, *114*, 10649–10650; (e) Azumaya, I.; Kagechika, H.; Yamaguchi, K.; Shudo, K. *Tetrahedron* **1995**, *51*, 5277–5290; (f) Tanatani, A.; Yamaguchi, K.; Azumaya, I.; Fukutomi, R.; Shudo, K.; Kagechika, H. *J. Am. Chem. Soc.* **1998**, *120*, 6433–6442.

8. (a) Azumaya, I.; Yamaguchi, K.; Okamoto, I.; Kagechika, H.; Shudo, K. *J. Am. Chem. Soc.* **1995**, *117*, 9083–9084; (b) Azumaya, I.; Okamoto, I.; Nakayama, S.; Tanatani, A.; Yamaguchi, K.; Shudo, K.; Kagechika, H. *Tetrahedron* **1999**, *55*, 11237–11246; (c) Azumaya, I.; Okamoto, I.; Takayanagi, H. *Anal. Sci.* **2003**, *19*, x3–x4, X-page; (d) Azumaya, I.; Kato, T.; Okamoto, I.; Yamasaki, R.; Tanatani, A.; Yamaguchi, K.; Kagechika, H.; Takayanagi, H. *Org. Lett.* **2003**, *5*, 3939–3942.
9. Bryan, J. C.; Rosenberg, J. M.; Kavallieratos, K. *Acta Crystallogr.* **2005**, *E61*, o396–o397.
10. Cheeseman, G. W. H. *J. Chem. Soc.* **1955**, 3308–3310.