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Chemical shift and coupling constant analysis of dibenzyloxy disulfides

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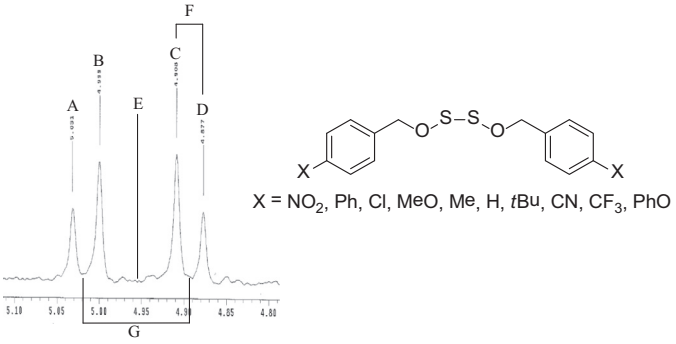
HIGHLIGHTS

- The chemical shift and coupling of a library of dibenzyloxy disulfides were analyzed.
- A linear relationship with Hammett's constants in all solvents was observed.
- The benzylic protons are parabolically related to Swain and Lupton's *F*-value.

GRAPHICAL ABSTRACT



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ABSTRACT

Dialkoxy disulfides have found applications in the realm of organic synthesis as an S_2 or alkoxy donor, under thermal and photolytic decompositions conditions, respectively. Spectrally, dibenzyloxy disulfides possess an ABq in the ^{1}H NMR, which can shift by over 1.1 ppm depending on the substituents present on the aromatic ring, as well as the solvent employed. The effect of the said substituents and solvent were analyzed and compared to the center of the ABq, geminal coupling, and the differences in chemical shifts of the individual doublets. Additionally, quantum-chemical calculations demonstrated the intramolecular H-bonding arrangement, found within the dibenzyloxy disulfides.

Introduction

Dialkoxy disulfides were first synthesized in the late 19th century by Lengfeld [1], however they lay in relative obscurity until the 1990's when Harpp and others began to examine this novel structural moiety [2–15]. Although examples of the isomeric form, thionosulfite (—OS(=S)O—) have been reported, however only in cyclic structures [3,12], the predominate form is believed to be the linear arrangement, (—OSSO—). It was revealed that dialkoxy disulfides could act as an S_2 donating group in pseudo-Diels Alder reactions [8,11]. Subsequently, Lunazzi and Placucci utilized this functionality as a photolytic source of alkoxy radicals [5]. We have also explored this class of compounds, specifically the dibenzyloxy disulfides [16–19]. Recently, we have reported on their photolytic [16] and thermolytic properties [17,18], as well as their unique interaction with gold nanoparticles and their subsequent interaction with the Alzheimer's association Aβ oligomers [19].

Through some of our aforementioned studies we observed spectral differences in the ^{1}H NMR of the dibenzyloxy disulfides depending on what functionality was placed in the *para*-position

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of the aromatic ring; specifically, the downfield/upfield chemical shift of the center of the characteristic ABq, the geminal coupling constant, and the spectral frequency difference between the two diastereotopic protons. The diastereotopic nature of this linear molecule is due to the geometry around the disulfide bond. Dialkoxy disulfides have a dihedral angle around the —O—S—S—O— bond of ~90° [2,8]. This has been attributed to the conjugation of a lone pair on a sulfur atom with the σ^* orbital of the adjacent —O—S— bond [13]. It has been postulated that this provides double bond character and a decrease in bond length of the –S—S— bond to 1.95 Å [2] from a typical 2.05 Å [19–22] for simple disulfides. In addition, there is an elevation in the rotational barrier energy around the disulfide bond from ~8 kcal/mol [19–22] to ~18 kcal/mol [8]. By augmenting the electronic nature of the substituents on the aromatic ring, we predict that the placement and coupling of the characteristic ABq would be altered. In addition, we also wanted to explore the role of the solvent on the spectral profile of the benzylic protons.

Previous studies have investigated the changes in the ^{1}H NMR chemical shift of protons and observed that a number of variables can influence proton resonance, including any substituents and the solvent used within the system. Both of these impact the electron density surrounding the proton, which alters resonance frequency. Protons that experience a deshielding of electron density, such as those adjacent to an electron withdrawing substituent, give signals at a higher resonance frequency.

Substitution of an aromatic ring has a large effect on the pi-electron density, affecting the aromatic proton shift. Yonemoto and his colleagues have looked at substituted anilines to study the influence various electron withdrawing/donating groups have on proton resonance, as well as the effect of the amine group. They found a correlation between Hammett's constant of a *para*-substituent and the degree of proton shift within the aromatic ring [23]. As Hammett's constant becomes more positive for a given substituent, indicating an electron-withdrawing group, total pi-electron density is reduced and proton resonance is shifted downfield. In addition, electron-withdrawing groups cause the N—H bond to become more polarized. Polarization leads to an increase in intermolecular hydrogen bonding as well as hydrogen bonding between the solute and solvent. The degree of solute–solvent interaction is increased for solvents such as DMSO and acetone, as they are hydrogen bond acceptors. Hydrogen bonds act to deshield the protons, shifting their resonance downfield [23–26].

This work investigates *para*-substituted dibenzyloxy disulfide proton shift using ^{1}H NMR. We are interested in the hydrogens adjacent to the —O—S—S—O— bond, as they are distinct from a typical disulfide system, in addition to the aromatic protons. By evaluating various electron donating and withdrawing groups, we can investigate how these substituents change the electron density of the molecule, thus shifting proton resonance. Moreover, this information will give insight into how these groups influence the solute–solvent interactions.

Experimental

Materials, preparation and characterization of compounds

All chemicals were reagent grade with the exception of 4-phenoxybenzyl alcohol which was synthesized according to published procedure [27]. ^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra were recorded on a Varian instrument with tetramethylsilane (TMS) as an internal standard. Chemical shifts (δ) are given in ppm, coupling constants (J) in Hz, and spin multiplicities as s (singlet), d (doublet), ABq (AB quartet) and m (multiplet).

Representative synthesis of a dibenzyloxy disulfide [18]

Bis(4-Nitrobenzyloxy) disulfide

p-Nitrobenzyl alcohol (0.25 g, 1.63 mmol) was dissolved in anhydrous CH_2Cl_2 under N_2. Triethylamine (0.227 mL, 1.63 mmol) was added and the resulting solution was cooled to 0 °C. S_2Cl_2 (65.3 μL, 0.82 mmol) was added dropwise over twenty minutes. The solution was stirred at 0 °C for two hours before being allowed to equilibrate to room temperature for three hours. The reaction was quenched with dH_2O, washed with 2 × 20 mL aliquots of brine. The aqueous phase was extracted with CH_2Cl_2 (2 × 10 mL), and the combined organic phase was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Column chromatography with a 2.5:1 ratio of hexanes:ethyl acetate afforded the below compounds. [Note: Bis(p-nitrobenzyloxy) disulfide, bis(4-methoxybenzyloxy) disulfide, bis(4-tertbutylbenzyloxy) disulfide, and bis(4-benzyloxy) disulfide have been previously synthesized in another laboratory with reported spectra in Ref. [13]. With the exception of bis(4-benzyloxy) disulfide, all spectra reported was almost identical to those reported below. For bis(4-benzyloxy) disulfide, Ref. [13] incorrectly assigned the aromatic signals as δ 7.39 (m, 15H) instead of our δ 7.17 (m, 10H). In addition, bis(p-nitrobenzyloxy) disulfide, bis(4-methoxybenzyloxy) disulfide, bis(4-methylbenzyloxy) disulfide, bis(4-benzyloxy) disulfide, and bis(4-chlorobenzyloxy) disulfide were also reported in Ref. [4]. The mp. and NMR matched our samples. Bis(4-phenylbenzyloxy) disulfide was first synthesized and fully characterized in our laboratory in Ref. [16]. Bis(4-phenoxybenzyloxy) disulfide, bis(4-cyanobenzyloxy) disulfide, and bis(4-cyanobenzyloxy) disulfide all were previously synthesized and fully characterized from our laboratory and reported in Ref. [18].

Bis(4-nitrobenzyloxy) disulfide (0.23 g, 93%) as an off white solid mp. 93–95 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.89, 5.01 (ABq, J = 12.6 Hz, 4H), 7.49 (d J = 8.8 Hz, 4H), 8.22 (d, J = 8.8 Hz, 4H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 75.1, 123.8, 128.7, 143.6, 147.9.

Bis(4-Phenylbenzyloxy) disulfide (0.23 g, 90%) as white solid. mp.105–107 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.85, 4.96 (ABq, J = 11.4 Hz, 4H), 7.35 (t, J = 7.6 Hz, 2H), 7.43 (d, J = 8.0 Hz, 4H), 7.59 (m, 12H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 76.5, 127.1, 127.3, 127.5, 128.8, 129.2, 135.5, 140.6, 141.4.

Bis(4-Chlorobenzyloxy) disulfide (0.23 g, 92%) as off white solid mp. 45–46 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.75, 4.86 (ABq, J = 11.4 Hz, 4H), 7.30 (d, J = 7.2 Hz, 4H), 7.33 (d, J = 7.2 Hz, 4H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 75.8, 128.8, 130.0, 134.4, 134.9.

Bis(4-Methoxybenzyloxy) disulfide (0.19 g, 76%) as a white low melting solid. mp. 20–22 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.81 (s, 6H), 4.73, 4.84 (ABq, J = 11.0 Hz, 4H), 6.88 (d, J = 8.4 Hz, 4H), 7.24 (d, J = 8.4 Hz, 4H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 55.3, 76.5, 113.9, 128.8, 130.5, 159.8.

Bis(4-Methylbenzyloxy) disulfide (0.21 g, 84%) as an off white low melting solid mp. 25–27 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.35 (s, 6H), 4.76, 4.87 (ABq, J = 11.2 Hz, 4H), 7.17 (d, J = 8.0 Hz, 4H), 7.24 (d, J = 8.0 Hz, 4H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.3, 77.2, 128.8, 129.2, 133.6, 138.2.

Bis(4-Benzyloxy) disulfide (0.20 g, 80%) as an off white solid mp. 47–49 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.80, 4.92 (ABq, J = 11.4 Hz, 4H), 7.17 (m, 10H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 76.8, 128.4, 128.5, 128.6, 136.6.

Bis(4-Tertbutylbenzyloxy) disulfide (0.19 g, 72%) as clear liquid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.32 (s, 18H), 4.77, 4.89 (ABq, J = 11.2 Hz, 4H), 7.29 (d, J = 8.0 Hz, 4H), 7.38 (d, J = 8.0 Hz, 4H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 31.3, 34.6, 76.7, 125.5, 128.6, 133.6, 151.6.

Bis(4-Trifluorobenzyloxy) disulfide (0.17 g, 68%) as clear liquid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.85, 4.96 (ABq, J = 12.0 Hz,