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Chemical shift and coupling constant analysis of dibenzyloxy disulfides

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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 differencesin 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 disulfidescould 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 ofthe aromatic ring; specifically, the downfield/upfieldchemical shift of the center of the characteristic ABq, the geminal coupling constant, and the spectral frequency difference between the two diastereotopicprotons.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^{o} [2,8]. This has been attributed to the conjugation of a lone pair on a sulfur atom with theσ^* 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 2.05Å [19-21] for simple disulfides. In addition, there is an elevation in the rotational barrier energy around the disulfide bond from ~8 kcal/mol [19-21] 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 (0.25g, 1.63mmol) was dissolved in anhydrous CH_2Cl_2 under N_2. Triethylamine (0.227mL, 1.63mmol) was added and the resulting solution was cooled to 0 °C. S_2Cl_2 (65.3µL, 0.82mmol) 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 x 20mL aliquots of brine. The aqueous phase was extracted with CH_2Cl_2 (2 x 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 ofhexanes: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 (0.23g, 93%) as an off white solid mp. 93-95°C. ^{1}H NMR (400MHz, $CDCl_3$): 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 (0.23g, 90%) as white solid. mp.105-107°C.^{1}H NMR (400MHz, $CDCl_3$): 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 (0.23g, 92%) as off white solid mp. 45-46°C. ^{1}H NMR (400MHz, $CDCl_3$): 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 (0.19g, 76%) as a white low melting solid. mp. 20-22°C.^{1}H NMR (400MHz, $CDCl_3$): 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 (0.21g, 84%) as an off white low melting solid mp. 25-27°C. ^{1}H NMR (400MHz, $CDCl_3$): 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 (0.20g, 80%) as an off white solid mp. 47-49°C. ^{1}H NMR (400MHz, $CDCl_3$): 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 (0.19g, 72%) as clear liquid. ^{1}H NMR (400MHz, $CDCl_3$): 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 (0.17g, 68%) as clear liquid. ^{1}H NMR (400MHz, $CDCl_3$): δ 4.85, 4.96 (ABq, J = 12.0 Hz, 4H), 7.44 (d, J = 7.2 Hz, 4H) 7.62 (d, J = 7.2 Hz, 4H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 75.7, 124.0 (J = 272.1 Hz), 125.5 (J = 3.8 Hz), 128.4, 130.6 (J = 32.2) 140.4.

Bis(4-Cyanobenzyloxy) disulfide (0.12g, 67%) as a white-yellow low melting solid mp. 27-29°C. ^{1}H NMR (400MHz, $CDCl_3$): δ 4.84, 4.96 (ABq, J = 12.6 Hz, 4H), 7.44 (d, J = 7.6 Hz, 4H) 7.44 (d, J = 7.2 Hz, 4H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 75.4, 112.0, 118.6, 128.6, 132.4, 141.6.

Bis(4-Phenoxybenzyloxy) disulfide (0.65g, 88%) as an off white low melting solid mp. 24-26°C. ^{1}H NMR (400MHz, $CDCl_3$): δ 4.77, 4.88 (ABq, J = 11.4 Hz, 4H), 6.98 (d, J = 8.4 Hz, 4H), 7.01 (d, J = 7.6 Hz, 4H), 7.13 (t, J = 7.2 Hz, 2H), 7.33 (m, 8H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 76.3, 118.6, 119.1, 123.5, 129.8, 130.5, 131.3, 156.8, 157.7.

Computational Procedures

Standard *ab initio* and density functional theory calculations were performed using Gaussian 09 [28] and Molpro 2009.1 [29] software packages. For non-substituted dibenzyloxy disulfide, a full conformational search at 120° resolution was performed in the gas phase at the M06-2X/6-31+G(d) level of theory. Three distinctly different conformations were identified and considered further for the various substituted dibenzyloxy disulfides. Accurate geometries, frequencies (scaled by the recommended scaling factors [30]) and electronic energies were obtained using

the M06-2X/6-31+G(d) method. For non-substituted dibenzyloxy disulfide, the M06-2X/6-31+G(d) relative energies of the three conformers were additionally benchmarked at higher levels – M06-2X/aug-cc-pVTZ and the composite *ab initio* G3(MP2)-RAD(+) [31] method (Supplemental Material). Gas-phase entropies and thermal corrections at 25 °C were calculated using the standard textbook formulae [32] for the statistical thermodynamics of an ideal gas under the harmonic oscillator approximation in conjunction with the optimized geometries and scaled frequencies. Free energies of solvation in DMSO and benzene were calculated using UAKS-CPCM/B3LYP/6-31+G(d) method in conjunction with relaxed solution-phase geometries [33]. Relative Boltzmann average concentrations of the each of the three considered conformers were evaluated according to the equation:

$$conc_i = \frac{e^{-\frac{\Delta G_i}{RT}}}{\sum_i e^{-\frac{\Delta G_i}{RT}}}$$

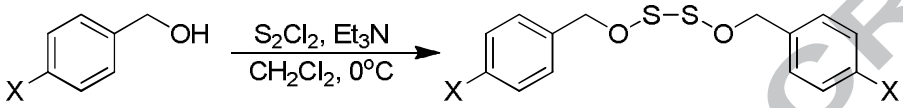
where ΔG_i is the relative free energy of the *i*-th conformer, *R* is the universal gas constant and *T* is the absolute temperature.

Results and discussion

Synthesis

Synthesis of the library was performed as previously described [4, 13, 16-18]. In short, two equivalents of a desired commercially available benzyl alcohol (with the exception of 4-phenoxybenzyl alcohol, which was synthesized from its corresponding acid following published procedure [27]) with two equivalents of Et_3N and one equivalent of S_2Cl_2 were reacted in CH_2Cl_2 for 2 h at 0^{o}C than 3 h at room temperature (**Scheme 1**). Compounds were purified via column chromatography and stored in a freezer until use. Even when stored cold, slight

decomposition was occasionally observed, and these particular dibenzyloxy disulfides were re-purified prior to any NMR studies. We next ran ^{1}H-NMR on all ten dibenzyloxy disulfides in six different aprotic deuterated solvents (i.e. $CDCl_3$, d_6-DMSO, d_6-Acetone, d_3-Acetonitrile, C_6D_6, and d_8-Toluene), as solvents such as D_2O and CD_3OD cause rapid decomposition of the compounds.



Scheme 1: Synthesis of dibenzyloxy disulfides

NMR spectra chemical shift

We began by examining the placement of the center of the ABq (**Figure 1**) versus the electronic nature of the *para*-substituent. [For convenience, the chemical shifts, center of the ABq, geminal coupling, and the Δ of center of doublets in Hz of the ten dibenzyloxy disulfides in the six solvents are presented in **Tables 1-6**]. Unsurprisingly, there is a linear correlation with Hammett's constant [33] due to the fact that we were analyzing the benzylic protons (**Figure 2**). Interestingly, with $CDCl_3$, d_6-DMSO, d_6-Acetone, and d_3-Acetonitrile, the expected downfield shift is observed as the ring substituent's electron withdrawing ability increases (i.e. higher Hammett's constant values) (**Figure 2**); however with C_6D_6, and d_8-Toluene a completely opposite trend was observed (**Figure 2**). For example, in d_6-Acetone, 4-nitrodibenzyloxy disulfide's benzylic protons were centered at 5.103ppm, whereas in C_6D_6, these protons were at 3.91 ppm. Conversely, in d_6-Acetone, 4-methoxydibenzyloxy disulfide's methylene protons were centered at 4.82 ppm, whereas in C_6D_6, these protons were at 4.29 ppm. Indeed, in both cases, the protons were further downfield compared tod_6-Acetone (*vide infra*); however, it was the fact that the shifts were near the extremes and in opposite directions that caught our interest. The

reversal of downfield shift in the presence of aromatic solvents has been previously observed [26]. It has been hypothesized that this is due to the H-bonding ability of the benzylic protons. As the electron withdrawing nature of the *para*-substituent increases (i.e. higher Hammett's constant values) the benzylic protons become more positively charged and will participate as a H-bond donor with the lone-pairs of the deuterated solvents (**Figure 3a**). The same phenomena exists in an aromatic solvent, however instead of lone pairs H-bonding with the benzylic protons, it is believed that the cloud of π electrons of C_6D_6 or d_8-Toluene is responsible (**Figure 3b**). When this occurs, the proton would fall not in an anisotropic region of the local magnetic field of the aromatic solvent, but instead in the shielded region. Thus, as the electron withdrawing nature of the *para*-substituent increases, enhanced H-bonding with the solvent causes the benzylic protons to shift further upfield.

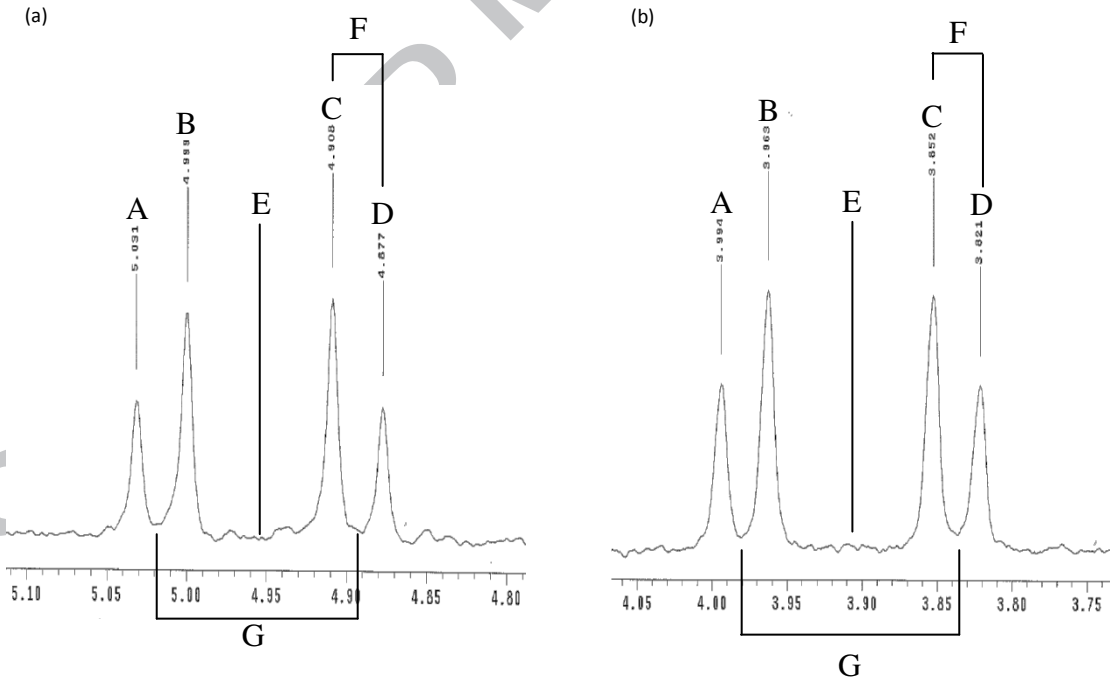


Figure 1: Expanded ^{1}H-NMR of ABq for 4-nitrodibenzyloxy disulfide in (a) $CDCl_3$ and (b) benzene. **A**-**D** represents signal placement in ppm; **E** represents center of ABq in ppm: **F** represents coupling constant in Hz; and **G** represents Δof center of doublets in Hz.

Table 1:^{1}H-NMR values of dibenzyloxy disulfides in$CDCl_3$

4-X	A (ppm)	B (ppm)	C (ppm)	D (ppm)	E (ppm)	F (Hz)	G (Hz)
Nitro	5.03	5.00	4.91	4.88	4.95	12.6	49.0
Biphenyl	4.97	4.94	4.86	4.83	4.90	11.4	44.2
Chloro	4.88	4.85	4.77	4.74	4.81	11.4	43.0
Methoxy	4.86	4.83	4.75	4.72	4.79	11.0	41.8
Methyl	4.88	4.85	4.77	4.75	4.81	11.2	43.2
Hydrogen	4.93	4.90	4.82	4.79	4.86	11.4	43.0
Tert-butyl	4.91	4.88	4.79	4.76	4.83	11.2	46.8
CF_3	4.97	4.95	4.86	4.83	4.91	12.0	44.0
Cyano	4.98	4.95	4.86	4.83	4.90	12.6	48.6
Phenoxy	4.90	4.87	4.79	4.76	4.83	11.4	43.8

Table 2: ^{1}H-NMR values of dibenzyloxy disulfides ind_6-DMSO

4-X	A (ppm)	B (ppm)	C (ppm)	D (ppm)	E (ppm)	F (Hz)	G (Hz)
Nitro	5.10	5.07	5.01	4.98	5.04	12.2	35.0
Biphenyl	5.00	4.97	4.92	4.89	4.94	11.4	33.0
Chloro	4.93	4.90	4.84	4.82	4.87	11.2	33.6
Methoxy	4.85	4.82	4.76	4.73	4.79	11.0	33.8
Methyl	4.88	4.85	4.79	4.76	4.82	11.6	34.8
Hydrogen	4.94	4.91	4.85	4.82	4.88	11.2	34.8
Tert-butyl	4.89	4.86	4.80	4.77	4.83	11.2	35.6
CF_3	5.05	5.02	4.97	4.94	4.99	12.0	32.4
Cyano	5.04	5.01	4.95	4.92	4.98	12.6	34.2
Phenoxy	4.91	4.88	4.82	4.80	4.85	11.2	34.0

Table 3: ^{1}H-NMR values of dibenzyloxy disulfides ind_6-Acetone

4-X	A (ppm)	B (ppm)	C (ppm)	D (ppm)	E (ppm)	F (Hz)	G (Hz)
Nitro	5.17	5.14	5.07	5.04	5.10	12.2	40.2
Biphenyl	5.02	5.00	4.93	4.90	4.96	11.6	37.2
Chloro	4.97	4.94	4.88	4.85	4.91	11.6	37.6
Methoxy	4.89	4.86	4.79	4.76	4.82	11.2	36.8
Methyl	4.92	4.89	4.82	4.79	4.86	11.4	38.2
Hydrogen	4.98	4.95	4.88	4.85	4.92	11.4	38.2
Tert-butyl	4.94	4.91	4.84	4.81	4.87	11.2	39.6
CF_3	5.11	5.08	5.01	4.98	5.04	12.2	38.6
Cyano	5.10	5.07	5.00	4.97	5.04	12.6	39.8
Phenoxy	4.96	4.93	4.86	4.84	4.90	11.2	37.6

Table 4: ^{1}H-NMR values of dibenzyloxy disulfides ind_4-Acetonitrile

4-X	A (ppm)	B (ppm)	C (ppm)	D (ppm)	E (ppm)	F (Hz)	G (Hz)
Nitro	5.06	5.02	4.96	4.92	4.99	12.6	40.2
Biphenyl	5.00	4.97	4.90	4.87	4.93	11.4	37.8
Chloro	4.91	4.88	4.81	4.78	4.84	11.6	38.4
Methoxy	4.85	4.83	4.76	4.73	4.79	11.2	37.6
Methyl	4.88	4.85	4.78	4.76	4.82	11.2	38.4

Hydrogen	4.94	4.91	4.84	4.81	4.88	11.6	38.8
Tert-butyl	4.90	4.87	4.80	4.77	4.84	11.4	38.2
CF_3	5.02	4.99	4.92	4.89	4.95	12.2	38.2
Cyano	5.00	4.97	4.90	4.87	4.93	12.4	39.2
Phenoxy	4.90	4.87	4.81	4.78	4.84	11.2	37.2

Table 5: ^{1}H-NMR values of dibenzyloxy disulfides ind_6-Benzene

4-X	**A (ppm)**	**B (ppm)**	**C (ppm)**	**D (ppm)**	**E (ppm)**	**F (Hz)**	**G (Hz)**
Nitro	3.99	3.96	3.85	3.82	3.91	12.4	56.8
Biphenyl	4.33	4.30	4.20	4.17	4.25	11.8	51.8
Chloro	4.06	4.04	3.94	3.91	3.99	11.6	48.8
Methoxy	4.36	4.33	4.24	4.21	4.29	11.0	46.6
Methyl	4.37	4.34	4.24	4.21	4.29	11.4	49.4
Hydrogen	4.32	4.29	4.20	4.17	4.24	11.4	48.2
Tert-butyl	4.42	4.39	4.30	4.27	4.35	11.4	51.0
CF_3	4.11	4.08	3.98	3.95	4.03	12.0	52.4
Cyano	3.97	3.93	3.83	3.80	3.88	12.2	55.4
Phenoxy	4.28	4.25	4.16	4.13	4.20	11.2	49.2

Table 6: ^{1}H-NMR values of dibenzyloxy disulfides ind_8-Toluene

4-X	**A (ppm)**	**B (ppm)**	**C (ppm)**	**D (ppm)**	**E (ppm)**	**F (Hz)**	**G (Hz)**
Nitro	4.41	4.38	4.27	4.24	4.33	12.6	57.8
Biphenyl	4.78	4.75	4.65	4.62	4.70	11.2	52.4
Chloro	4.49	4.46	4.36	4.33	4.41	11.6	49.6
Methoxy	4.72	4.69	4.60	4.57	4.64	10.8	47.2
Methyl	4.72	4.69	4.60	4.57	4.65	11.0	49.8
Hydrogen	4.69	4.65	4.56	4.53	4.61	11.4	48.6
Tert-butyl	4.77	4.75	4.65	4.62	4.70	11.2	51.6
CF_3	4.51	4.48	4.37	4.34	4.43	11.8	54.2
Cyano	4.38	4.34	4.23	4.20	4.29	12.2	57.0
Phenoxy	4.66	4.63	4.54	4.51	4.59	11.2	49.6

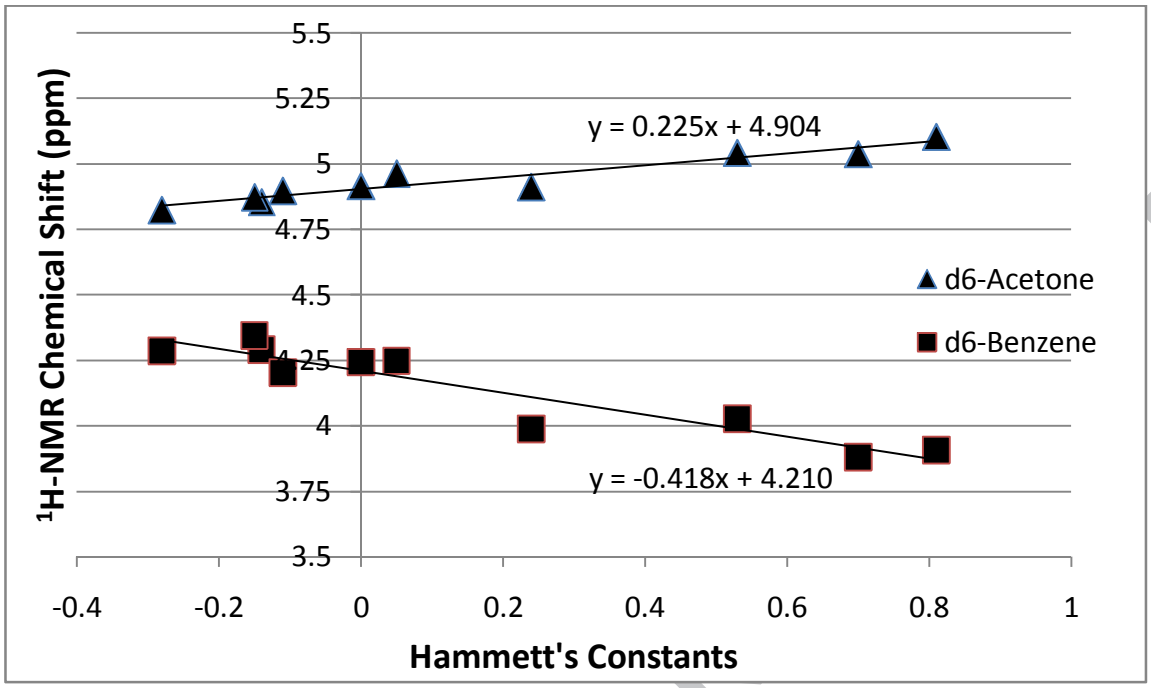


Figure 2: ^{1}H-NMR chemical shift of the center of the ABq for the library of dibenzyloxy disulfides in d_6-Acetone and d_6-Benzene compared to Hammett's Constants.Line-of-best-fit is a guideto the eye.

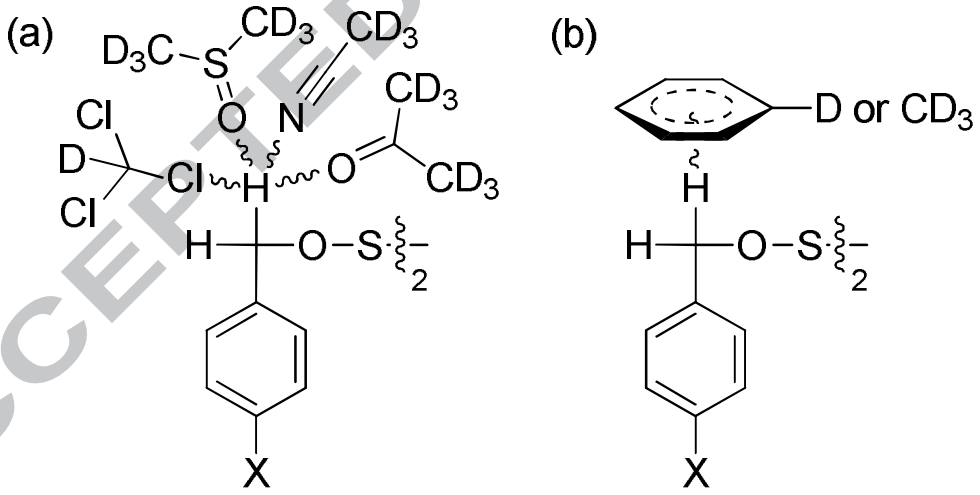


Figure3: H-bonding interaction of the benzylic protons with (a) the lone pair of electrons on polar aprotic solvents and (b) pi-cloud of aromatic solvents.

Theoretical Calculations

Typical measures of the H-bond strength are: (1) the distances C–H and H–Y in H-bonded complex C–H…Y (where Y is an electronegative proton acceptor); (2) energy difference between the H-bonded complex and infinitely separated components (for intermolecular H-bonds) or between H-bonded and non-H-bonded conformers (for intramolecular H-bonds); (3) the red shift of the C–H stretch. These are the characteristics we have focused on in order to probe for the intramolecular H-bonding in the studied set of dibenzyloxy disulfides. This has been done for the three key conformers we have identified for non-substituted dibenzyloxy disulfide (**Figure 4**) – as well as their variously substituted derivatives in gas and solution phases. The three conformers are denoted ddh1 (highest in energy), ddh2 and ddh3 (lowest in energy).

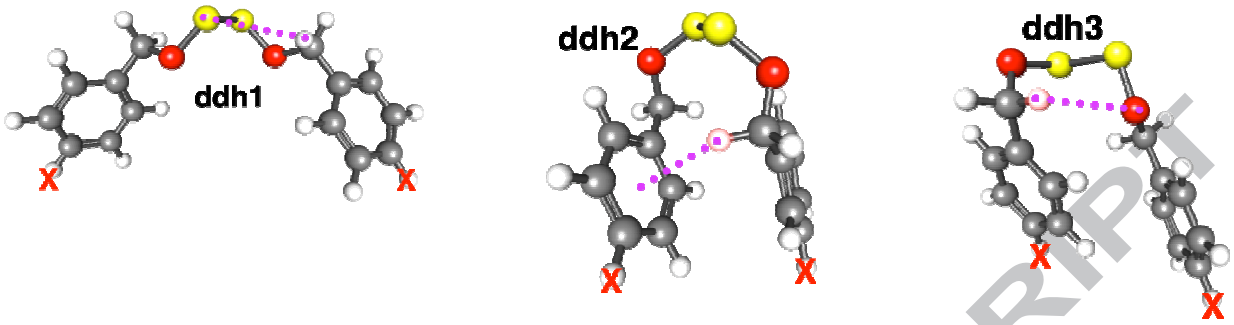
All three conformers appear to involve interactions that potentially discriminate between the two hydrogens of thebenzylic CH_2 group. Conformer ddh1 affords an overlap between the lone pairs on the sulfur atoms and the S–Oσ* (see **Figure 1** of the Supplementary Material) at a distance of approx. 3 Å (**Table 7**). However, this conformer is not the lowest energy conformer as there are two distinctly different conformations that are more stable (see Table 1 in the Supplementary Information). Conformer ddh2 involves interaction between the hydrogen of CH_2 group with the π-density of the phenyl ring; this interaction is stronger in the presence of electron-donating substituents (such as OCH_3, allowing for a *ca.* 2.5 Å H-bonding to the ring, see**Figure 5a**), and is reduced by the electron-withdrawing substituents that promote π-stacking of two phenyl rings instead (e.g. NO_2, correspondingly longer H-bonding of *ca.* 3.5 Å, see **Figure 5b**). This is also demonstrated by the H-bond lengths in **Table 7**. Finally, conformer ddh3 involves a 6-membered cycle comprising intramolecular H-bond to the oxygen atom,

approx. 2.8-3.0 Å long. This conformer is universally the *global minimum* for all derivatives in the gas phase. We note that there are no appreciable differences in the lengths of C–H bonds between the different conformers and substituents.

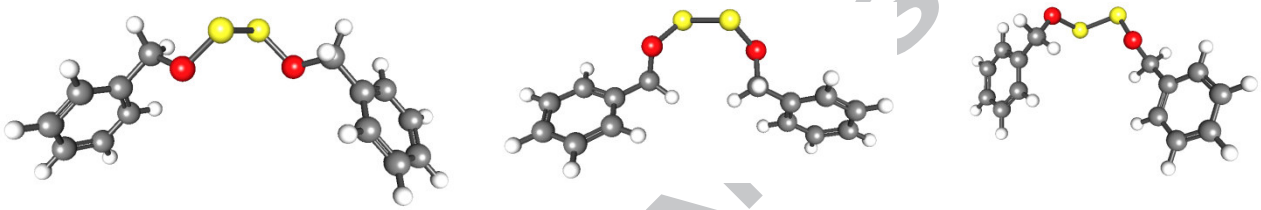
As noted above, substituents with greater Hammett's constants (stronger electron acceptors) promote π-π stacking of the two rings over the competitive H-π interaction. The π-π stacking affords greater energetic benefit than the H-bonding, and hence the relative energy of conformer ddh2 with electron-withdrawing substituents X is lower than with the electron-donating groups (see Figure 2 of the Supplementary Information). In other words, the protons are deshielded as the π-density is involved in a competing interaction.

Solvation tends to disrupt the intramolecular H-bonding, as has been noted earlier. π-Stacking and interaction of H with the aromatic electron density in conformer ddh2 disappears in both benzene and DMSO. Nonetheless, in the solvent-phase analogue of the conformer ddh2 benzylic protons are still in the shielded region of the opposite aromatic rings. Moreover, relative weight of this conformer increases upon solvation compared to that of ddh3 (**Table 7**). Finally, the disrupted H-bonds are formally less elongated upon solvation in less polar benzene compared to DMSO. In summary, these observations are consistent with the fact that in less polar solvents the protons are interacting with the π-density to a greater extent, *i.e.* are shielded and hence their signals are shifted upfield.

gas



DMSO



Benzene

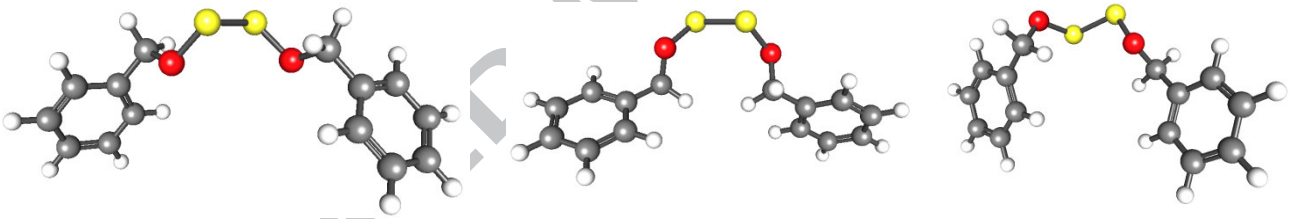


Figure 4:Optimized geometries of the three conformers in the gas and solution phases, X=H. H-bonds of interest are denoted with purple dash lines.

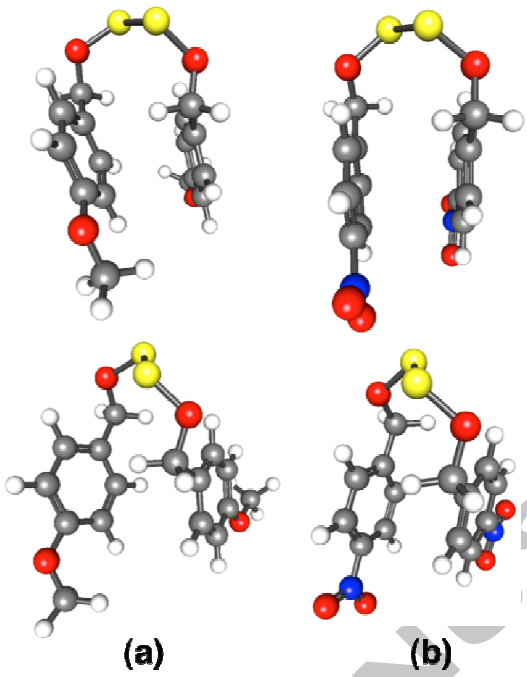


Figure 5: Gas-phase M06-2X/6-31+G(d) optimized geometries of dibenzyloxy disulfides with X=OCH_3 (a) and X=NO_2 (b), shown in two projections.

Table 7:M06-2X/6-31+G(d) free energies at 25 °C (in kJ mol^{-1}), H-bond lengths (in Å) and relative Boltzmann concentrations (in %) of the three conformers for a series of substituted dibenzyloxy disulfides.

X	ddh #	*gas*			*DMSO*			*benzene*		
		H-bond	**ΔG**	**%**	**H-bond**	**ΔG**	**%**	**H-bond**	**ΔG**	**%**
H	**1**	3.0	12.6	1	3.2	6.0	7	3.2	6.9	5
	2	2.7	11.3	1	5.9	4.4	14	5.7	5.1	11
	3	2.9	**0.0**	98	3.4	**0.0**	79	3.2	**0.0**	84
Cl	**1**	3.0	5.1	11	3.3	**0.0**	48	3.2	1.3	35
	2	2.5	9.5	2	5.7	3.8	11	5.6	5.3	7
	3	2.9	**0.0**	87	3.5	0.4	41	3.4	**0.0**	58
CN	**1**	2.9	11.6	01	3.3	8.0	2	3.2	7.2	3
	2	3.4	5.6	10	5.8	1.0	39	5.7	0.2	47
	3	2.9	**0.0**	90	3.5	**0.0**	59	3.3	**0.0**	50

NO_2	**1**	3.0	9.6	2	3.2	9.1	1	3.2	8.2	2
	2	3.6	3.2	21	5.6	**0.0**	56	5.8	0.1	49
	3	2.8	**0.0**	77	3.4	0.7	43	3.4	**0.0**	49
CF_3	**1**	2.9	12.0	1	3.2	6.6	5	3.2	8.1	3
	2	3.6	8.4	3	5.8	2.2	27	5.7	4.4	14
	3	2.8	**0.0**	96	3.4	**0.0**	68	3.2	**0.0**	83
CH_3	**1**	3.0	8.5	3	3.2	4.3	12	3.2	2.5	18
	2	2.6	6.9	6	5.7	2.7	22	5.7	1.0	33
	3	2.9	**0.0**	91	3.4	**0.0**	66	3.2	**0.0**	49
***t*Bu**	**1**	3.0	7.7	4	3.2	3.6	18	3.2	2.6	24
	2	2.7	10.6	1	5.7	6.8	45	5.7	5.6	7
	3	2.9	**0.0**	95	3.6	**0.0**	77	3.3	**0.0**	69
OCH_3	**1**	3.0	9.1	3	3.3	4.2	15	3.3	4.7	13
	2	2.5	13.4	0	5.7	8.7	3	5.6	9.3	2
	3	2.9	**0.0**	97	3.4	**0.0**	82	3.4	**0.0**	85
Ph	**1**	3.0	11.2	1	3.2	7.4	5	3.1	5.6	9
	2	2.6	12.0	1	5.9	7.8	4	5.5	6.8	6
	3	3.0	**0.0**	98	3.6	**0.0**	91	3.3	**0.0**	85
OPh	**1**	3.0	14.5	0	3.3	11.6	1	3.2	10.3	2
	2	2.5	18.5	0	5.8	15.4	0	5.6	14.3	0
	3	2.8	**0.0**	100	3.5	**0.0**	99	3.5	**0.0**	98

NMR spectrageminal coupling and proton separation

We also used theory to study the geminal coupling constants for our ten dibenzyloxy disulfides. Regardless of the solvent employed, there was a linear correlation observed with Hammett's constants. As the electron withdrawing ability increased (i.e. higher Hammett's

constant value) the coupling value increases to a high of 12.6 Hz for nitro substituents to a low of 10.8 Hz for methoxy. Very minor fluctuations were observed between the various solvents.

In addition, we examined how similar the two benzylic protons are by comparing the difference (in Hz) of the center of their corresponding doublets. Regardless of which solvent was used, all were logarithmically related to the solvents dielectric constant and polarity index. The more polar the solvent, the more similar the benzylic protons are spectrally. On the contrary, the less polar solvents show greater differences between the benzylic protons. This trend can be attributed to the fact the lower polarity solvents will prevent free rotation in the molecule, as reflected in the H-bonding distances (**Table 7**). In virtually every case, whether in the ddh1, ddh2, or ddh3 conformation, the intramolecular H-bonding length was shorter in benzene compared to DMSO. This suggests a more compact solution structure of the dibenzyloxy disulfides in less polar solvents.In addition, from **Table 7**, the surface area minimizing conformation, ddh3, was the global minimum for all ten dibenzyloxy disulfides in benzene. However, in DMSO this was not the case universally, in particular with *para*-Cl and *para*-NO_2, where conformations ddh1 and ddh2 were the minima, respectively.

Finally, we analyzed the difference between the two benzylic protons as a function of the actual substituent on the *para*-position. By graphing with either Hammett's Constant [34] or Swain and Lupton's R-value [35], no visible trends were observed. However, when graphing with Swain and Lupton's F-value [35], we observed a parabolic relationship (**Figure 6**and **7**). This was unsurprising; we have observed this parabolic phenomenon with Swain and Lupton's F-value in previous studies, particularly with the analogous dibenzylicdialkoxy disulfides which underwent both photolytic [16] and thermolytic [17] decomposition at rates that parabolically correlated to F-values, in addition to a bis(benzyl) sulfites photolytic decomposition study [36].It

can be rationalized that a substituent with a high F-value, such as nitro, withdraws the electron cloud towards it and away from the benzylic protons, hence allowing for the proton, that is participating with intramolecular H-bonding, to do so at a greater extent. As the magnitude of the F-value decreases, this polarization difference decreases, "bottoming-out" with methoxy [37] at an F-value of 0.29. Substituents with F-values lower than methoxy, such as *t*-Bu, Me, etc., donates its electron density towards the ring or the oxygen which causes it to participate in H-bonding, as an acceptor, to a greater extent. In both of these extremes the benzylic protons are situated in the shielded region of the aromatic ring and thus increasing it electronic environment more so than its geminal hydrogen neighbor.

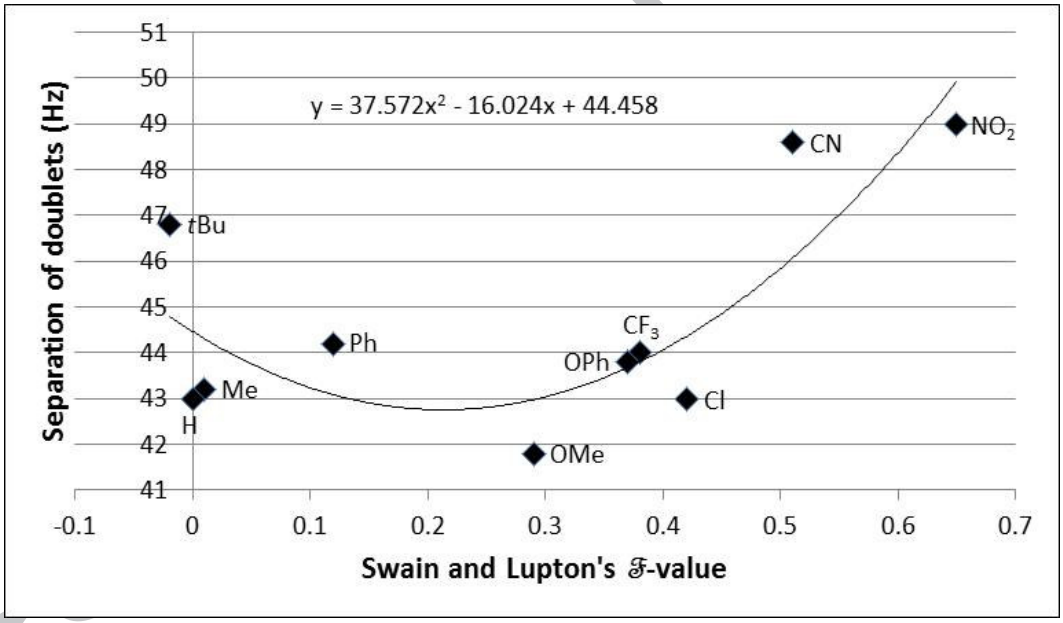


Figure 6: ^{1}H-NMR chemical shift separation of the two doublets of the library of dibenzyloxy disulfides in $CDCl_3$ compared to Swain and Lupton's F-value.Line-of-best-fit is a guideto the eye.

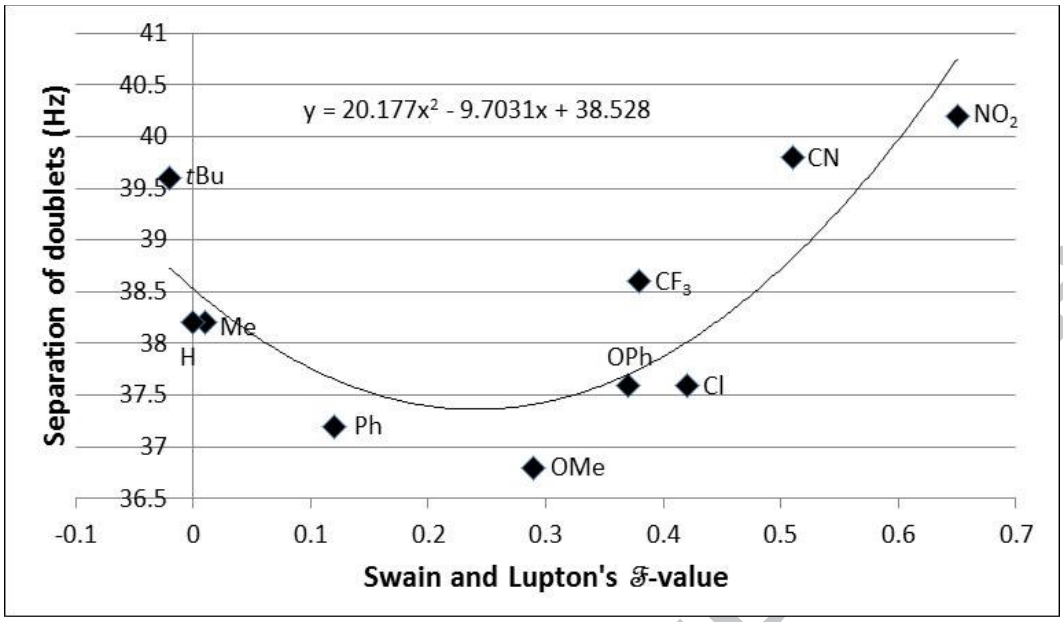


Figure 7: ^{1}H-NMR chemical shift separation of the two doublets of the library of dibenzyloxy disulfides in d_6-Acetone compared to Swain and Lupton's F-value.Line-of-best-fit is a guideto the eye.

Conclusion

The effect of electron donating and withdrawing groups attached to the dibenzyloxy disulfide has been shown to not only affect the chemical shift of the benzylic protons, but also the geminalcoupling. We also observed that there is a linear relationship with Hammett's constants with all solvents used, and that the trend is in the opposite direction if the solvent involves aromatic fragments. In addition, as the polarity of the solvent decreases the downfield chemical shift of the benzylic protons also decreases. These findings were rationalized via quantum-chemical modeling on the basis of the competition between several conformations of the dibenzyloxy disulfides, differing in the H-bonding modes, and affected variously by both the nature of the para-substituent and the solvent polarity. Finally, we observed that the difference between the two benzylic protons as a function of the substituent on the *para*-position is parabolically related to Swain and Lupton's F-value.

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Chemical shift and coupling constant analysis of dibenzyloxy disulfides

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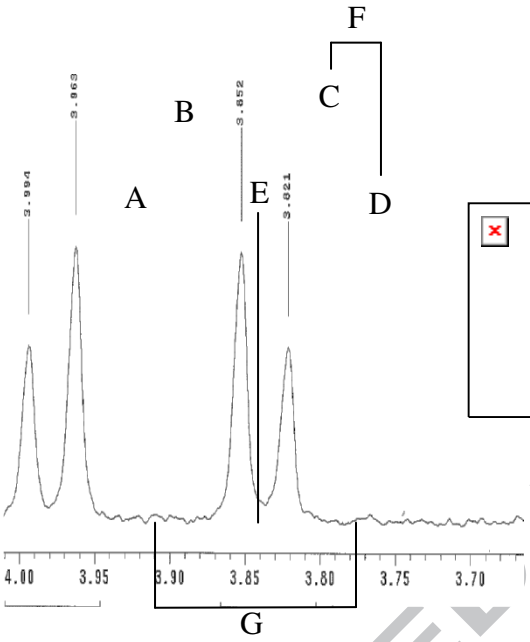
Graphical Abstract



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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.