Articles

Molecular Association of 2,3-Dihydro-2-alkyl-3-hydroxybenzisothiazole 1,1-Dioxides: Formation of Novel Bicyclic Dimers Containing 12/14-Membered Rings†

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2,3-Dihydro-3-hydroxybenzisothiazole 1,1-dioxides constitute a self-complementary hydrogen-bond donor−acceptor system. 2,3-Dihydro-2-isopropyl-3-hydroxybenzisothiazole 1,1-dioxide exhibits interesting concentration and temperature-dependent NMR spectra due to association in solution. The intermolecular association of these molecules through S−O···H−O interactions resulting in the formation of novel hydrogen-bonded dimers containing 12/14-membered bicyclic bridge is revealed by X-ray crystallography. X-ray crystallographic studies also confirm the existence of *N*-alkyl-2-formylbenzenesulfonamides exclusively as 2,3-dihydro-2-alkyl-3-hydroxybenzisothiazole 1,1-dioxides in the solid state.

Introduction

An understanding of noncovalent interactions between molecules is essential for the development of new materials and supramolecular assemblies. Compounds possessing hydrogen-bonding groups such as carboxylic acids, amides, ureas, imines, sulfonamides have been extensively studied[1] and several artificial receptors and molecules with catalytic properties have been synthesized.[2] However, the search for new molecules that associate to form supramolecular structures continues. Most organic molecules that form dimers through hydrogen bonding give rise to a cyclic array of eight atoms. Hydrogen-bonded dimers containing a cyclic array of more than eight atoms are seldom encountered.[3] We had

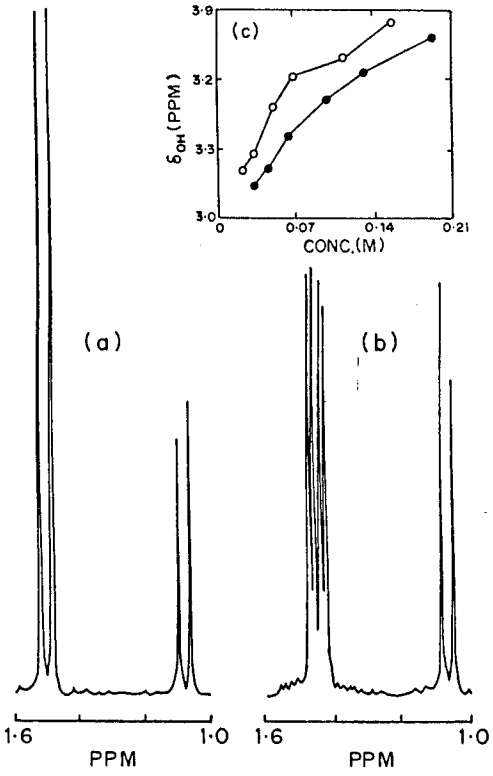

Figure 1. ^{1}H NMR spectral regions corresponding to the absorptions of the isopropyl methyl groups of **2** and **5**: (a) 0.016 M of **2** and 0.045 M of **5**, (b) 0.070 M of **2** and 0.194 M of **5**, and (c) variation of ^{1}H NMR chemical shift of the OH proton of **5** and **6** with concentration: filled circles for **5** and open circles for **6**.

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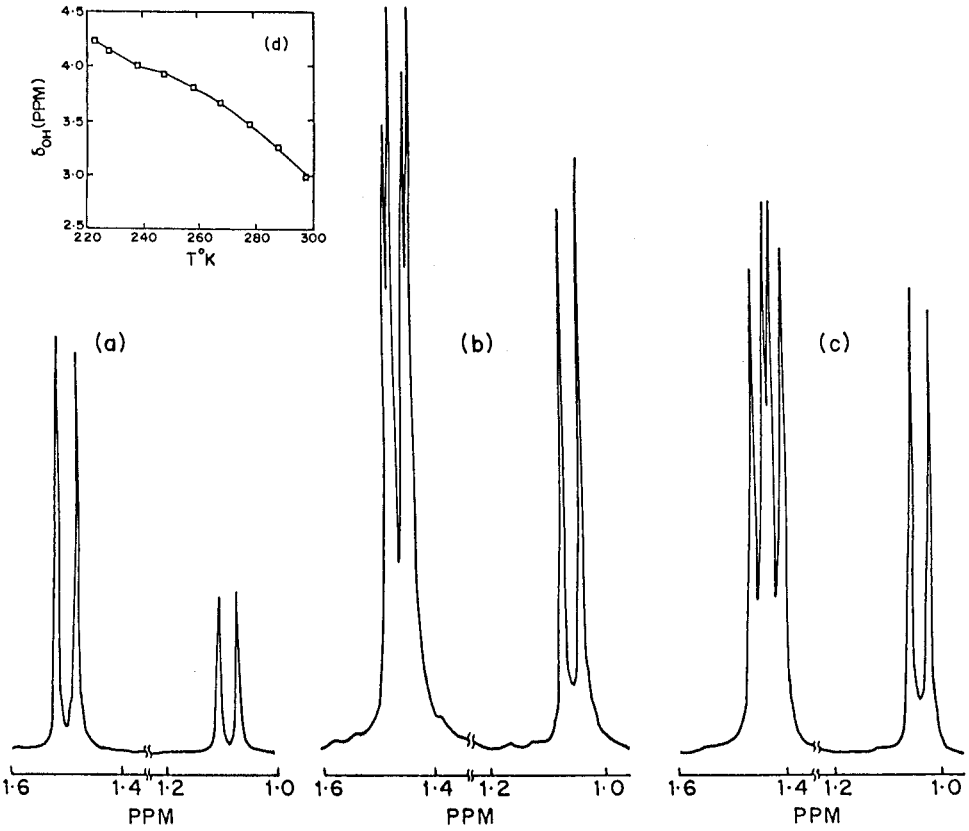

Figure 2. [1]H NMR spectral regions corresponding to the isopropyl methyl groups of **5** (0.052 M) at different temperatures: (a) 298 K, (b) 268 K, (c) 248 K, and (d) variation of [1]H NMR chemical shift of OH proton of **5** (0.052M) with temperature.

Scheme 1

1 R = *n*-propyl
2 R = isopropyl
3 R = *t*-butyl

4 R = *n*-propyl
5 R = isopropyl
6 R = *t*-Butyl

earlier reported[4] the synthesis and study of the ring−chain tautomerism of 2-formylbenzenesulfonamide ↔ 2,3-dihydro-2-alkyl-3-hydroxybenzisothiazole 1,1-dioxide system in solid, liquid, and gas phases (Scheme 1). We herein report spectroscopic and X-ray crystallographic studies on the molecular association of 2,3-dihydro-2-alkyl-3-hydroxybenzisothiazole 1,1-dioxides and show that they form novel hydrogen-bonded dimers in solid state through S═O···HO interactions. These dimers comprise of bicyclic array of 12/14 atoms.

Results and Discussion

NMR Spectroscopy. [1]H NMR spectra of the equilibrium mixture **2** ↔ **5** at different concentrations (at 298 K) and at different temperatures as well as the variation of OH proton chemical shift (of **5**) with concentration and temperature are shown in Figure 1 and Figure 2, respectively.

The [1]H NMR spectrum of an equilibrium mixture of isopropyl derivatives **2** ↔ **5** (10−20 mg/mL) showed two doublets for the isopropyl methyl groups of **2** and **5** at

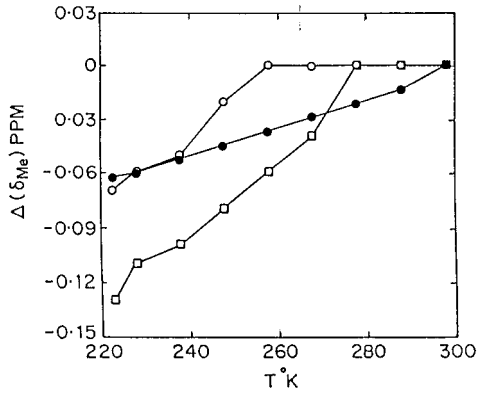

Figure 3. Plot of ($\delta_{Me,298K} - \delta_{Me,T}$) ppm for isopropyl groups of **2** and **5**: open circles for one of the methyl groups of **5**, squares for the second methyl groups of **5**, and filled circles for methyl groups of **2**.

1.1 and 1.5 ppm respectively,[5] indicating the equivalence of the two methyl groups in both the isomers. However, the [1]H NMR spectrum of the same equilibrium mixture at a higher concentration showed a doublet for the isopropyl methyl groups of **2** but two doublets for the isopropyl methyl groups of **5**. The lowest concentration at which the isopropylmethyl hydrogens of **5** exhibit nonequivalence is 24 mg/mL (0.028 M of **2** and 0.078 M of **5**) in $CDCl_3$. Variation of chemical shifts for the OH proton of the *tert*-butyl derivative **6** with concentration was similar to that of **5** (Figure 1c), but no change in the signal due to the *tert*-butyl group with increase in

(5) See ref 4 for a discussion on assignment of peaks due to open and cyclic forms, in the NMR spectra of compounds under study.

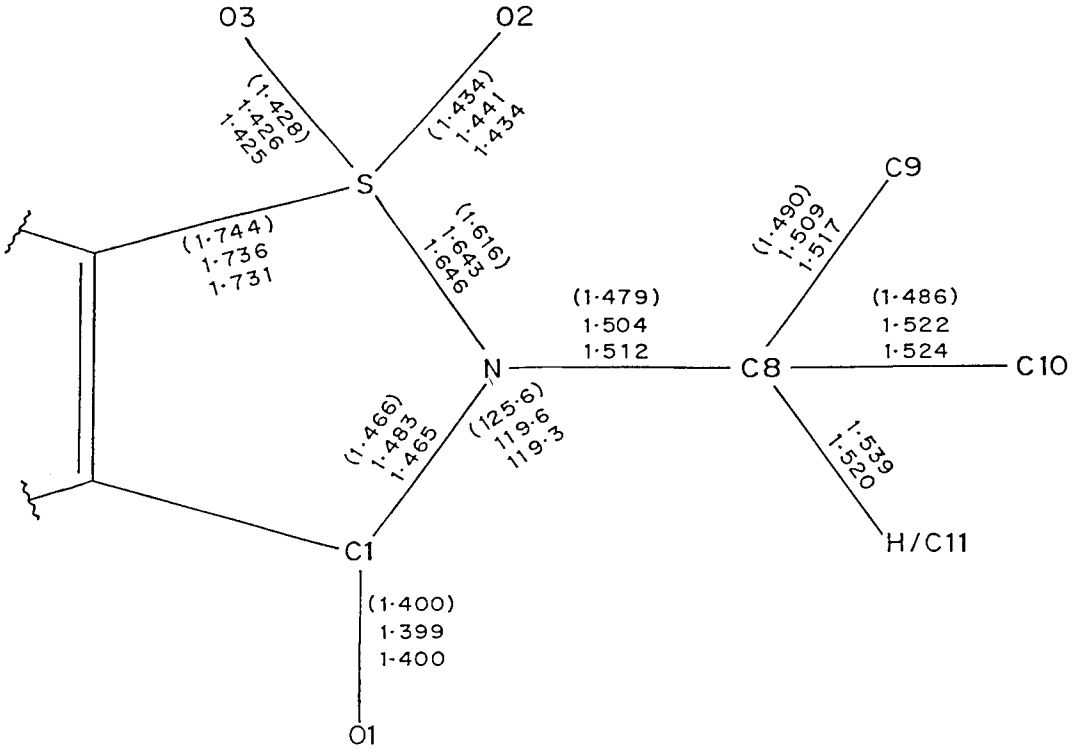

Figure 4. Selected bond lengths (Å) and angles (deg) shown against the molecular diagram (the upper value, in parentheses, is for **5**, and the lower ones are for the two molecules of **6**). The standard deviations are in the range 0.002−0.006 Å and 0.3°, respectively.

concentration was observed.[6] It is important to note that changes in the ^{1}H NMR spectra of **5** due to variation in temperature is similar (but with a larger magnitude) to the changes observed on varying the concentration.

A plot of the difference in chemical shift of the isopropyl methyl groups of **5** ($\delta_{Me,298K} - \delta_{Me,T}$) versus temperature (Figure 3) showed a greater shielding of one of the isopropyl methyl groups compared to the other. A similar plot for the sulfonamide **2** is shown for comparison. The isopropyl methyl groups of **5** are diastereotopic due to the presence of a chiral center at the benzylic position, which should have resulted in different chemical shifts for them, irrespective of their concentration.[7] However, accidental equivalence of diastereotopic groups is not uncommon.[8] The observed changes in the ^{1}H NMR spectra of **5** with variation of solvent[9] and temperature can be accounted for (based on accidental equivalence) since the chemical shift of diastereotopic groups is known to depend on various factors including solvent and temperature, but the sign and magnitude of these changes cannot be predicted with ease.[8] Since diastereotopicity is inherent to the structure of a molecule, the chemical shifts of such groups may not be expected to depend on concentration. However, molecular association might have an effect on the chemical shifts of diastereotopic methyl groups and result in changes observed in the NMR spectra of **5** with variation in concentration. This is supported by the fact that one of the isopropyl methyl groups of **5** is in close contact (Table 1) with the aromatic ring of the other molecule of the hydrogen-bonded dimer (see Figure 5). This could result in larger shielding of one of the isopropyl methyl groups of **5** due to the ring current effect[10] of the benzene ring. In the case of *tert*-butyl derivative **6**, none of the methyl groups is at a distance less than 4 Å (Table 1). Changes in the ^{1}H NMR spectra of 2,3-dihydro-2-alkyl-3-hydroxybenzisothiazole 1,1-dioxides discussed above could also result from the retardation of the rates of ring−chain tautomerism (Scheme 1) at higher concentration, due to molecular association through intermolecular hydrogen bonding between OH groups.[11,12]

Table 1. Geometric Parameters for the Alkyl Group Juxtaposed over the Benzene Ring within a Dimer

		distance (Å) between the methyl C and the benzene		
compd	methyl C	plane	centroid	C (nearest atom)
5	C(10)	3.665	3.932	3.676 (C4)
6[a]	C(10)	4.000	4.749	4.223 (C4)
	C(11)	4.212	4.376	4.250 (C6)
	C(10′)	4.000	4.761	4.230 (C4′)
	C(11′)	4.215	4.385	4.256 (C6′)

[a] For compound **6** values for both the molecules in the asymmetric unit are given. Although not within the dimer, C(9) and C(9′) of **6** have comparable close contact with symmetry-related benzene rings.

(6) A considerable change in the chemical shift (~1 ppm) for the OH proton of the *n*-propyl derivative **4** was observed on changing the concentration from 2 mg/mL to 40 mg/mL. But the exact chemical shift of the OH proton could not be obtained at intermediate concentrations due to the overlap of the OH peak with other peaks in the ^{1}H NMR spectra.

(7) The ^{13}C NMR spectrum of an equilibrium mixture of **2** ↔ **5** showed three peaks at 20.5 and 23.1 ppm (due to **5**) and 23.8 ppm (due to **2**) for the isopropyl methyl groups irrespective of the concentration.

(8) Jennings, W. B. *Chem. Rev. (Washington, D.C.)* **1975**, *75*, 307.

(9) Change of solvent from chloroform-*d* to methanol-d_4, DMSO-d_6, benzene-d_6 or acetone-d_6 resulted in the splitting of the isopropyl methyl group signal to two doublets in the ^{1}H NMR spectra.

(10) Haigh, C. W.; Mallion, R. B. in *Prog. NMR Spectrosc.* **1980**, *Vol. 13*, pp 303 and references cited there in.

(11) We thank one of the referees for drawing our attention to this aspect.

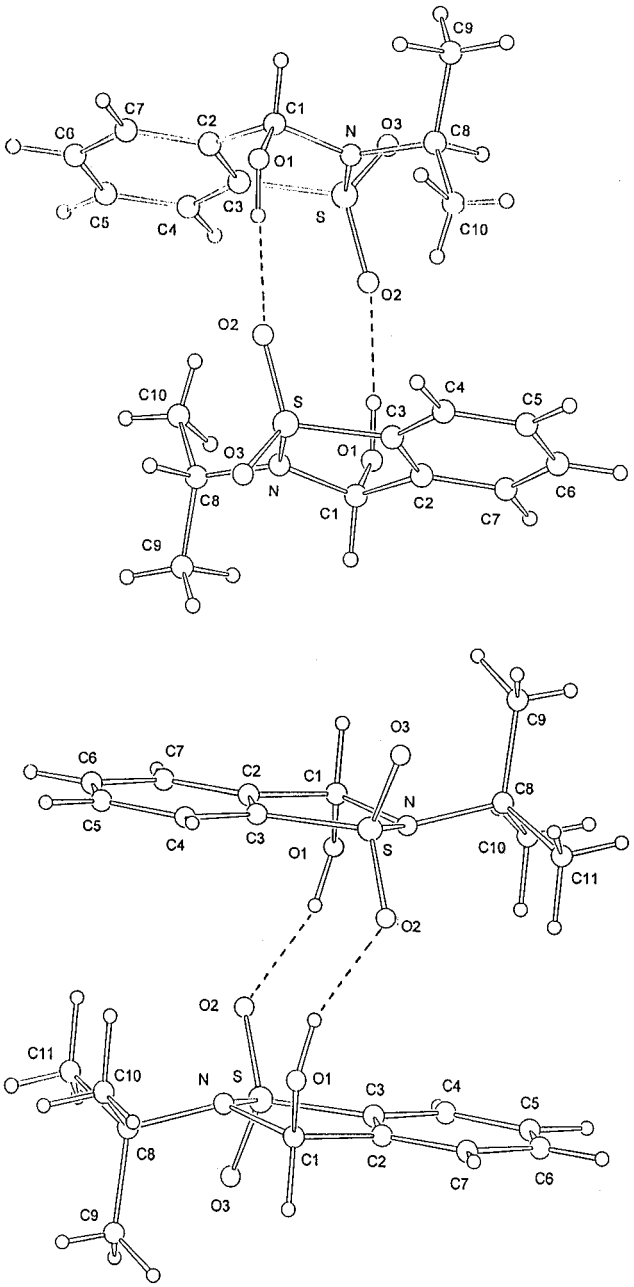

Figure 5. Pair of molecules related by inversion center and connected by hydrogen bonds (shown in dashed line) of (a) **5** and (b) **6**. Dimer arising out of only one molecule in the asymmetric unit is shown for the latter.

The results presented above indicate[13] association of 2,3-dihydro-2-alkyl-3-hydroxybenzisothiazoles in solution through hydrogen bonding at low temperatures (<273 K for **5**) or at high concentrations (>0.079 M for **5** and >0.070 M for **6** at 298 K). The nature of the aggregates of **5** or **6** present in solution is not obvious due to the presence of more than one type of hydrogen-bond acceptor in the compounds under study. Hence we carried out single-crystal X-ray structural analysis of **4**−**6**.

(12) This mode of intermolecular association should perhaps involve the N−H group of **2** (N−H···O−H) and result in a change in chemical shift for the N−H proton. The increase in chemical shift of the NH proton was about 0.14 δ with change of concentration from 0.016 to 0.070 M in $CDCl_3$ and about 0.50 δ with temperature between 238 K and 298 K for **2**.

(13) Intramolecular hydrogen bonding can however be ruled out since this would require OH chemical shift to be independent of concentration.

Table 2. Geometry of the Hydrogen-Bond Interactions in the Crystal

compd	atoms involved D−H···A	distance (Å) D···A	angle (deg) D−H···A
5	O(1)−H(O1)···O(2)[a]	2.806	164.18
6	O(1)−H(O1)···O(2)[b]	2.802	163.75
	O(1′)−H(O1′)···O(2′)[c]	2.809	169.77

Symmetry: [a] $-x, 2-y, -z$; [b] $1-x, 1-y, 1-z$; [c] $1-x, 2-y, -z$.

X-ray Crystallographic Analysis. The solid-state structures of **4**−**6** were revealed through X-ray crystallography.[14] The conformation of the isopropyl group in **5** is such that one of the methyl groups essentially eclipses the hydroxyl group, making the C8−H bond lie between the two sulfonyl oxygens. The eclipsing may be the reason for the widening of the C1−N−C8 angle (Figure 4). The conformation of the *tert*-butyl group in **6** is different from that of the isopropyl group by a rotation of 42°, such that one C8−CH_3 bond is nearly perpendicular (78°) to the ring (and on the side opposite to the OH group). Because of the more steric crowding due to the *tert*-butyl group in **6**, the S−N, N−C8, and C8−CH_3 distances are 0.02−0.03 Å longer than those of **5** (Figure 4).

In the crystal, molecules of **5** and **6** form compact dimers related by a crystallographic center of inversion (Figure 5). The dimers are held together by hydrogen bonding (Table 2); as the C1−O1 and S=O2 in the donor and acceptor sites have very comparable lengths, the hydrogen-bonded ring structure is quite symmetric.

However, other forces such as the CH/π interaction[15] can also provide stability, especially for **5**. As can be seen from Table 1, a methyl group comes very close to the face of the benzene ring of the partner. The two groups do not show such close contact in **6**, and there could be two reasons for this. First, because of the increase in a few bond lengths, as discussed above, the methyl groups in **6** go out of the periphery of the benzene ring of the centrosymmetrically related partner. Second, the conformation of the *tert*-butyl group is such that the methyl group which is nearly perpendicular to the ring and which could have the closest contact with the aromatic face of the partner is pointing in the opposite direction. The head-on orientation of a C−CH_3 group relative to the benzene ring in **5**, in contrast to the rather inclined positioning of two such groups in **6**, causes the two aromatic planes in the dimer to come closer (4.43 Å) in the latter than the former (5.02 Å).

A 16-membered hydrogen-bonded dimeric structure has been reported recently.[3a] In our case the hydrogen-bonded ring is 12- or 14-membered, depending on whether one traverses N or C3 and C2 while going from S to C1 along the cyclic hydrogen-bond motif. Another unique feature of this dimeric structure is the additional involvement of the CH/π interaction, which can play an important role in molecular association.[15] The hydrogen-

(14) The hydroxyl group (O1 and O1′) in both the molecules in the asymmetric unit of **4** occupy two disordered positions (in the ratio 8:2 and 6:4), and the *n*-propyl group has very high-temperature factors. The disorder is caused by both the enantiomorphic forms of the molecule occurring at the same position in the crystal, resulting in the hydroxyl group to appear at two places and the alkyl chain to have a diffused electron density. Because of the lesser accuracy of the structure it is no further included in our discussion.

(15) (a) Nishio, M.; Umezawa, Y.; Hirota, M.; Takeuchi, Y. *Tetrahedron* **1995**, *51*, 8665. (b) Dougherty, D. A. *Science* **1996**, *271*, 163.

bonded aromatic systems, like the DNA bases, usually form planar structures; but here is a system where the hydrogen bonding is in a direction normal to the two rings arranged in a parallel fashion.

In conclusion, we have shown that 2-formylbenzenesulfonamides exist exclusively as 2,3-dihydro-3-hydroxybenzisothiazole 1,1-dioxides in the solid state. 2,3-Dihydro-3-hydroxybenzisothiazole 1,1-dioxides constitute a self-complementary hydrogen-bonding donor−acceptor system that dimerize in the solid state. Intermolecular interactions discussed in the present work could contribute significantly toward stabilizing the hydroxy benzisothiazole structure in solution[4] as well as in the solid state. Perhaps, this is the first report on hydrogen-bonding interactions between a sulfonyl group and a hydroxy group resulting in the formation of a 12/14-membered ring. Delineation of these interactions could help in the design and synthesis of supramolecular structures with interesting properties.

Experimental Section

Preparation of 2,3-Dihydro-2-alkyl-3-hydroxybenzisothiazole 1,1-Dioxides and NMR Spectra. All the compounds used in the present study were prepared as reported earlier[4] and crystallized by the slow diffusion of light petroleum into a solution of 2,3-dihydro-2-alkyl-3-hydroxybenzisothiazole 1,1-dioxide in ethyl acetate. Solutions for the recording of NMR spectra at various concentrations were prepared by directly weighing the appropriate compound in the NMR tube and dissolved in 0.5 mL of chloroform-*d*. The spectra were recorded at 298 K unless otherwise stated. For VT-NMR experiments, **5** (8 mg) was dissolved in chloroform-*d* (0.5 mL), and ^{1}H NMR spectra were recorded between 223 and 298 K by decreasing the temperature in steps of 10 K.

X-ray Crystallography. Data were collected on an Enraf Nonius CAD4 diffractometer with graphite-monochromatized Mo Kα radiation (λ = 0.7093 Å). Data reduction and the structure solution were carried out with the PC version of the NRCVAX system of programs.[16] The refinement was done with all data on F^2 with SHELXL-93.[17] For hydrogen positions of **4** were calculated; for the other two compounds they were obtained from difference Fourier maps. Crystal data for **4**: a = 16.071(5) Å, b = 8.490(2) Å, c = 17.078(4) Å, β = 104.70(2)° Å, V = 2254.0(10) Å,^{3} space group $P2_1/c$, and Z = 8. Crystal data for **5**: a = 8.003(2) Å, b = 15.894(2) Å, c = 9.127(3) Å, β = 109.51(2)°, V = 1094.2(5) Å,^{3} space group $P2_1/c$, and Z = 4. Crystal data for **6**: a = 9.485(3) Å, b = 10.388(4) Å, c = 12.363-(4) Å, α = 89.83(3), β = 106.78(2)°, γ = 90.26(3)°, V = 1166.2-(7) Å,^{3} space group P_1, and Z = 4. The authors have deposited atomic coordinates for **4**−**6** with the Cambridge Crystallographic Data Center. The coordinate can be obtained, on request, from the Director, Cambridge Crystallographic Data Center, 12 Union Road, Cambridge, CB21EZ, U.K.

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Supporting Information Available: Concentration and temperature dependent ^{1}H NMR spectra of **2** ↔ **5** and ORTEP diagrams for compounds **4**−**6** (8 pages). The 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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