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To cite this article: Pankaj Attri , Shweta Gupta & Rupesh Kumar (2012) Green methodology for the preparation of disulfide, Green Chemistry Letters and Reviews, 5:1, 33-42, DOI: [10.1080/17518253.2011.578080](https://doi.org/10.1080/17518253.2011.578080)

To link to this article: <https://doi.org/10.1080/17518253.2011.578080>



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Published online: 16 Jun 2011.



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## RESEARCH LETTER

### Green methodology for the preparation of disulfide

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*(Received 24 September 2010; final version received 21 March 2011)*

A very simple, green method for the efficient oxidation of thiols to disulfides catalyzed by ascorbic acid was found to be practical, inexpensive, and reusable and has a simple work-up procedure. This oxidation is suitable for a variety of thiols at room temperature and proceeds cleanly in short reaction time and with high yields.

**Keywords:** thiols; disulfides; oxidation; ascorbic acid; water

#### Introduction

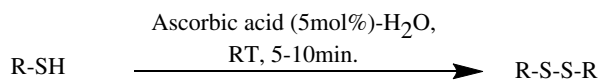
The oxidative coupling of thiols to disulfides under neutral and mild conditions is of practical importance in synthetic chemistry and biological processes (1, 2). Various reagents and oxidants such as cerium(IV) salts (3, 4), transition metal oxides (5), sodium perborate (6), H<sub>2</sub>O<sub>2</sub> (7), 2,6-dicarboxypyridinium-chlorochromate (8), and 1,3-dibromo-5,5-dimethylhydantoin (9) have been utilized for oxidation of thiols to disulfides under a range of experimental conditions (10–13). Disulfides have industrial applications as vulcanizing agents (14, 15) and are important synthetic intermediates with many applications in organic synthesis (16–18). There are still many reagents and oxidants that have been employed for the conversion of thiols to disulfides, under a range of various experimental conditions (19–24). Some of these methods suffer from one or more disadvantages such as long reaction times, difficult work-up, lack of general applicability to thiol substrates bearing alkyl, aryl, cyclic, and heteroaromatic moieties, formation of overoxidation products leading to lower yield, use of stoichiometric excess amount of the reagents for successful oxidation, and requirements of strong oxidizing agents, strong acidic or basic media, and use of expensive reagents. The oxidation of thiols to disulfides is a characteristic reaction (25–29) and further oxidation to disulfide *S*-oxides (thiosulfonates), 1,1-dioxides (thiosulfonates), and sulfonic acids is possible. In addition, the weak S–S bonds formation in compounds imparts high reactivity and less stability (30–32). From an economic and environmental viewpoint, there is an urgent need for inexpensive and intrinsically

waste-free oxidants and a recyclable catalyst that may be used for the synthesis of symmetrical disulfide mainly from thiols, because a large number of thiols are already commercially available or easily prepared. In order to understand the conversion of thiols to their corresponding symmetrical disulfides in a better way, in this report we show a new, very simple, one-pot, oxidation of a variety with good to excellent isolated yields of disulfide, after a simple work-up.

#### Results and discussion

Our group is researching the field of green chemistry and organic chemistry (33–38). In this paper we describe the ascorbic acid effectiveness in organic synthesis. Ascorbic acid (vitamin C) – water-soluble and well-known antioxidant (powerful electron donor) – is being projected as a versatile vitamin. The autoxidation and single-electron-transfer reactions in aqueous phase of vitamin C are some of its important properties, which demonstrate its versatile role (24, 25). Ascorbic acid (AH<sub>2</sub>) is a dibasic acid (pK values 4.1 and 11.8). Both of its enolic hydroxyl groups can dissociate. It forms salts, the most important of which are the monosodium, disodium, and calcium salts, the aqueous solutions of which are strongly acidic. In the case of thiols, water used as a solvent was necessary for solubility of ascorbic acid, leading to the disulfide. The optimum conditions for this oxidation reaction were found to be the use of ascorbic acid (10 mol%) in 5 mL of water at room temperature under the atmosphere of nitrogen gas (Scheme 1). In this paper we report the results of the oxidation of thiols to disulfides utilizing ascorbic acid in water. The present experimental methods are

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
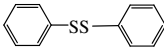
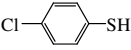
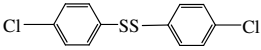
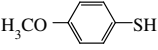
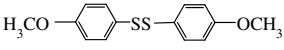
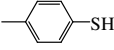
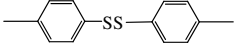
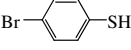
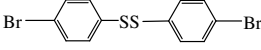

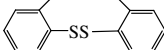
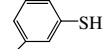
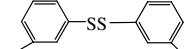

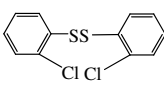

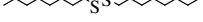
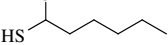
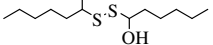
Scheme 1. Formation of disulfide using ascorbic acid.

simple, clean, and efficient oxidative ways that would produce the target disulfides in high yields without complicated work-up steps. The greatest advantages of this procedure arise from its employment of aqueous media. Our process is highly economic and eco-friendly as it requires neither elevated temperature nor harsh acids or bases, produces high yield with excellent chemoselectivity, reduces the reaction time, and is applicable to a variety of aliphatic and aromatic thiols substrates. From Table 1, it can be seen that the present method is of general applicability to aromatic (Entries **a–h**) and aliphatic thiols (Entries **i** and **j**). From Table 1, we can also see that benzenethiol is converted to 1,2-diphenyl disulfane in 5 min with 99% yield. Also, *p*-chlorobenzenethiol is converted to 1,2-bis(4-chlorophenyl) disulfane in 7 min and the yield is 100%, while *o*-chlorobenzenethiol gives the product in 10 min

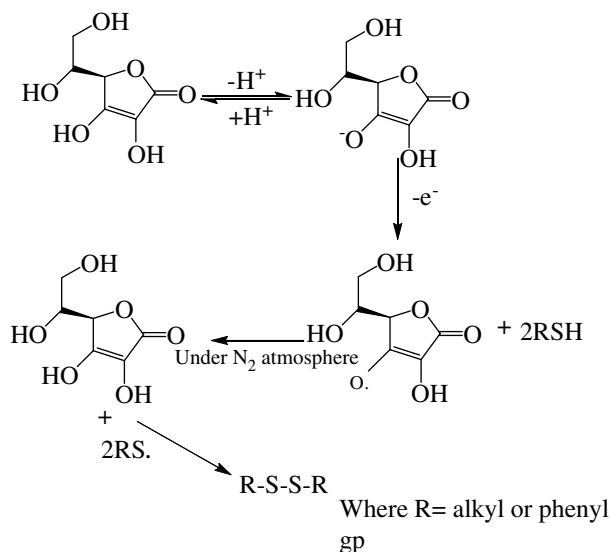
with yield of 94%. This result mainly leads to the steric hindrance of chlorine molecule. Ascorbic acid also has the capacity to convert aliphatic thiols such as octane-1-thiol and 1-mercaptohexan-1-ol to 1-heptyl-2-octyl disulfane and 1,1'-heptyl-2-octyl disulfanediylohexan-1-ol with 92–98% yield, respectively. As entry **j**, a hydroxyl functional group can be present in the substrate thiols and it remains intact during the formation of the product disulfides. The observed inertness of the acidic hydroxyl–hydrogen (entry **j**) is consistent with the higher acidity of S–H than O–H. The presence of electron withdrawing/donating groups had negligible effect on the yield but had some influence on the rate of the reaction. This results explicitly shows the efficiency of ascorbic acid to act as a catalyst and water as reaction medium.

The probable mechanism for this oxidation reaction is showed in Scheme 2. In the first step ascorbic acid is oxidized under mild conditions to semidehydroascorbic acid (AH<sup>-</sup>, commonly known as ascorbate) and then to free radical intermediate (AH<sup>•</sup>; ascorbyl-free radical) (Scheme 2). Two thiol molecules are reacted with the ascorbyl-free radical to

Table 1. Oxidation of various thiols to disulfide in the presence of ascorbic acid.

S. no.	Substrate	Time (min)	Product	Yield (%) <sup>a</sup>
<b>a</b>		5		99
<b>b</b>		7		100
<b>c</b>		5		98
<b>d</b>		7		95
<b>e</b>		7		96
<b>f</b>		8		98
<b>g</b>		9		95
<b>h</b>		10		94
<b>i</b>		6		92
<b>j</b>		8		90

<sup>a</sup>Isolated yield.



Scheme 2. Mechanism for the formation of disulfide from thiol.

yield two thiol radicals that combine to generate disulfide moiety.

There are several advantages of this reaction over other methods reported in the literature (3–9): the reactions were very clean, gave excellent reproducible yields, and were facile to apply to various thiols. In addition, the excellent selectivity and recyclability of ascorbic acid (Figure 1) obtained from these reactions play significant role.

## Experimental

### General

The materials (ascorbic acid) were purchased from Sigma-Aldrich and used without any additional purification. All reactions were monitored by thin-layer chromatography (TLC) on gel F<sub>254</sub> plates. The silica gel (250–400 meshes) for column chromatography was

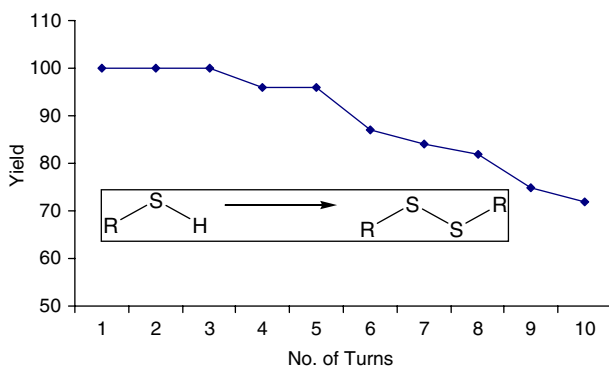


Figure 1. Catalytic cycles of ascorbic acid–water system for *p*-chloro thiols (1 mmol) with ascorbic acid (5 mol%) and H<sub>2</sub>O for subsequent turns.

purchased from Spectrochem Pvt. Ltd. India. <sup>1</sup>H and <sup>13</sup>C NMR spectra were recorded on a Bruker Spectrospin 300 MHz spectrometer in CDCl<sub>3</sub> (with tetramethylsilane for <sup>1</sup>H NMR and CDCl<sub>3</sub> for <sup>13</sup>C NMR as internal references). Mass spectra were recorded on a time-of-flight-mass spectrometer model no. KC455.

### General procedure for the preparation of disulfides

A round-bottom flask was charged with water (5 mL) and ascorbic acid (10 mol%). The mixture was stirred for 1 min; then the thiol (2 mmol) was added and reaction stirred under atmosphere of nitrogen at room temperature for 5–10 min (Table 1). The progress of the reaction was monitored by TLC. After completion of the reaction, dichloromethane (5 mL × 3) was added and the reaction mixture was washed with NaHCO<sub>3</sub> saturated solution and water and dried over Na<sub>2</sub>SO<sub>4</sub>. The solvent was removed and the residue purified by recrystallization or silica gel chromatography. The reaction products were analyzed with <sup>1</sup>H and <sup>13</sup>C NMR spectroscopy (Table 1). Analysis of compounds (Table 1, Entries **a**, **b**, **i**, and **j**) has been given in the Supporting Information. The rest of the spectra are in excellent agreement with the literature (39).

## Conclusion

In summary, we report a new, simple, and efficient method for the oxidation of thiols to symmetrical disulfides in good to excellent yields, using ascorbic acid in water as the oxidant. This procedure offers several advantages, such as: (1) ascorbic acid is a cost-effective and environmentally benign catalyst, (2) green synthesis (avoiding hazardous and toxic organic solvents for work-up), (3) applicability to a wide range of substituted thiols, and (4) room temperature reaction condition. Further, our protocol avoids the use of expensive and harsh chemicals and elevated temperatures, and a high yield of the product is obtained in short reaction time under ambient conditions.

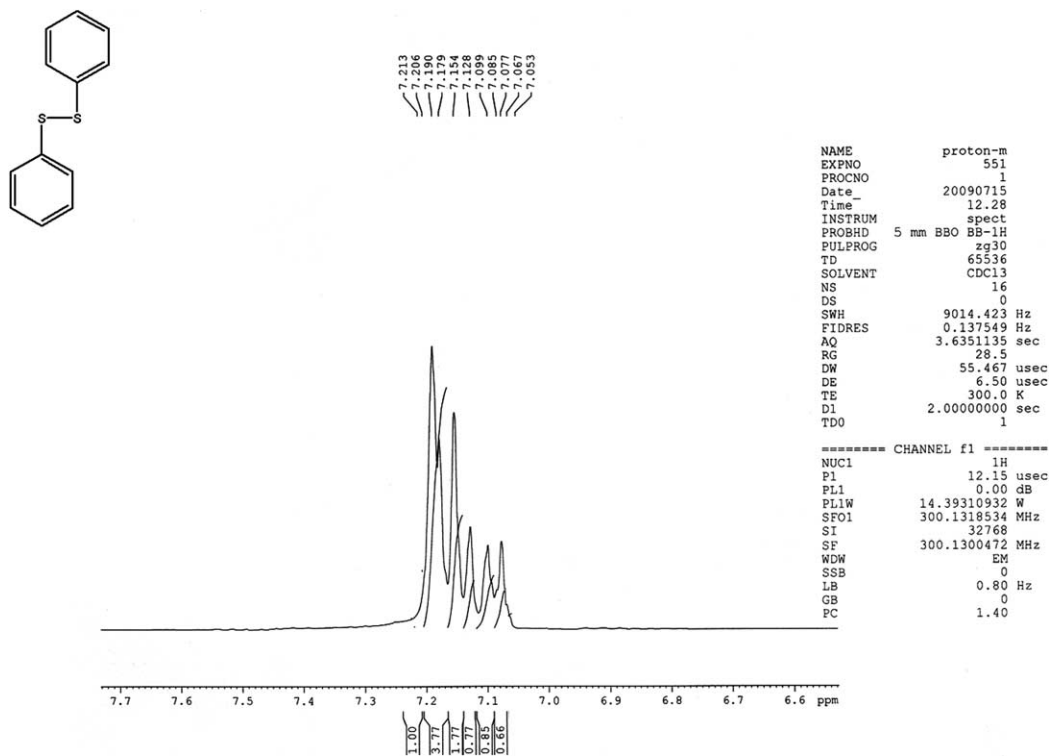
## Acknowledgements

We are pleased to acknowledge the financial support (Grant No. SR/FTP/CS-62/2006) for this investigation from DST, New Delhi.

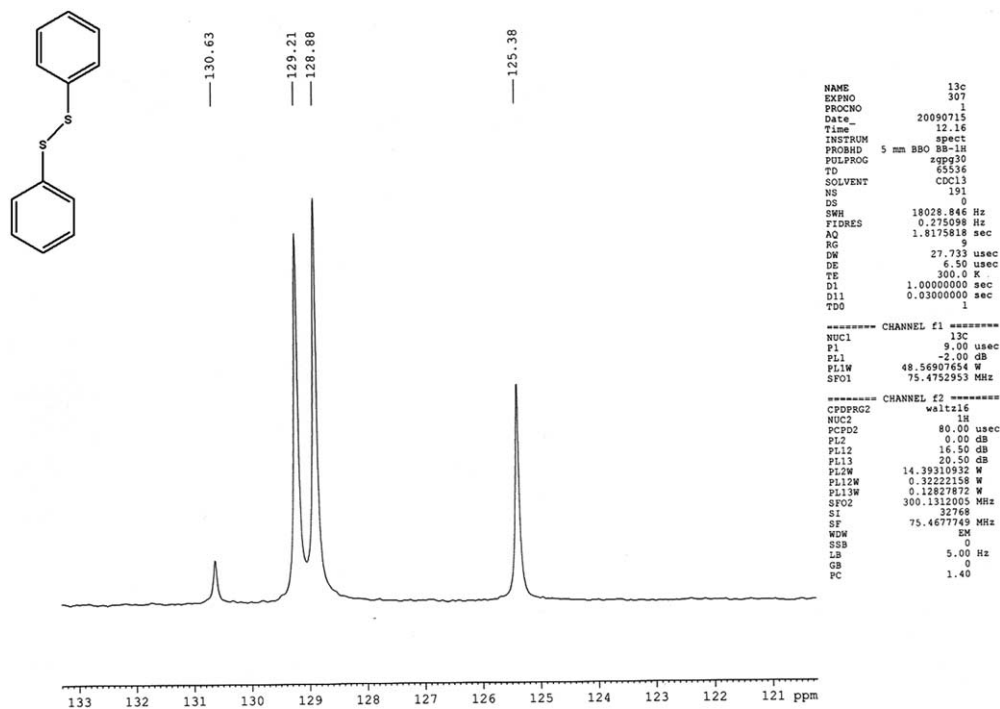
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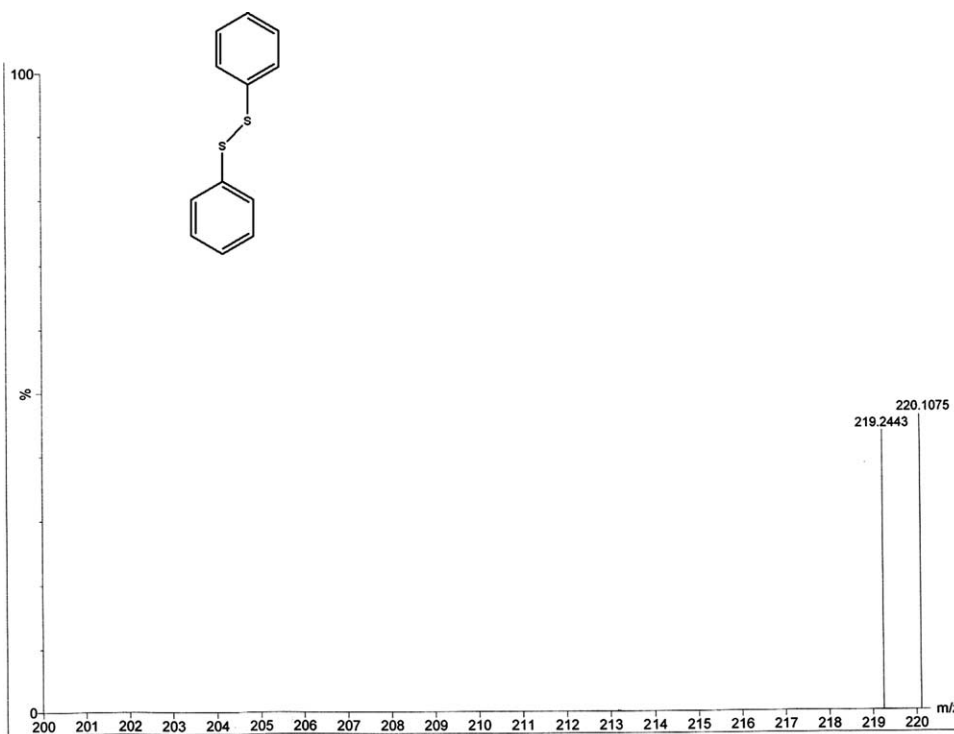
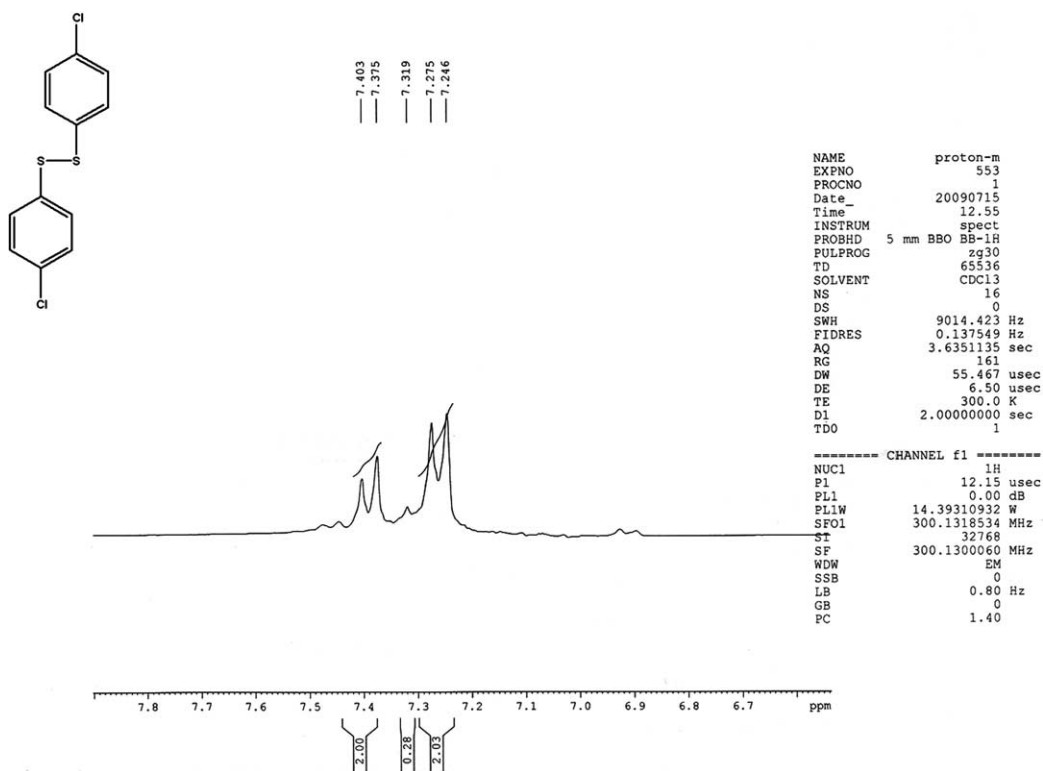
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Supporting information <sup>1</sup>H NMR (Table 1, entry a)

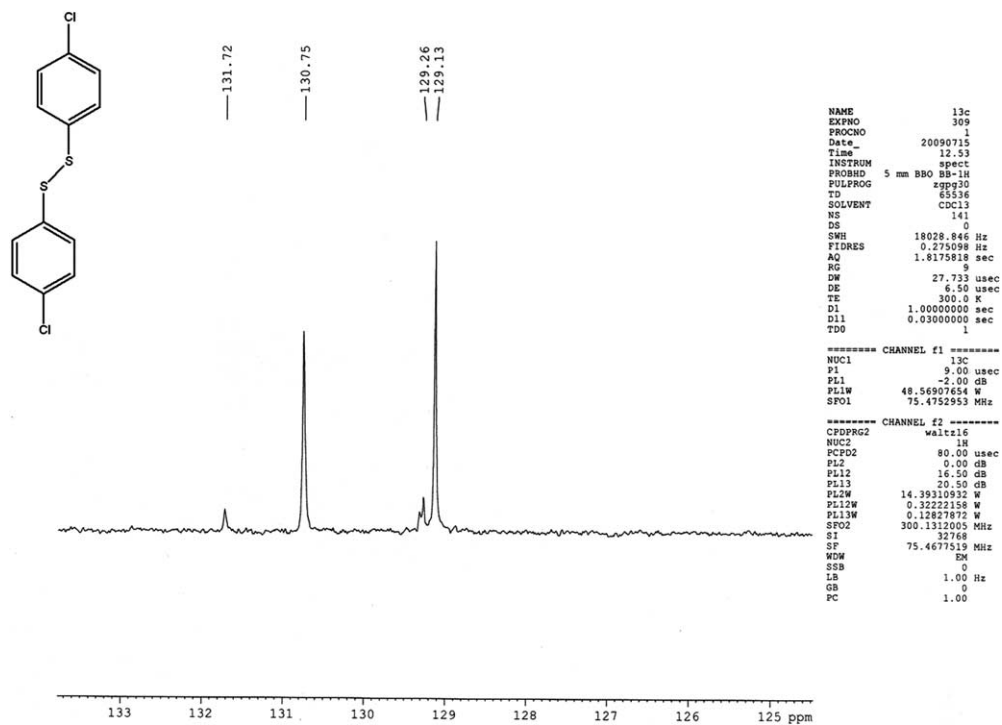
## C-13 NMR (Table 1, entry a)



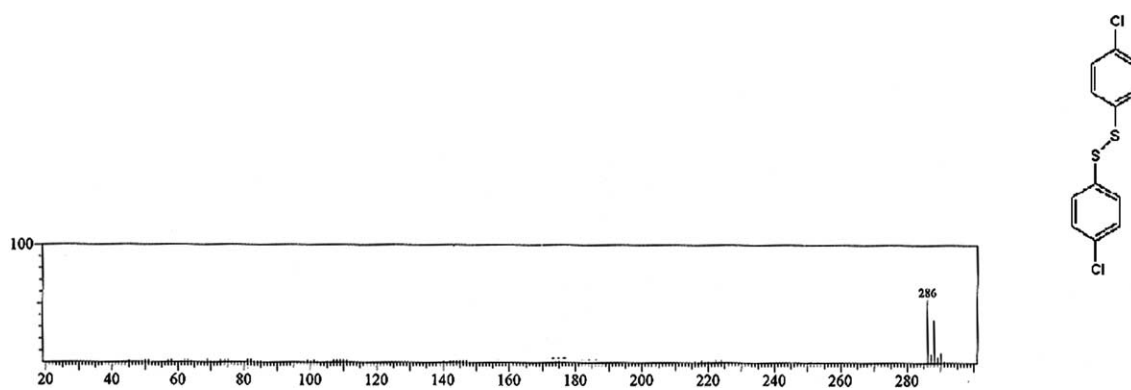
## Mass spectra (Table 1, entry a)

<sup>1</sup>H NMR (Table 1, entry b)

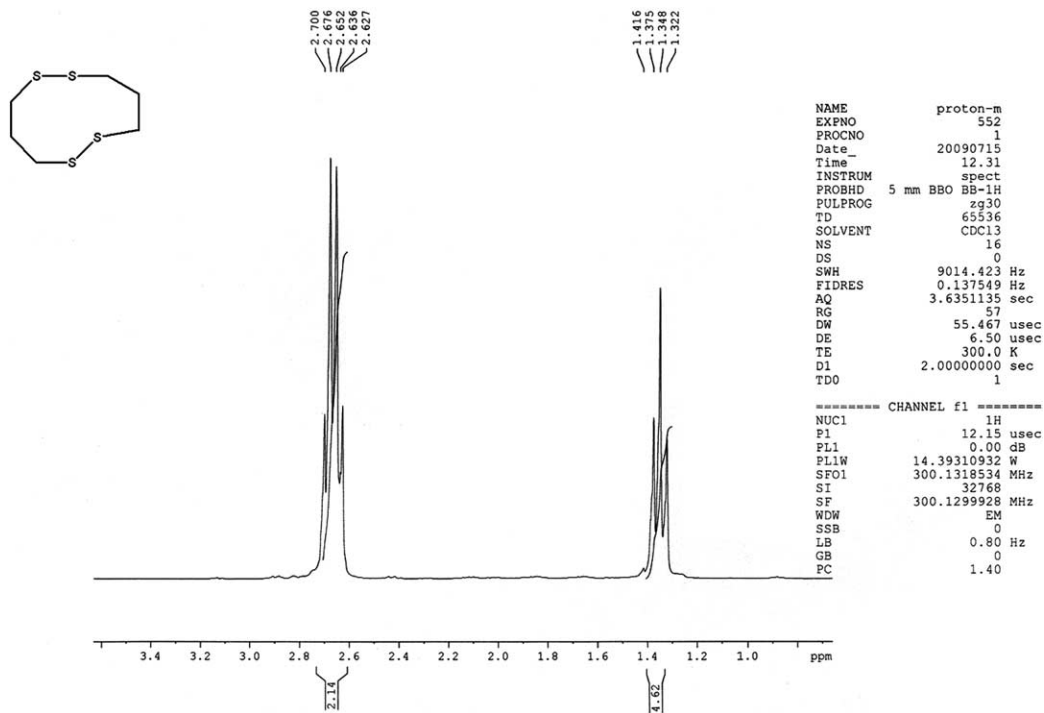
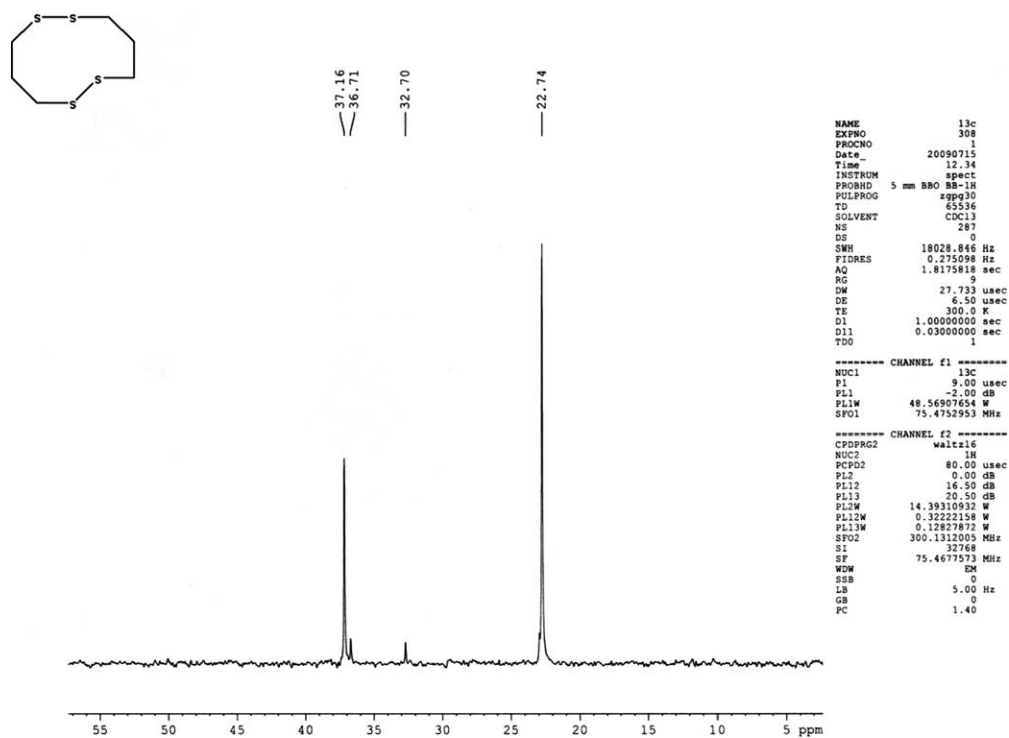
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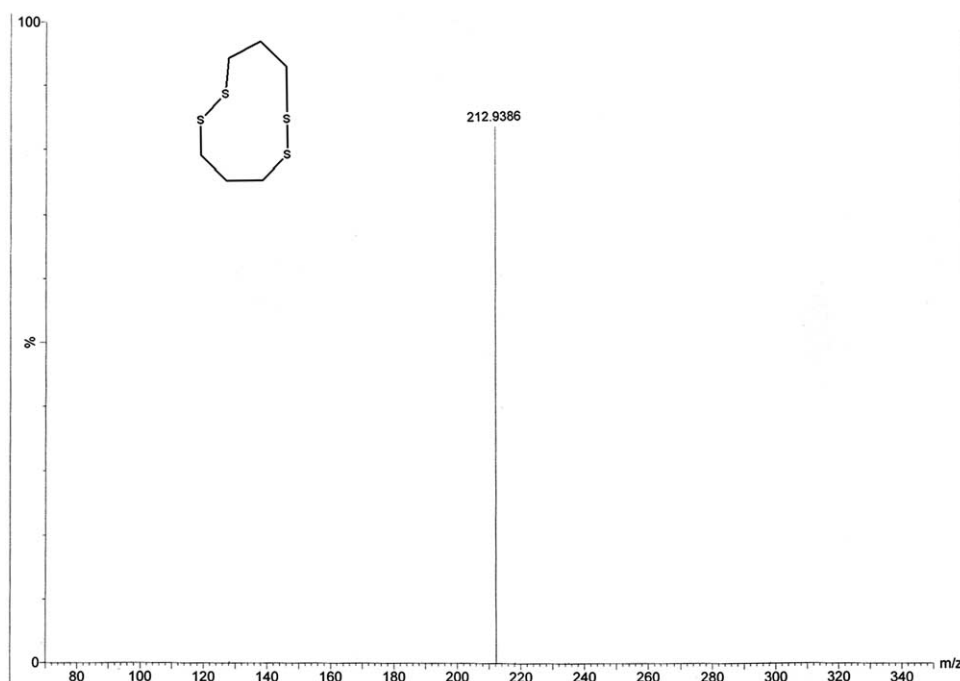
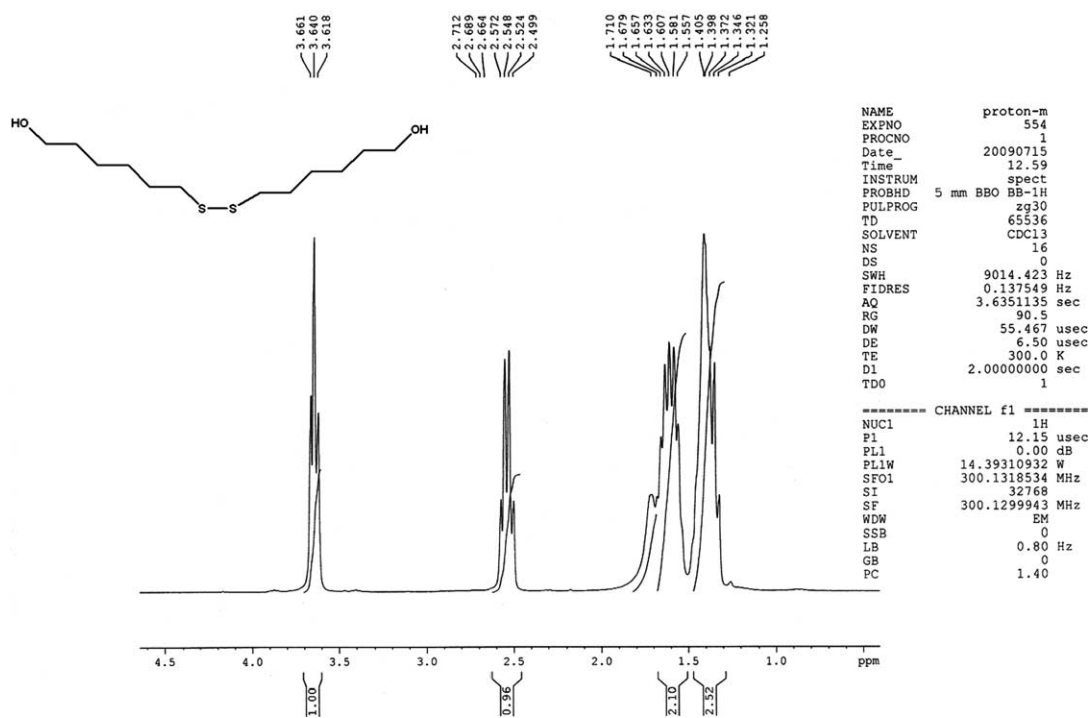
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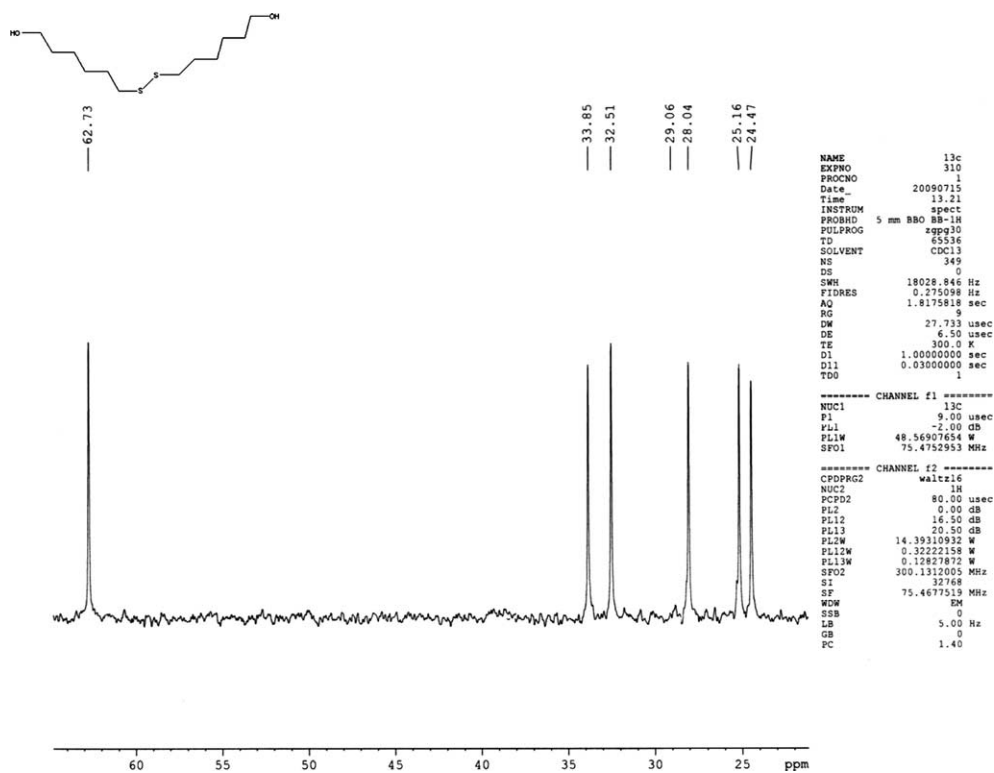


<sup>1</sup>H NMR (Table 1, entry i)<sup>13</sup>C NMR (Table 1, entry i)

Mass spectra (Table 1, entry i)

 $^1\text{H}$  NMR (Table 1, entry j)

## C-13 NMR (Table 1, entry j)



## Mass spectra (Table 1, entry j)

