Electronic properties of *para*-substituted thiophenols and disulfides from ^{13}C NMR spectroscopy and *ab initio* calculations: relations to the Hammett parameters and atomic charges†

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Received (in New Haven, CT, USA) 2nd January 2003, Accepted 27th January 2003
First published as an Advance Article on the web 22nd May 2003

A large number of para-substituted benzene thiols and the corresponding disulfides were synthesized and characterized by ^{1}H NMR, ^{13}C NMR, and IR spectroscopies. Geometries of all sixteen thiols and fourteen disulfide compounds were optimized at the B3LYP/6-31G(d) level, while the electronic structure and the ^{13}C isotropic shifts were calculated by *ab initio* Hartree-Fock method coupled with the Gauge-Independent Atomic Orbital (GIAO) algorithm and a 6-31+G(d,p) basis set. The calculated ^{13}C NMR isotropic shifts exhibit admirable agreement (δ rmsd ~4.6 ppm) with the experimental data. The chemical shift of *para*-substituted carbon showed a linear correlation with Hammett constants (σ_p and σ_p^+). Using this methodology the σ_p^+ constants for the dendritic ligands have been estimated to be 0.25 and 0.24 for **2(n)** and **2(o)**, respectively. In addition, the NBO charges on the sulfur atoms shows a latent response with the σ_p^+ parameter. The atomic charge on the thiophenolato sulfur is invariant with the electron withdrawing ability of the substituents, however, the charge increases with increasing electron-withdrawing power.

Introduction

In biological systems only a few elements function as donor atoms to metals and among them sulfur compounds occupy a special place in part due to their unusual chemistry.[1–3] The two sulfur containing amino acids, cysteine and methionine, are involved in a variety of physiological functions often by ligating metal ions; although methionine bound metal centers are relatively sparse. Prominent examples of methionine bound metal centers can be found in the blue copper proteins, the c-type cytochromes and bacterioferritin. In contrast, metal centers coordinated by cysteine residues are ubiquitous and they are involved in more diverse functions like in electron transfer processes (*e.g.*, ferredoxin, blue copper protein), catalysis (*e.g.*, NO synthase, cytochrome P450), storage/detoxification (*e.g.*, metallothioneins), and transport (*e.g.*, MerP, Atx). The organic cysteine residues are also found to carry out important physiological functions. For example, cysteine residues in thioredoxin, are involved in redox chemistry and cycle between the reduced cysteine and oxidized cystine forms. In addition, organic cysteine residues are also involved in hydrolysis reactions *e.g.*, in papain, where cysteine residues function in an analogues manner to the serine proteases.[2]

The physiologically prevalent cysteine coordination to metal centers is often modeled with aryl thiol ligands.[4] These model studies have provided vehicles for detailed understanding of the structure-function relation of the native systems. However, such systems frequently require derivatization of the benzene ring to finely tune the observed properties (*e.g.*, the stability, redox potential, spectral signature *etc.*). In most cases this derivatization involves the use of simple substituents, while the use of more complex functional groups as substituents is not uncommon. For example, dendritic thiolate ligands have been used for investigating the redox properties of iron-sulfur clusters as in ferridoxin centers;[5] as well as encapsulating oxo-molybdenum centers as models for DMSO reductase.[6]

Substituent effects are often discussed in terms of the Hammett parameters.[7] The Hammett constants, where available, are correlated with an observed property such as the reduction potential, the vibrational frequency or the energy of the charge transfer transition.[8] However, the use of the Hammett constant is not always straightforward, especially for ligands with complex architectures. The σ-constant accounts for both the inductive and the resonance effect while the σ^+-constant accounts only for the resonance effect.[7] The soft sulfur atom, with its diffuse electron density, poses an interesting question as to which of the above mentioned Hammett constant is more suitable. Despite years of intense research and continuing interest, no in-depth report has quantified the effect of substituents on the electronic properties of the sulfur donor of thiophenols.

The parameters describing the electron donating/withdrawing properties of substituents can provide useful information on the charge of the sulfur atom, which influences the effective nuclear charge on the metal center. Substituents can also influence the energy of the sulfur-based orbitals and thus these orbitals can more effectively interact with the metal orbitals. The energy of the sulfur based orbital is particularly important for ligand architectures where accurate information about complex functionality is desirable. The ^{13}C NMR chemical shifts account for the charge density on the carbon atom of the interest, which gives an excellent probe for studying the electronic effects through the molecular frame.[9] *Ab initio* quantum chemical methods such as the Hartree-Fock have been used for predicting ^{13}C chemical shifts for a variety of organic

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† Electronic supplementary information (ESI) available: all characterization data are tabulated in Table S1. A figure showing the dependence of the natural charge of the C1 atom of the disulfides on the ^{13}C NMR chemical shift is also provided. See http://www.rsc.org/suppdata/nj/b3/b300048f/

DOI: 10.1039/b300048f

compounds.[10] The same methodology has also been used for calculating ^{15}N, ^{31}P, and ^{19}F chemical shifts.[11] The calculated isotropic chemical shifts, *i.e.*, magnitude and orientations of the shielding tensor components, can be used for predicting structures.[12,13]

Molecular properties, especially the electronic effects, can be understood with the aid of atomic charges. Unfortunately, the atomic charge is not a physically observable quantity but can be computed using a variety of algorithms. The relative magnitude of the atomic charge depends on the choice of the method by which the electron density is partitioned among contributing atoms in a molecule. Mulliken population analysis[14] has long been the method of choice for calculating the atomic charge as it is computationally less demanding and has given satisfactory results for a number of systems.[15] Although it is convenient, Mulliken's method does not always provide the most accurate value and thus should be used with caution.[16] In contrast to Mulliken's equal partition method, natural population analysis[17] (NPA) has been used to calculate the natural atomic charges by considering localized atomic orbitals. The method is based on occupancies of the orthonormal natural atomic orbitals (NAOs) on each center, where the diffused molecular wave functions are transformed into localized orbitals using unitary transformations. Because the NAOs are the intrinsic to the wavefunction, the choice of basis set does not significantly alter the results, NPA has been suggested to exhibit superior numerical stability over the Mulliken population analysis.[18]

Oxo-molybdenum(V) complexes of dendrimer derived thiopheolato ligands exhibit a variation in the Mo(V)/Mo(IV) reduction potential. The Mo(V/IV) reduction potentials have often interpreted in terms of the Hammett constants of the substituents, however, such correlation is not straight forward in dendritic systems as other factors such as the solvent accessibility and the geometric distortion can also influence the reduction potentials. Very importantly, the Hammett parameters of the dendritic functionalities are often not known. We have correlated the Hammett constants[19] of a series of substituted aryl thiols and the corresponding disulfides (Chart 1) with the observed ^{13}C chemical shifts, computed their electronic structures, and discussed the dependency of the atomic charges. Using this methodology we have determined the Hammett constants (σ and σ^+) for novel dendritic functionalities.

Experimental

4-Hydroxythiophenol **2(a)**, 4-methoxythiophenol **2(b)**, 4-tert-butylthiophenol **2(c)**, 4-methylthiophenol **2(d)**, thiophenol **2(e)**, 4-chlorothiophenol **2(h)**, 4-mercaptobenzoic acid **2(k)**, 4-nitrothiophenol **2(m)**, oxalyl chloride, methyl amine hydrochloride, dimethyl formamide (DMF), were obtained commercially from the Aldrich chemical company or TCI America, and were used without additional purification. A majority of the solvents were purchased from the Fisher chemical company and were purified as follows: dichloromethane (DCM) from CaH_2; toluene and tetrahydrofuran (THF) from Na-benzophenone; and ethanol (EtOH) by refluxing with magnesium ethoxide. Triethylamine was dried by distilling over KOH pallets. Unless specified, all the reactions were done in oven-dried glassware in an atmosphere of dry argon using standard Schlenk techniques. For adsorption chromatography, silica gel (60 Å, 63–200 μm) from Sorbent Technologies was used. Thin layer chromatography was performed on silica gel-coated plastic plates also purchased from Sorbent Technologies.

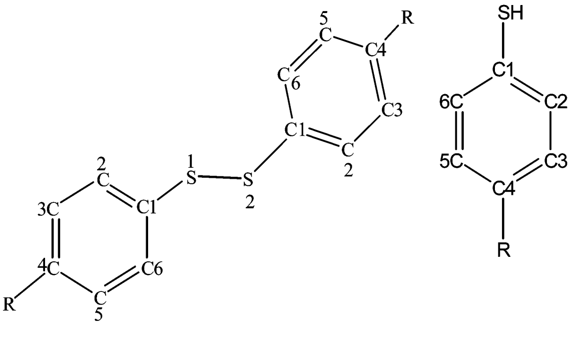

Chart 1 Abbreviations of the disulfides (**1**) and thiols (**2**): a) R = OH, b) R = OMe, c) R = t-Bu, d) R = Me, e) R = H, f) NHCOMe, g) R = $NHCOCF_3$, h) R = Cl, i) R = $CONMe_2$, j) CONHMe, k) R = COOH, l) R = COCl, m) R = NO_2, n) R = $CONHC[CH_2O(CH_2)_2CN]_3$, o) R = $CONHC[CH_2O(CH_2)_2CO_2CH_2CH_3]_3$.

Spectroscopy

Room temperature ^1H and ^{13}C NMR spectra were recorded using a Bruker ACP-300 spectrometer at 300.133 MHz and 75.469 MHz frequencies, respectively. NMR spectra of all disulfides were collected in dmso-d_6, while the NMR spectra of the thiols were recorded either in $CDCl_3$ or in methanol-d_4. To evaluate the solvent effect on the chemical shifts, NMR spectra of 4-chlorothiophenol were recorded in pure methanol-d_4, 3:1, 1:1, and 1:3 mixtures of $CDCl_3$ and methanol-d_4, and pure $CDCl_3$. The difference in the chemical shifts in these solvents was found to be small. For example, the ^{13}C chemical shifts deviates only 0.3–0.9 ppm for carbons that are not directly attached to sulfur (C2–C6), while the deviation for C1 is 2.5 ppm. The larger difference for C1 carbon is probably due to the hydrogen bond formation between thiol group and methanol molecules. Interestingly, in CH_3OH the C2 and C6 carbons resonate at different positions suggesting magnetic nonequivalence. This finding again lends support to the suggestion of hydrogen bond formation between the solvent methanol and thiol. Infrared spectra were recorded on a Perkin-Elmer FT-IR 1760X spectrometer on NaCl plates or in KBr pellets. The ^1H and ^{13}C NMR, IR, and melting points of all of the compounds are given in Table S1 (supporting information).

General method for the preparation of the disulfides

Compounds **1(a)**, **1(b)**, **1(c)**, **1(d)**, **1(e)**, **1(h)**, **1(k)**, and **1(m)** (Table S1) were synthesized by oxidizing their respective thiols with a saturated solution of I_2 in 95% EtOH in air.[20] The disappearance of the brown color of I_2 indicated the progress of reactions, and light yellow coloration of the reaction mixture indicated the completion of the reaction. For **1(k)** and **1(m)**, the products precipitated out from the solution, and were filtered, and washed with cold EtOH. Further purification to remove traces of iodine was done by sublimation under reduced pressure. In other cases, except **1(f)**, **1(g)**, **1(i)**, **1(j)**, and **l(o)** (see below) the solvent was evaporated under the reduced pressure, and the remaining product was purified by flash chromatography on silica gel using a mixture of 5% ethyl acetate in hexane. In all cases 90–95% yields were obtained.

N-(4-{[4-(acetylamino)phenyl]disulfanyl}phenyl)acetamide, 1(f). **1(f)** was synthesized by modifying a literature procedure.[21] In a flame dried round bottom flask bis(4-aminophenyl)disulfide (1.0 g, 4 mmol) was dissolved in DCM (20 mL) and Et_3N (2.8 mL, 20 mmol) was added with stirring to the resulting solution. The reaction mixture was cooled to 0 °C and CH_3COCl (0.7 mL, 9 mmol) was slowly added using a syringe. After completing the addition, the reaction mixture was warmed to room temperature and stirred overnight, followed by addition of 5 mL of water resulting a yellowish solid precipitate. The precipitate was filtered and recrystallized from acetonitrile/water to give 98% yield (1.3 g).

2,2,2-trifluoro-N-(4-{[4-(2,2,2-trifluoroacetylamino)phenyl]disulfanyl}phenyl)acetamide, 1(g). **1(g)** was synthesized using the same procedure described for **1(f)** using bis(4-aminophenyl)disulfide (1.0 g, 4 mmol), $(CF_3CO)_2O$ (1.3 mL, 9 mmol) and Et_3N (2.8 mL, 20 mmol) in DCM (20 mL) at 0 °C. The reaction was completed within 4 h forming a white precipitate that was filtered and washed with DCM (30 mL). The excess Et_3N in the filtrate was treated with dilute HCl resulting in a white precipitate, which was collected by filtration and washed with cold DCM. The combined yield of the final product was 90% (1.6 g).

N,N-dimethyl(4-{[4-(N,N-dimethylcarbamoyl)phenyl]disulfanyl}phenyl)carboxamide, 1(i). **1(i)** was synthesized by modifying the published procedure.[6] In a flame dried flask, 4, 4′-dithiobenzoic acid **1(k)** (0.5 g, 1.6 mmol) was dissolved in THF (10 mL), and DMF (3–4 drops) was added. The solution was cooled to 0 °C and oxalyl chloride (1.4 mL, 16 mmol) was slowly added into the reaction mixture *via* a syringe. The resultant solution was stirred for 3 h and evaporated to dryness under reduced pressure, yielding a yellow solid. The yellow solid was dissolved in DCM (15 mL) and transferred to a flask containing a mixture of $Me_2NH{\cdot}HCl$ (0.4 g, 8 mmol) and triethylamine (2.4 mL, 17 mmol) in DCM (15 mL) at 0 °C. The reaction mixture was gradually warmed to room temperature and stirred for overnight. Water was added and the organic layer was separated and dried over anhydrous magnesium sulfate. The organic layer was evaporated and the crude product was purified by chromatography on silica gel using 1:3 mixture of acetonitrile and toluene. The final product was a white solid. Yield: 85% (0.5 g).

N-methyl(4-{[4-(N-methylcarbamoyl)phenyl]disulfanyl}phenyl)carboxamide, 1(j). **1(j)** was synthesized by using the same procedure described for **1(i)** using disulfide **1(k)** (1.0 g, 3 mmol), $MeNH_2{\cdot}HCl$ (0.55 g, 8 mmol) and triethylamine (2.4 mL, 17 mmol) in DCM (7 mL). Upon addition of water a white precipitate formed,[22] which was filtered and washed with DCM. Yield: 65% (0.7 g).

Disulfide of [G_1–CN]-amide 1(n) and of [G_1-ester]-amide 1(o). These compounds were synthesized according to the procedure described for **1(i)**[6,23] with yields 85% and 89% yields, respectively.

N(4-sulfanylphenyl)acetamide 2(f). Disulfide **1(f)** (0.3 g, 1 mmol) was dissolved in a mixture of EtOH/THF (10 mL/10 mL) and $NaBH_4$ (0.14 g, 3.6 mmol) was added in small portions at 0 °C. After the complete addition, the temperature was allowed to attain the room temperature and the reaction mixture was stirred for an additional 4 h. After removing the solvents under the reduced pressure, the resultant light yellow solid was dissolved in distilled water (10 mL) and then dilute HCl was added until the pH reaches ~4.0. The precipitate was extracted with EtOAc (2 × 25 mL), the organic layer was dried over anhydrous $MgSO_4$ and evaporated under reduced pressure to afford an off-white solid with 77% (0.23 g) yield.

2,2,2-trifluoro-N(4-sulfanylphenyl)acetamide 2(g). **2(g)** was synthesized by reducing **1(g)** (0.3 g, 0.7 mmol) with $NaBH_4$ (0.1 g, 2.7 mmol) using the same procedure given for **2(f)**. The yield of the final off-white product was 73% (0.22 g).

N,N-dimethyl(4-sulfanylphenyl)carboxamide 2(i). The reduction of the disulfide **1(i)** (0.2 g, 0.56 mmol) by $NaBH_4$ (0.9 g, 2.5 mmol) was achieved by using the same procedure given for **2(f)**. The crude compound was purified by column chromatography on silica using 1:3 mixture of acetonitrile and toluene as an eluent. Yield 45% (0.09 g).

N-methyl(4-sulfanylphenyl)carboxamide 2(j). **2(j)** was synthesized using the same procedure given for **2(f)** using **1(j)** (1 g, 3 mmol) and $NaBH_4$ (0.5 g, 12 mmol.) yield 75% (0.75 g) of final compound.

Thiol of [G_1–CN]-amide 2(n) and thiol of [G_1-ester]-amide 2(o). These compounds were synthesized following the procedure described for **2(f)** with 90% and 96% yields, respectively.[6,23]

Computational details

All the computations were done using Gaussian 98W[24] and Hyperchem 6.03[25] software packages. The starting geometries were obtained by optimization with the PM3 Hamiltonian[26] implemented to the Hyperchem 6.03 program. These structures were used for the full optimization without any symmetry restrictions by density functional theory (DFT) implemented in the Gaussian 98W program. For the DFT calculations, Becke's three-parameter hybrid exchange functional[27] and Lee-Yang-Parr non-local correlation functional[28] (B3LYP) were used with the 6-31G(d) basis set[29] applied to all atoms.

Table 1 Selected distances and angles for the optimized structures of the disulfides **1(b)**–**1(m)** and thiols **2(a)**–**2(o)**

R in p-R–C_6H_4SSMe or p-R–C_6H_4SH	Disulfides S1–S2 bond distance	C–S1 bond distance	∠C1–S1–S2	Torsion angle C2–C1–S1–S2	Torsion angle C1–S1–S2–CH_3	Thiols C1–S bond distance
OH	2.101	1.793	104.9	−104.6	81.2	1.791
OMe	2.101	1.793	104.8	−106.3	80.6	1.792
t-Bu	2.097	1.798	104.5	−114.6	80.3	1.789
Me	2.095	1.799	104.7	−118.5	80.9	1.790
H	2.091	1.802	104.9	−128.2	80.6	1.789
NHCOMe	2.100	1.795	104.7	−105.4	81.4	1.789
$NHCOCF_3$	2.093	1.798	104.7	−124.9	81.0	1.786
Cl	2.090	1.800	104.8	−129.6	81.0	1.787
$CONMe_2$	2.080	1.803	106.1	−157.2	81.9	1.785
CONHMe	2.078	1.802	106.4	−164.5	82.6	1.784
CO_2H	2.078	1.800	106.4	−165.6	82.6	1.782
COCl	2.078	1.795	106.6	−171.1	84.5	1.776
NO_2	2.078	1.797	106.5	−169.4	84.2	1.778
$CONHC[CH_2O(CH_2)_2CN]_3$						1.782
$CONHC[CH_2O(CH_2)_2CO_2CH_2CH_3]_3$						1.784

Frequency calculations on the optimized structures were conducted to ensure that a minimum energy conformation for individual molecules was achieved. The NMR shielding tensors were calculated using the Gauge-Independent Atomic Orbital (GIAO) method[30] coupled with the Hartree-Fock level of theory using 6-31+G(d,p) basis set.[31] The ^{13}C chemical shifts were calculated as a difference between the calculated isotropic shift on the carbon of interest and the carbon of the tetramethyl silane standard as calculated at the same level of theory. The charges on the atoms of interest were calculated by using the Mulliken[14] and the NPA[15] algorithms. The percentage of atomic orbital contributions to their respective molecular orbitals were calculated by using the VMOdes program[32] from single point energy calculation on optimized geometries using 6-31G(d,p) basis set. Because geometry optimization, as well as the calculation of the NMR shielding tensors at 6-31+G(d,p) basis set on the disulfides were computationally expensive, the disulfide structures were modeled as p-R–C_6H_4–SSMe, where R is the *para*-substitutent on the thiol phenol ring. In order to understand the effectiveness of the simplified structure in replicating the electronic features of the complete structure, we have computed on full-size, symmetric (p-R–C_6H_4–S)$_2$ molecules with R = OH, H, COCl, and NO_2 and compared the results with those obtained from simplified structures of p-R–C_6H_4–SSMe. Surprisingly, calculations suggest that the geometric parameters and calculated NMR chemical shifts are nearly the same for both sets of calculations (Table S2, supporting information). For example, S–S bond distances in symmetrical disulfides are similar to for the unsymmetrical ones. In addition a very good agreement has been observed between the NBO charges on sulfur in both sets of calculations (Table S2). Thus, in the present case the simplified structures p-R–C_6H_4–SSMe represent the original structures quite well. Due to the computational limitations, the geometries of the disulfides of the dendritic ligands **1(n)** and **1(o)** were not optimized, and the NBO charges of the thiols were not calculated.

Results and discussion

Synthesis

Compounds with a disulfide linkage were synthesized either by oxidation of the corresponding thiol or derivatization of a preformed disulfide. In the first method, thiols were oxidized using an ethanolic solution of iodine. Compounds **1(k)** and **1(m)** precipitated out from the reaction mixture had adsorbed iodine, which was removed by sublimation. Oxidation by iodine in alcoholic solutions provides an efficient, mild and clean reaction with high yields of the target disulfides. Interestingly, the more common procedure of iodine oxidation of thiols involves an acidic media such as acetic acid.[33] In case of preformed disulfides, the amine or carboxylate groups in the para position were functionalized to form an amide bond. Compounds **1(f)**, **1(g)**, **1(i)**, **1(j)**, **1(n)**, and **1(o)** were synthesized using this method. Compound **1(l)** was synthesized *in situ* by reacting oxalyl chloride with **1(k)** and used without further purification. Thiols **2(f)**, **2(g)**, **2(i)**, **2(j)**, **2(n)**, and **2(o)** were synthesized by reducing the corresponding disulfides **1(f)**, **1(g)**, **1(i)**, **1(j)**, **1(n)**, and **1(o)** by $NaBH_4$.[34] The thiols were found to be moderately sensitive towards air and DMSO.

Molecular and electronic structure of the thiols and disulfides

As mentioned in the previous section, the symmetric disulfides are adequately represented by simplified structure, p-R–$C_6H_4SSCH_3$. The results of the calculations on p-R–$C_6H_4SSCH_3$ are discussed below. The most important distances and angles for the optimal geometry of the molecules **1(a)**–**1(m)** and **2(a)**–**2(o)** calculated at B3LYP/6-31G(d) level are presented in Table 1. Where available, the calculated geometries were compared with either previously reported optimized geometry[35] or crystallographically determined geometry (Table S3).[36,37] In these cases the metric parameters of the optimized structures are found to be close to those reported earlier, although for the disulfides the S–S and C1–S distances are overestimated while the C1–S–S angles are underestimated. For disulfides, the average S–S distance was calculated to be 2.09 Å; while the average C1–S distance is 1.80 Å; however, the average C1–S distance in the thiols is slightly smaller, 1.79 Å. For all disulfides, the skew conformations represent the minimum energy, while the two dihedral angles C1–S–S–C(Me) and C2–C1–S–S measure the skewness. The average C1–S–S–C(Me) dihedral angle is 81.67° with the maximum deviation of 2.70°; however, the C2–C1–S–S dihedral angle shows a larger variation, 69°. For **1(e)** and **1(h)** the crystal structures are known, and the observed C1–S–S–C(Me) angles are 85.0° and 103.5° while the calculated values are 80.6° and 81.0° for **1(e)** and **1(h)**, respectively.[36] A similar situation is also observed for the C2–C1–S–S dihedral angles. In this case the calculated values are 55.3° and 54.0°, while the reported values are 19.8° and 140.3° for **1(e)** and **1(h)**, respectively.[36] The difference in the dihedral angles has been suggested to be a reflection of the deviation of molecular

Table 2 Electronic parameters of substituted disulfides

R in p-R–C_6H_4SSMe	σ (σ$^+$)	Energy of HOMO, eV	Percentage of S1-atom in HOMO[a]	Percentage of benzene-ring in HOMO[a]	NBO Charges[c]			Mulliken Charges[c]		
					S1	S2	C1	S1	S2	C1
OH	−0.37 (−0.92)	−8.765	8.5	67.3	0.1292	0.0704	−0.2909	−0.1927	−0.0658	0.9286
OMe	−0.27 (−0.78)	−8.624	8.9	64.9	0.1291	0.0692	−0.2890	−0.2100	−0.0671	0.8976
t-Bu	−0.20 (−0.26)	−8.783	19.5	61.1	0.1277	0.0712	−0.2491	−0.2702	−0.0266	1.0213
Me	−0.17 (−0.31)	−8.750	22.6	60.5	0.1277	0.0713	−0.2493	−0.2614	−0.0150	0.7617
H	0.00 (0.00)	−8.869	33.7	52.3	0.1297	0.0740	−0.2270	−0.2362	0.0215	0.6922
NHCOMe	0.00 (−0.60)	−8.542	7.0	62.0	0.1289	0.0683	−0.2767	−0.1908	−0.0754	0.9881
$NHCOCF_3$	0.12 (−0.30)[b]	−8.830	21.2	53.6	0.1327	0.0778	−0.2510	−0.2867	0.2605	1.0142
Cl	0.23 (0.11)	−8.978	28.2	49.0	0.1346	0.0773	−0.2300	−0.2788	0.0302	0.6325
$CONMe_2$	0.31 (0.10)[b]	−8.762	39.7	48.5	0.1428	0.0834	−0.1802	−0.4434	0.1639	0.2609
CONHMe	0.36 (0.24)[b]	−8.779	41.1	48.1	0.1455	0.0858	−0.1710	−0.4854	0.1937	0.1126
CO_2H	0.45 (0.42)	−8.931	42.7	46.2	0.1505	0.0867	−0.1535	−0.4799	0.1961	0.0831
COCl	0.61 (0.79)	−9.185	44.3	44.3	0.1588	0.0906	−0.1408	−0.5107	0.2228	0.1486
NO_2	0.78 (0.79)	−9.366	46.7	42.3	0.1590	0.0914	−0.1490	−0.4610	0.2198	0.4272

[a] Calculated using 6-31G(d,p) basis set. [b] Hammett constant (σ_p^+) derived in this study. [c] S1 and S2 denote sulfur atoms attached to the benzene ring and methyl group, respectively.

Table 3 Electronic parameters of the thiols

R in *p*-R–C_6H_4SH	Energy of HOMO, eV	Percentage of S-atom in HOMO[a]	Percentage of benzene-ring in HOMO[a]	NBO Charge S	NBO Charge C1	NBO Charge H[b]	Mulliken Charge S	Mulliken Charge C1	Mulliken Charge H[b]
OH	−8.083	34.5	55.8	0.0357	−0.2267	0.1305	−0.1862	0.0873	0.0406
OMe	−7.982	33.1	55.0	0.0340	−0.2245	0.1305	−0.4605	−0.0788	0.0360
t-Bu	−8.179	38.5	56.1	0.0368	−0.1926	0.1316	−0.2706	−0.0738	0.0370
Me	−8.191	39.3	57.1	0.0365	−0.1947	0.1312	−0.2573	−0.0206	0.0391
H	−8.436	44.3	55.7	0.0404	−0.1810	0.1318	−0.1833	0.0309	0.0432
NHCOMe	−7.971	30.5	53.6	0.0349	−0.2126	0.1337	−0.2675	0.1667	0.0373
$NHCOCF_3$	−8.401	33.7	52.4	0.0456	−0.2008	0.1350	−0.2612	0.1331	0.0378
Cl	−8.594	37.7	51.0	0.0488	−0.1853	0.1336	−0.2121	−0.0526	0.0439
$CONMe_2$	−8.658	42.2	53.2	0.0519	−0.1604	0.133	−0.2653	−0.0354	0.0388
CONHMe	−8.727	42.9	52.9	0.0546	−0.1569	0.1329	−0.2686	0.0026	0.0389
CO_2H	−8.895	44.4	51.6	0.0601	−0.1404	0.1349	−0.2579	0.015	0.0420
COCl	−9.191	45.9	49.5	0.0710	−0.1308	0.1369	−0.2459	0.1055	0.0406
NO_2	−9.373	48.1	48.4	0.0725	−0.1363	0.1376	−0.1871	0.2691	0.0475
$CONHC[CH_2O(CH_2)_2CN]_3$	−9.042	44.3	51.3	–	–	–	−0.2945	0.0403	0.0385
$CONHC[CH_2O(CH_2)_2CO_2CH_2CH_3]_3$	−8.687	42.6	52.8	–	–	–	−0.2904	−0.0440	0.0377

[a] Calculated using 6-31G(d,p) basis set. [b] Thiolate H.

conformations from the solid-state structure perhaps due to the crystal packing (Table S3).[38] For thiols, the calculated C1–S distances (Table 1) are in the good agreement with the experimental values.[37] Interestingly, for disulfides with electron withdrawing substituents C2–C1–S–S dihedral angle is closer to 180° providing an effective delocalization between the sulfur p-orbitals and the π-orbitals of the benzene ring. In contrast, for electron donating substituents C2–C1–S–S dihedral angle is closer to 90° leading to a less effective interaction between the π-orbitals of the sulfur atom and the benzene ring orbitals. The dihedral angle shows a sigmoidal behavior with the both types (σ_p and $\sigma_p{}^+$) of Hammett constant with a higher correlation coefficient for $\sigma_p{}^+$. This conformational feature is also manifested in the shortening of the S–S distance in the case of electron withdrawing substitutents. Fig. 1 shows the dependency of the S–S distance on the Hammett parameters, σ_p or $\sigma_p{}^+$. The disulfide molecules can be reduced and the rate constants for this reduction for a series of para-substituted aryl disulfides show a non-linear dependency on the Hammett constants.[39] The origin of this behavior has been attributed to the difference in the reorganization energy,[40] which is dependent on the C2–C1–S–S dihedral angle.

For the thiols and disulfides the highest occupied molecular orbital (HOMO) is delocalized between the π-orbital of benzene ring and p_z-orbital of the sulfur atom(s) (Fig. 2, Tables 2 and 3). For the disulfides, the contribution from the phenyl ring to the HOMO varies from 42 to 67%, while their contribution to the thiols spans 48% to 67%.

In most cases the contribution of the sulfur atom linked to the benzene ring (*i.e.* the C1-atom) to the HOMO is smaller in the disulfide than that in the thiols. Electron-donating substituents are expected to destabilize the energy of the HOMO, while electron withdrawing substituents are expected to stabilize the HOMO. Higher the energy of the HOMO, easier it is to oxidize the thiol. Indeed, this behavior was observed when the energies of the HOMO of the thiols were correlated with the available oxidation potentials (Fig. 3).[41] Although a limited data set was available for this correlation, the linear relation can be exploited to predict the redox potentials of thiols that are otherwise difficult to measure experimentally. This relation predicts that the dendritic thiols **2(n)** and **2(o)** have reduction potential 335 mV and 209 mV (*vs.* SCE), respectively.

In the case of the disulfides, the contribution of the sulfur orbitals to the HOMO not only depends on the electron donating/withdrawing properties of the substituents, but also on the C2–C1–S–S dihedral angle. There are three sulfur p-orbitals that can be involved in bonding: two mutually perpendicular π-orbitals may be involved in π-acceptor or π-donation, while the third p-orbital (in-plane with the benzene ring) is involved in σ-interaction. By changing the C2–C1–S–S dihedral angle these two S π-orbitals mix and the relative importance of the individual orbitals is dictated by the dihedral angle. The Hammett parameter, σ_p, can be viewed as the combination of the inductive effect and the resonance effect, while $\sigma_p{}^+$ primarily indicates the resonance effect. Thus, it is conceivable that Hammett constants would correlate poorly with the sulfur

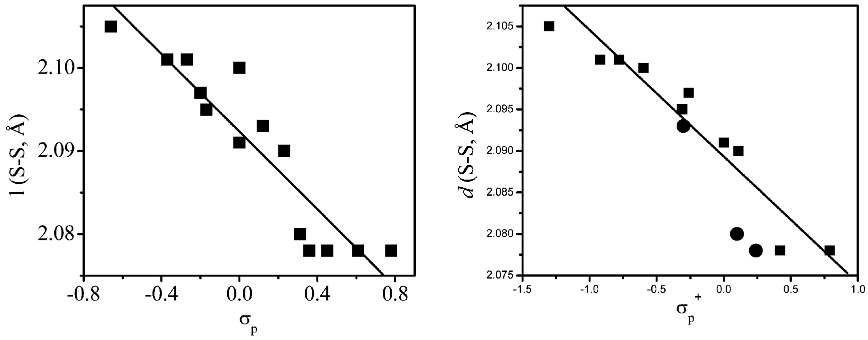

Fig. 1 Dependence of S–S bond distance (d, Å) on Hammett parameters (σ_p or $\sigma_p{}^+$): (a) $r^2 = 0.927$, rmsd = 0.004, d = −0.023 (±0.003)*$\sigma_p + 2.09$ (±0.001); b) $r^2 = 0.966$, rmsd = 0.003, d = −0.014 (±0.001)*$\sigma_p + 2.09$ (±0.001). Substituents with known Hammett constants are represented by ■, while those derived in this study are represented by ●.

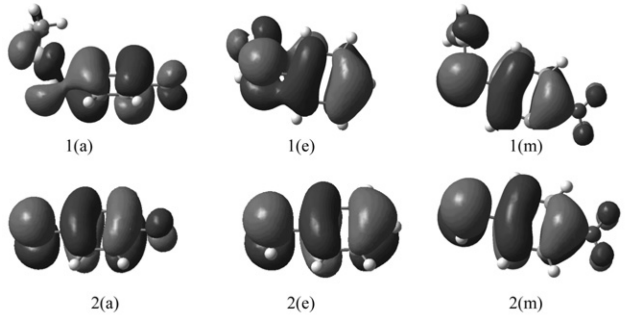

Fig. 2 Pictorial representation of the HOMOs for selected compounds.

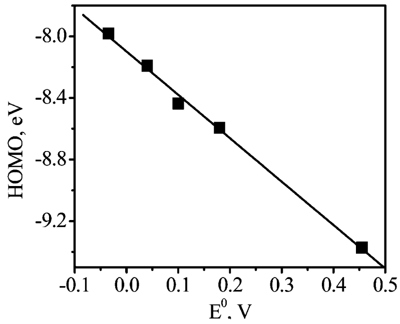

Fig. 3 The relationship between the first oxidation potential (E^0, V *vs.* SCE) of the thiophenolate ions (references 8a, and 8b) and the calculated energies (E, eV) of the HOMOs for **2(b)**, **2(d)**, **2(e)**, **2(h)**, **2(m)**. $r^2 = 0.998$, rmsd = 0.037, $E = -2.818\ (\pm 0.097)^* E^0 - 8.098\ (\pm 0.022)$.

contribution to the HOMO. Indeed, both the Hammett constants correlate poorly, although $\sigma_p{}^+$ constants correlate better than the σ_p constants.

Correlation between the experimental and calculated ^{13}C NMR chemical shifts and Hammett constants

Using the GIAO methodology at the Hartree-Fock level ^{13}C chemical shifts for both disulfides and thiols (Table 4) were calculated. The calculated shifts compared well with the experimental values for each of the carbon atoms in all 28 compounds used in this work (Fig. 4). The correlation coefficient $r^2 = 0.992$ with the rmsd = 4.79 ppm and a slope of 1.01 were observed. The agreement between the calculated and observed chemical shifts for C1 and C4 is better than those for other carbon atoms in the benzene ring. Overall, the results strongly suggest that the ^{13}C isotropic chemical shifts of the thiols and disulfides can be successfully reproduced by the Hartree-Fock GIAO method. Interestingly, in solution the C2 and C6 carbon atoms are magnetically equivalent due to conformational averaging. Similarly, C3 and C5 carbon atoms are equivalent. However, in computing the chemical shifts only one conformation is used resulting magnetic non-equivalence among the above pairs. This situation is reflected in chemical shift deviation of C2 from C6, as well as C3 from C5. Although at times, this deviation is more than 5 ppm, such a magnitude has been observed before.[42] Interestingly, solid-state ^{13}C NMR measurements also exhibit such magnetic nonequivalence among the aromatic carbon atoms in 4,4′-dimethoxybiphenyl.[43] The chemical shift is dependent on the electron density on the atom of interest, which is related to substituent parameters such as σ_p and $\sigma_p{}^+$. Thus, a correlation between the ^{13}C isotropic shift at C1(S) atom and the Hammett parameters is expected. Fig. 5 presents a linear correlation between the Hammett constants (σ_p and $\sigma_p{}^+$) and ^{13}C chemical shifts (both calculated and observed) for the carbon atom attached to the thiophenolato sulfur atom of the disulfide and the thiol. Again, this linear correlation can be used for predicting Hammett constants (σ_p or $\sigma_p{}^+$) for substituents that are yet to be observed. For example $\sigma_p{}^+$ values (calculated from the experimental

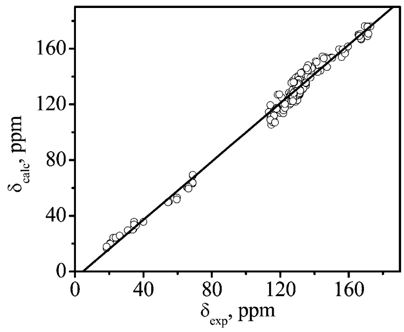

Fig. 4 Correlation between the experimental and the calculated ^{13}C NMR isotropic shifts (in ppm). $r^2 = 0.992$, rmsd = 4.79, $\delta_{calc} = 1.01\ (\pm 0.003)^* \delta_{exp}$.

Table 4 Calculated values of the aromatic region of the ^{13}C Chemical Shifts

	Disulfides						Thiols					
R[a]	C1	C2	C3	C4	C5	C6	C1	C2	C3	C4	C5	C6
OH	128.44	140.48	108.61	159.14	115.45	143.12	126.93	130.51	117.08	153.99	111.96	128.29
OMe	128.39	141.79	118.00	161.56	105.41	139.97	127.20	129.73	119.48	156.51	108.93	127.81
t-Bu	136.04	136.98	127.91	153.43	122.35	135.44	135.26	125.97	129.40	146.79	125.79	125.31
Me	136.33	137.35	128.62	142.12	126.25	135.52	135.08	126.45	130.00	135.46	129.70	126.19
H	140.92	133.16	126.94	129.34	126.71	134.92	139.5	125.98	130.10	124.13	129.90	125.71
MeCONH	131.15	139.51	113.85	144.78	115.60	140.15	130.46	126.94	115.71	139.34	119.67	128.89
CF_3CONH	135.85	139.07	118.98	140.13	113.61	134.97	134.57	127.02	117.40	135.57	120.20	128.40
Cl	139.60	135.3	129.36	141.58	127.48	133.38	138.18	126.54	130.56	136.37	130.32	126.27
Me_2NCO	145.46	124.85	135.13	133.68	130.38	123.70	144.50	125.04	135.85	131.74	131.44	121.94
MeNHCO	146.85	122.77	135.37	131.83	127.66	123.24	146.01	124.98	135.72	130.66	128.38	122.59
CO_2H	151.04	120.82	137.25	124.47	134.46	122.74	150.39	123.27	137.55	123.15	135.21	122.32
COCl	154.44	119.89	136.96	126.79	137.23	122.19	153.71	123.09	137.08	125.72	138.04	122.32
NO_2	153.76	120.20	129.10	144.13	128.84	122.80	153.11	123.02	129.48	143.26	129.52	122.73
G1CN[b]							148.09	124.98	135.93	128.03	128.19	122.57
G1Ester[b c]							146.08	124.78	135.90	129.92	128.17	122.30

[a] R = substituents para to the thiol or disulfide functionality on the phenyl ring. [b] Calculations were done only for thiol compounds. [c] For decreasing the computation time, the peripheral C_2H_5– groups were replaced by CH_3– groups.

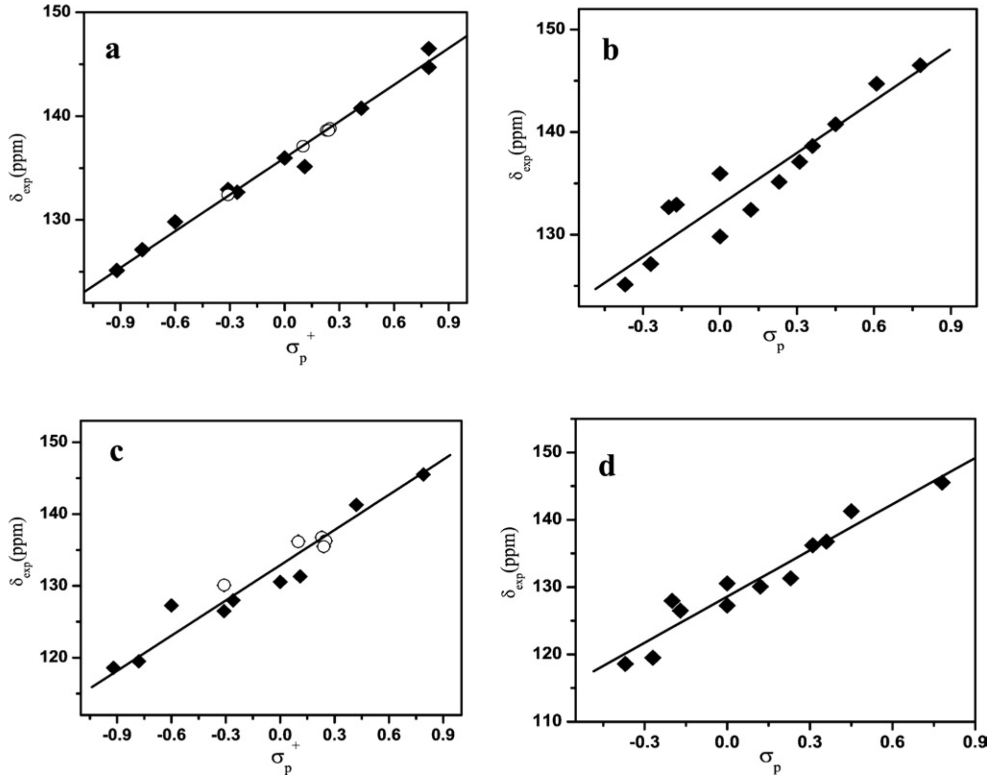

Fig. 5 Correlation between the experimental ^{13}C NMR chemical shifts of the C1 atom with the Hammett parameters σ_p^+ and σ_p. For disulfides: a) $r^2 = 0.992$, rmsd = 0.976, $\delta_{exp} = 11.56\ (\pm 0.53)^* \sigma_p^+ + 135.96\ (\pm 0.31)$; b) $r^2 = 0.943$, rmsd = 2.21, $\delta_{exp} = 16.9\ (\pm 1.81)^* \sigma_p + 133\ (\pm 0.66)$; and for thiols: c) $r^2 = 0.968$, rmsd = 1.98, $\delta_{exp} = 15.32\ (\pm 1.14)^* \sigma_p^+ + 133\ (\pm 0.54)$; d) $r^2 = 0.964$, rmsd = 2.24, $\delta_{exp} = 22.89\ (\pm 2)^* \sigma_p + 128.59\ (\pm 0.68)$. '◆' represents known substitutent constants and '○' represents substituent constants derived in this study.

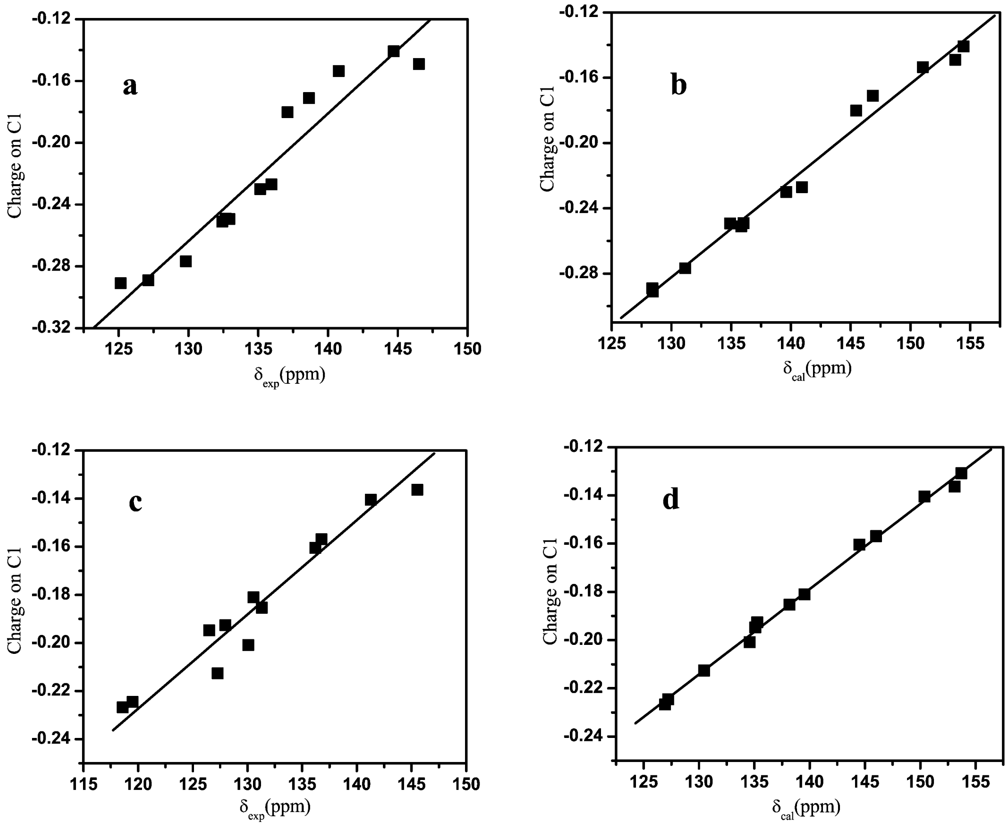

Fig. 6 Correlation between the experimental and calculated ^{13}C NMR isotropic shifts and NBO charges at C1 carbon atom. For disulfides: a) $r^2 = 0.961$, rmsd = 0.016, charge = δ_{exp}^* 0.008 (±0.001)−1.34 (±0.1); b) $r^2 = 0.993$, rmsd = 0.007, charge = δ_{calc}^* 0.006 (±0.0002)−1.052 (±0.029); for thiols: c) $r^2 = 0.970$, rmsd = 0.008, charge = δ_{exp}^* 0.004 (±0.0003)−0.667 (±0.038); d) $r^2 = 0.998$, rmsd = 0.002, charge = δ_{calc}^* 0.004 (±0.00001)−0.674 (±0.009).

^{13}C NMR spectra of the disulfides) for well-known substituents such as NHCOCF$_3$, CONMe$_2$, CONHMe were estimated to be −0.30, 0.10, and 0.24, respectively; while those for dendritic units in **2(n)** and **2(o)** are 0.25 and 0.24, respectively. On the other hand, σ_p may be calculated for dendritic ligands as 0.35 for **2(n)** and 0.34 for **2(o)** based on the relation obtained from Fig. 5(c).

Correlation between atomic charges and Hammett constants

Atomic charge is a sensitive indicator for substituent effects on the phenyl ring. On first approximation, it is expected that the inductive and the resonance effects of the substituents in the para-position should influence the charge of the sulfur and the C1 carbon atom. In such a case, a linear correlation between the atomic charges and Hammett parameters is expected. However no linear relation could be observed between the Mulliken charge, at the sulfur atom or the C1 atom, in the thiols and disulfides with the Hammett parameters. This behavior can be attributed to the fact that the Mulliken's equipartition method is less effective when diffuse functions are included into the basis set.[44] The natural population analysis (NPA), included as a part of the natural bond orbital (NBO) package, offers an alternative to Mulliken's method where the NBO charges are calculated by transforming the delocalized molecular orbitals into localized ones. Indeed, when the NBO charges were used for the C1 carbon atom, a good correlation was observed between the charges and the Hammett parameters (supporting information Figure S1). Interestingly, the σ_p^+ parameters correlate better than the σ_p parameters suggesting that the resonance effect is a dominant contributor for the charge on the C1 carbon. This behavior is not surprising as the inductive effect decreases significantly within three to four bonds.

The electron density on a carbon atom influences the shielding/deshielding of the atomic core and thus the NMR isotropic shift. In addition to electron density, hybridization and the chemical environment influence the ^{13}C chemical shifts. In the present molecules, similar chemical environments of the C1 carbon atom makes it a good candidate to test the dependency of ^{13}C chemical shifts on the atomic charges. Fig. 6 represents the relationship between the experimental and calculated ^{13}C NMR isotropic shifts for the C1 carbon atom with the NBO charges. While a reasonable correlation was observed for the experimental ^{13}C values, excellent correlation was observed for calculated ^{13}C isotropic shifts. To our knowledge, this is the first example where linear relationships between ^{13}C NMR parameters and the NBO charges for the thiols and disulfides were observed. Thus, ^{13}C chemical shifts provide a convenient probe for evaluating the NBO charges.

In principal the atomic charge on sulfur can be determined by ^{33}S NMR spectroscopy, however, ^{33}S NMR spectroscopy is not a straightforward process, as it requires isotopic enrichment of compounds with expensive ^{33}S isotope. In order to evaluate the charge on the sulfur, we correlated the calculated charge on sulfur with the Hammett constants. Fig. 7 shows the charge on sulfur of the disulfides that vary as a function of the electronic effects of the substituents. For electron donating substituents, the atomic charge on the sulfur is nearly invariant while the charges vary progressively with increasing electron-withdrawing properties of these substituents (Fig. 7). For both the disulfides and the thiols, the pattern is similar for σ_p and σ_p^+, with a more pronounced effect for the disulfides. This behavior suggests that the use of electron withdrawing groups in the benzene ring does not increase the charge on the sulfur atom in the disulfides. This latent response of charge on the sulfur with the Hammett constant is reminiscent of the 'electronic buffer' proposal put forward for the ene-dithiolato metal complexes to explain highly covalent metal-sulfur bonds.[45] A similar, albeit less pronounced, relation is also observed for the thiols.

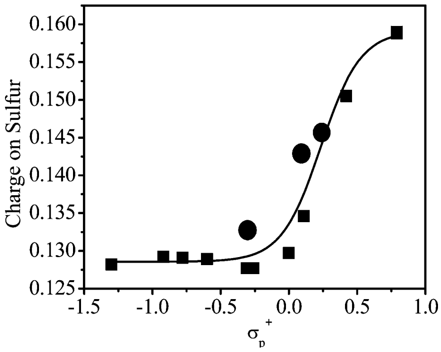

Fig. 7 Latent response of the charge on the S1 atom of disulfides on the Hammett constant. (■, known substituent constants; ●, substituent constants derived in this study).

Summary

A large number of *p*-substituted thiols and disulfides with varying electronic properties, including four dendritic molecules, were synthesized and characterized by the ^{1}H NMR, ^{13}C NMR, and IR spectroscopy. The electronic structures and the ^{13}C isotropic shifts were calculated for the majority of the molecules using the *ab initio* Hartree-Fock method coupled with the GIAO algorithm. The calculated ^{13}C NMR isotropic shifts are in admirable agreement with the experimental results. The atomic charge on the thiophenolato sulfur atom increases with increasing electron-withdrawing power, but is invariant with the electron donating ability of the substituents. However, the HOMO energies do not show direct correlation with the substituents. The ^{13}C chemical shifts linearly correlate with the Hammett constants providing a direct probe for parameterizing new groups.

Acknowledgements

This research is supported in part by the National Institutes of Health (GM 61555). We also thank Dr. Jeffry Madura for helpful discussions.

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