

MESO AND RACEMIC 1,1-BIS (BENZYLSULFINYL)-2-ETHYLBUTANE. A b-DISULFOXIDE PRO-LIGAND WITH STERIC RESTRICTIONS

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ABSTRACT

Coordination chemistry of disulfoxides is of interest in inorganic chemistry given the well-known metal coordination through oxygen or sulfur atoms.¹ Ethylene and propylene bridged disulfoxide pro-ligands, coordinate to metals, forming coordinated and chelated complexes, demonstrating its flexibility in the formation of such complexes.² Some of these compounds have demonstrated interesting properties in medicinal chemistry³ and asymmetric catalysis⁴ and their synthesis is of importance for bioorganic studies. The presence of two stereogenic centers allows the existence of the *meso* and *racemic* forms in disulfoxides. Previous studies on b-disulfoxides⁵ in our laboratories have led to the synthesis and spectroscopic study (¹H-NMR, FT-IR) of both diastereomeric forms. In this work we report the synthesis and structural analysis of *meso*-**(2)**- and *racemic*-**(3)**-1,1-bis(benzylsulfinyl)-2-ethylbutane (Scheme 1), with high steric requirement around both sulfinyl groups when a branched aliphatic carbon chain is introduced in the α-carbon. An increase in selectivity for small radius metal ions was achieved by compression of the pro-ligand coordination radius. These kind of compounds have not been previously studied.

EXPERIMENTAL

¹H and ¹³C NMR spectra were recorded on a Bruker AC 250 spectrometer (250 MHz for ¹H and 62.4 MHz for ¹³C) in CDCl₃ and TMS as internal standard. Chemical shifts are expressed in delta units (ppm) and coupling constants in Hertz (Hz). FT-IR spectra were recorded on a Nicolet 550 IR spectrometer.

1,1-bis(benzyl)-2-ethylbutyl dithioacetal (1)

To a mixture of 25 g (0.25 mol) of 2-ethylbutanal, 1 mL of HCl (c) and 200 mg of AlCl₃, was slowly added 0,55 mol of benzylthiol. The mixture was kept at room temperature and stirred for 6 h. After that, water (20 mL) and CH₂Cl₂ (3x20 mL) was added to extract the product. The organic phase was treated with NaOH 3.0 M (2x20 mL) and dried over anhydrous sodium sulfate. Removal of the solvent and vacuum distillation (99-102 °C/ 0.1 mmHg) gave **(1)**, 70.1 g, 85 % yield. Anal. Found (calcd.): S 19.4(19.4). ¹H-NMR (d ppm) 7.35-7.20 (10 H, m), 3.68 (4H, s), 3.58 (1H, d, J= 5.0 Hz), 1.67 (2H, m), 1.55 (1H, m), 1.35 (2H, m), 0.72 (6H, t, J= 5.0 Hz). ¹³C-NMR (d ppm) 139.07 (s), 129.62 (d), 128.0 (d), 127.46 (d), 53.81 (d), 46.61 (d), 36.50 (t), 23.71 (t), 12.47 (q).

1,1-bis(benzylsulfinyl)-2-ethylbutane (2)

To a solution of 33.0 g of **(1)** (0.1 mol) in glacial acetic acid 80 mL, a solution of 30.77 g (0.2 mol) of trihydrated sodium perborate in glacial acetic acid (80 mL) was slowly added. The reaction mixture was kept at 42°C for 3 h., and monitored by TLC until evidence of the formation of trioxidated products was observed. The mixture was poured on ice and slowly neutralized with 1.0 M NaOH solution. The mixture was extracted three times with CH₂Cl₂ (25 mL) and dried with anhydrous sodium sulfate rendering a residue containing disulfoxides **(2)** and **(3)**. A previous column chromatography purification of the residue (silica gel 60G, particle size 0.2-0.5 mm.) with a mixture of ethyl acetate/n-hexane of increasing polarity, gave, after concentration, a mixture of oxidation products, 88% yield. Pure *meso* **(2)** and *racemic* **(3)** was obtained after medium pressure column chromatography (silica gel 60G, particle size 0.02-0.006) with 40% ethyl acetate in n-hexane.

Meso 1,1-bis(benzylsulfinyl)-2-ethylbutane (2)

Solid, m.p. 108 -109°C. ¹H-NMR (d ppm) 7.24-7.10 (10H, m), 4.72 (1H, d, J= 12.9 Hz), 3.96 (1H, d, J= 12.9), 3.47 (1H, d, J= 2.7 Hz), 1.71 (1H, m), 1.47 (4H, m), 0.53 (6H, t, J= 7.4 Hz). ¹³C-NMR (d ppm) 130.39 (s), 129.07 (d), 127.97 (d), 71.99(d), 55.30 (t), 40.63 (d), 40.06 (t), 11.07 (q).

Racemic 1,1-bis(benzylsulfinyl)-2-ethylbutane (3)

Solid, m.p. 112-113°C. ¹H-NMR (d ppm) 7.33 (5H, m), 4.23 (1H, d, J=12.87 Hz), 3.96 (1H, d, J=12.86 Hz), 3.83 (1H,d, J=2.21 Hz), 1.93 (2H, m),

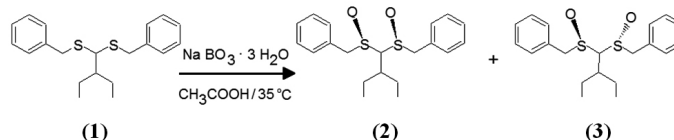
1.56(m), 1.29 (1H, m), 0.89 (3H, t, J=7.17 Hz), 0.70 (3H, 7.39 Hz). ¹³C-NMR (d ppm) 130.79 (s), 130.52 (d), 130.45 (d), 129.11 (s), 128.99 (d), 128.83 (d), 128.69 (d),128.48 (d), 73.81 (d), 58.72 (t), 39.56 (d), 24.59 (t), 23.04 (t), 12.18 (q), 11.85 (q).

Computing calculations

The neutral structure was full optimized using B3LYP/6-31+(d',p') level of theory. A vibrational frequency calculation is used to determine whether the structure is a minimum or saddle point on the potential energy surface and to compute the zero-point energy, ZPE. The computations were carried out with the Gaussian 09 suite of programs.⁶

RESULTS AND DISCUSSION

The synthesis of disulfoxides 1,1-bis(benzylsulfinyl)-2-ethylbutane (2 and 3) was achieved by controlled oxidation of dithioacetal (1), with sodium perborate in glacial acetic acid, producing a 1:1 mixture of *meso* (2) and *racemic* (3) modifications, quantified by ¹H-NMR. This synthesis is summarized in Scheme 1:



Both compounds were isolated and purified by column chromatography. The expected goal of this work was to incorporate a branched hydrocarbon chain in the α-carbon of the b-disulfoxide to reduce the coordination sphere of the pro-ligand to increase the coordination selectivity for small radius metal ions. See Figure 1. Previously we have reported ¹H-NMR studies to demonstrate that in 1,1-bis(phenylsulfinyl)-methane both sulfinyl oxygens and the phenyl groups are located in an *anti* orientation.^{5b} This disulfoxide does not present a significant steric congestion around the methylene bridge, and it was expected both mutual coplanarity as well as facile coordination towards metal ions. X-rays studies by other authors,⁷ have proven this assertion.

In the case of *meso* 1,1-bis(benzylsulfinyl)-2-ethylbutane an *anti* orientation for both sulfinyl oxygens and benzyl groups it is to be expected for the free pro-ligand in solution. However, oxygen coordination to a metal ion makes both coplanar benzyl groups closer together, introducing an important steric strain. This steric factor makes coordination less likely. The most probable conformation of *meso*-1,1-bis (benzylsulfinyl)-2-ethylbutane is indicated in Figure 2. Table 1 shows some selected distances and angles

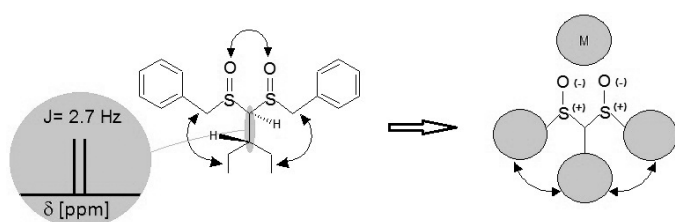


Fig. 1.-Disulfoxide model of high steric compression.

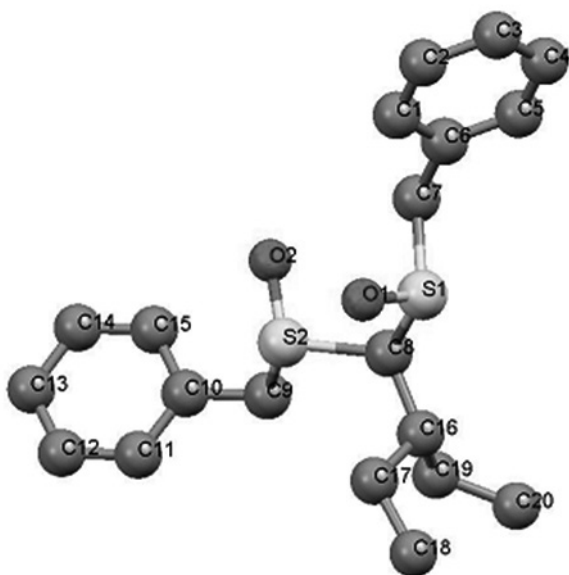
Fig. 2. Proposed structure for *Meso*-1,1-bis(benzylsulfinyl)-2-ethylbutane

Table 1: selected distances and angles.

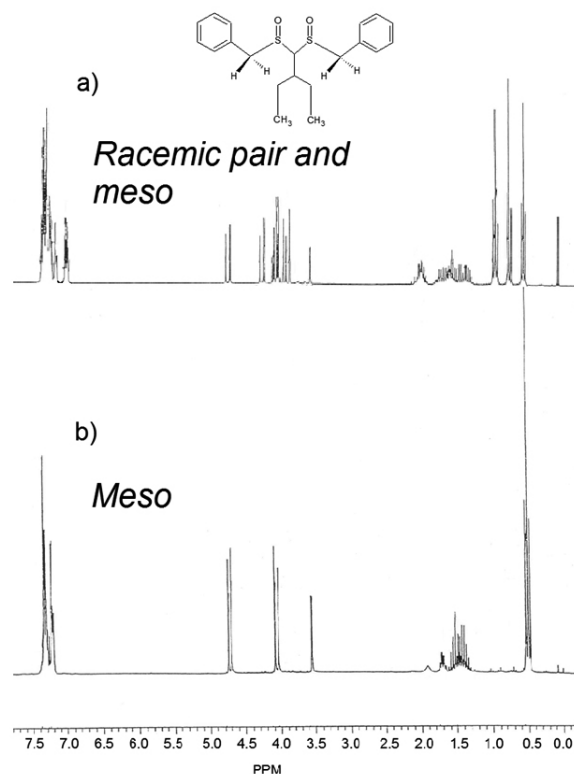
Distance	Å	Angle	°
S1-O1	1.519	S1-C8-S2	107.65
S2-O2	1.522	C7-S1-C8	99.94
S1-C8	1.898	C9-S2-C8	98.33
S2-C8	1.886	O1-S1-S2-O2	97.59
S1-C7	1.875	C17-C18-C19-C20	32.46
S2-C9	1.879	O1-S1-S2-O2	97.59
		C17-C18-C19-C20	32.46

A $^1\text{H-NMR}$ analysis of 1,1-bis(benzylsulfinyl)-2-ethylbutane clearly distinguishes *meso* from the racemic pair. Figure 3, shows the $^1\text{H-NMR}$ spectrum for the mixture of diastereomers, *dl* and *meso* compounds (a) and that of *meso* compound (b)

Two AB quartets centered at 4.72 and at 3.96 (ppm) with, $J = 12.93$ Hz for the *meso* and 4.23 and at 3.83 (ppm) with $J = 12.87$ Hz for the *dl* pair. The coupling constant between hydrogens in carbons C_8 and C_{16} , $J_{\text{HSH16}} = 2.7$ Hz is small, indicating a dihedral angle smaller or more than 90° between H_8 and H_{16} . Methyl groups have been shifted to high field, appearing at 0.53 ppm in the *meso* compound and 0.70 and 0.89 (ppm) respectively in the racemic form. These values suggest a fairly perpendicular orientation of both phenyl groups with respect to the alkyl chain. However, the high steric hindrance introduced by both coplanar benzyl results in a closer proximity of both oxygens promoting rotation to minimize steric hindrance. In this conformation, shown as structure Figure 2, ethyl groups should appear at high field and hydrogens in C_8 and C_{16} should be *synperiplanar* with a small value for J_{HSH16} . This analysis is consistent with $^1\text{H-NMR}$ data.

In conclusion methyl and methylene groups have been shifted to high field; 0.53 (ppm) for “*meso* methyl” and 0.89 and 0.70 (ppm) for “racemic methyl groups” due to the proximity of aromatic’s rings anisotropy. An $^1\text{H-NMR}$

analysis of J_{HSH16} for *meso* and *racemic* compounds indicates small values for both constants (2.7 and 2.1 Hz, respectively). $^{13}\text{C-NMR}$ data, on the other hand, confirm the shielding experienced by methyl and methylene groups due to the proximity of both benzyl groups, shifting their resonances to 40.6 and 11.0 ppm respectively in *meso* and 24.6; 24.0 and 12.2; 11.8 ppm respectively in the racemic pair. This shielding effect has not been observed in other *b*-disulfoxides studied so far.⁵

Fig. 3. $^1\text{H-NMR}$ (a) racemic pair and *meso* 1,1-bis(benzylsulfinyl)-2-ethylbutane (b) *meso* 1,1-bis(benzylsulfinyl)-2-ethylbutane.

A conformation such as structure *meso* 1,1-bis(benzylsulfinyl)-2-ethylbutane in solution should not form metal complexes due to the steric requirements imposed by coplanar benzyl groups. This hinders bonding through oxygens of this disulfoxide; however, we have observed that the racemic modification of compound (3) gives a precipitate with copper (II) ions in solution, reaction not observed for the *meso*-proligand. *Meso*-disulfoxide pro-ligands, different to disulfoxides with methylene bridges from 2 up to 4 carbons have successfully produced bridged and chelated complexes with different metal ions.⁷ It is expected that *b*-disulfoxide pro-ligands behave chemically as *b*-diketones and *b*-difosfonates. Studies to elucidate both the crystal structure of the copper complex by X-rays and the formation of a complex with the racemic pair are in progress in our laboratory.

CONCLUSION

It has carried out the synthesis of a new disulfoxide compound with a branched aliphatic carbon chain introduced into the alpha carbon. It has obtained and resolved the *Meso* and *Racemic* forms of the disulfoxide 1,1-bis(benzylsulfinyl)-2-ethylbutane. The $^1\text{H-NMR}$ analysis has clearly differentiate these forms and theoretical calculus are in agreement with the experimental data

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