Reactive Intermediates

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2,7-Di-*tert*-butylnaphtho[1,8-*cd*][1,2]dithiole 1,2-dioxides: Thermally Stable, Photochemically Active *vic*-Disulfoxides**

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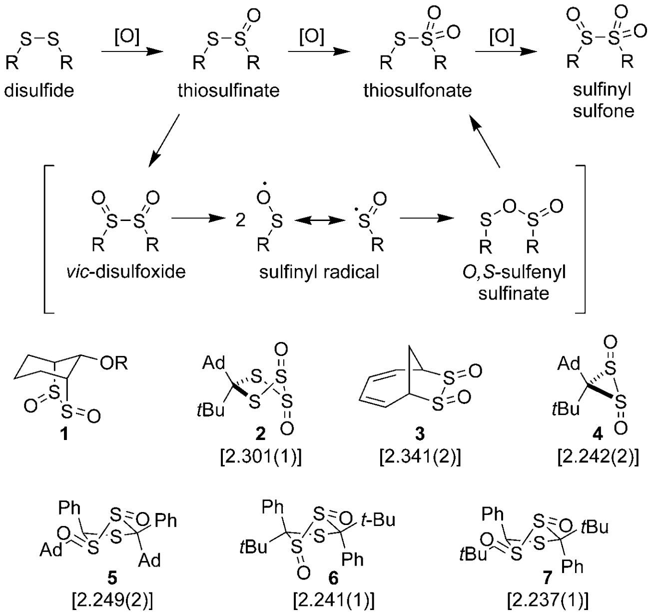
Oxidation and reduction of the disulfide (S–S) bond are fundamental transformations of importance not only in chemistry, but also in many biological systems (e.g. proteins containing S–S bridges) and in materials science (e.g. in the vulcanization of rubber). *vic*-Disulfoxides (α-disulfoxides) are reactive intermediates in the electrophilic oxidation of thiosulfinates to thiosulfonates (Scheme 1).[1] Compared with acyclic *vic*-disulfoxides,[2] cyclic variants show greater stability. Folkins and Harpp were able to identify *vic*-disulfoxides of type **1** that persist above 0 °C in solution.[3] More recently, Nakayama, Ishii, and co-workers succeeded in isolating *vic*-sulfoxides **2**–**7** in the solid state.[4–7] However *vic*-disulfoxides **2**–**7** still undergo further reaction in solution at room temperature or below. Herein, we report two novel diastereomeric *vic*-disulfoxides that have a significantly higher barrier to thermal rearrangement than **1**–**7**. Also, the first example of a photomediated epimerization reaction for this bonding motif is reported.

The low thermal stability of *vic*-disulfoxides is generally ascribed to the weakness of the sulfur–sulfur (S–S) bond, thus resulting in ready homolytic fission to give stabilized (pi-type) sulfinyl radicals.[8] The sulfinyl radicals rapidly recombine in a "head-to-tail" manner to form *O*,*S*-sulfenyl sulfinates (again rarely observed[3]), which subsequently rearrange to the thermally more stable thiosulfonate (Scheme 1). This propensity for dissociation is reflected in the longer S–S bond length of *vic*-disulfoxides compared with disulfides, thiosulfinates, or thiosulfonates. To stabilize the *vic*-disulfoxide linkage we have explored an approach based on constraining the two sulfur atoms of the sulfur–sulfur bond to remain in close proximity. Formation of the disulfide bond in 1,8-naphthalene disulfides from the corresponding 1,8-naphthalenedithiol is particularly facile owing to an associated reduction in the *peri*-interaction—in the dithiol, the two sulfur atoms are in closer proximity than the combined van der Waals radii of sulfur (3.7 Å). To this end we have investigated the oxidation of naphtho[1,8-*cd*][1,2]dithiole (**8**)[9] and the more sterically encumbered 2,7-di-*tert*-butylnaphthalene disulfide **11**[10] (see Scheme 2). In the latter case, we expected that steric buttressing about the sulfur–sulfur linkage should further disfavor bond fission (which must occur through bond elongation) by forcing the two sulfur atoms into even closer proximity.



Scheme 1. Formation and rearrangement of *vic*-disulfoxide, and known examples of thermally stable *vic*-disulfoxides (values in parentheses are (O)S–S(O) bond lengths (Å) from X-ray analysis). Ad = 1-adamantyl.

Thiosulfinates **9** and **12** were prepared in good yield by oxidation of disulfides **8** and **11** with one equivalent of *m*CPBA or DMDO (Scheme 2).[11] Further oxidation of **9** with *m*CPBA or DMDO gave the known thiosulfonate **10**.[10a,12] Clearly any *vic*-disulfoxide, if formed, is too unstable to be isolable under these reaction conditions. In contrast, oxidation of *tert*-butyl-substituted thiosulfinate **12** with one equivalent of *m*CPBA or DMDO gave a clean transformation into *trans vic*-disulfoxide **13**, which was obtained as a white, crystalline solid after purification by standard column chromatography on silica gel. *vic*-Disulfoxide **13** was also obtained in one step from disulfide **11** using two equivalents of oxidant

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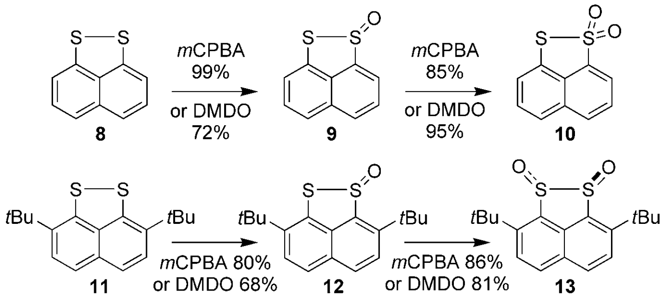


Scheme 2. Oxidation of 1,8-dithianaphthalenes. mCPBA = m-chloroperbenzoic acid, DMDO = 2,2-dimethyldioxirane.

(*m*CPBA, 92 % yield or DMDO, 80 % yield). Analytic data (^{1}H NMR, ^{13}C NMR, and IR spectra) for **13** were consistent with a symmetrical structure, and the *trans* configuration of the sulfinyl groups was ultimately determined by X-ray crystallographic analysis (Figure 1).[13,14]

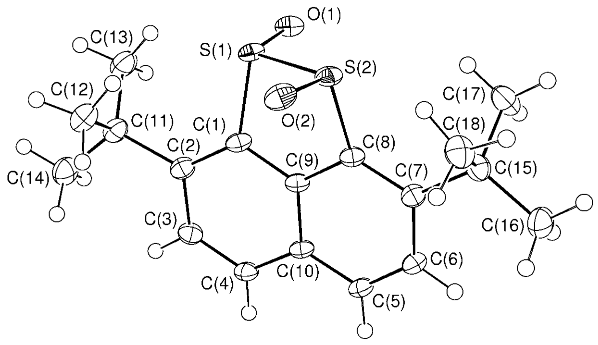


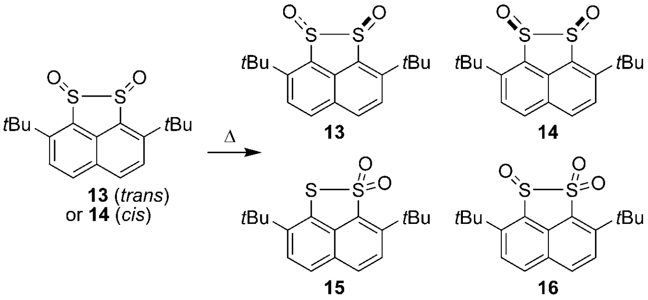
Figure 1. X-ray crystal structure of **13**. Thermal ellipsoids are drawn at the 50 % probability level. The group comprising S(1), O(1), S(2), and O(2) is disordered over two positions with an occupancy ratio of 87/13 %. Only the major component is shown. (In the minor component the S=O groups point in roughly the opposite direction to their counterparts in the major component).

In the solid state structure of **13** atoms O(1)-S(1)-S(2)-O(2) are virtually coplanar, with the largest deviation being 0.04 Å for S(1) and the O(1)-S(1)-S(2)-O(2) torsion angle being 174.06 (10)°. The 1,2-dithiolane ring is twisted relative to the plane of the naphthalene ring, with the C(1)-S(1)-S(2)-C(8) torsion angle being 29.08 (10)° and the average distance between the sulfur atoms and the least squares plane through C(1)-C(10) being 0.44 Å. The S–S bond length (2.1983(9) Å) is notably shorter than that in the known *vic*-disulfoxides **2–7** (Figure 1).

vic-Disulfoxide **13** is stable both in the solid state and in $CDCl_3$ solution at room temperature. Addition of TFA to an NMR sample of **13** failed to induce any reaction, whereas treatment of **13** with HCl in dioxane resulted in clean reduction to the thiosulfinate **12** (94 % yield) rather than epimerization.[15]

The thermal stability of **13** was also evaluated (Table 1). At temperatures greater than 80 °C, slow formation of thiosulfonate **15** was observed along with *cis vic*-disulfoxide **14**, although the predominant product at this temperature remained the starting *trans vic*-disulfoxide **13** (Table 1, entry 1). Complete conversion of *trans*-**13** into thiosulfonate **15** required heating in mesitylene at reflux (167 °C) over 38 hours (Table 1, entry 5). At intermediate temperatures it proved possible to also isolate the unexpected sulfinyl sulfone **16** from the reaction mixture (Table 1, entries 2–4).

Table 1: Thermal rearrangement of **13** and **14**.



Entry	Disulfoxide	Reaction conditions[a]	Yield [%][b]			
			13	**14**	**15**	**16**
1	*trans*-**13**	C_6H_5Cl, 80 °C, 38 h	70	10	4	–
2	*trans*-**13**	C_6H_5Cl, 108 °C, 38 h	55	10	5	4
3	*trans*-**13**	mesitylene, 108 °C, 38 h	55	10	5	3
4	*trans*-**13**	C_6H_5Cl, 132 °C, 38 h	49	18	4	2
5	*trans*-**13**	mesitylene, 167 °C, 38 h	–	–	92	–
6	*cis*-**14**	C_6H_5Cl, 80 °C, 38 h	10	75	5	–
7	*cis*-**14**	C_6H_5Cl, 108 °C, 38 h	15	50	5	5
8	*cis*-**14**	C_6H_5Cl, 132 °C, 38 h	20	45	10	5
9	*cis*-**14**	mesitylene, 167 °C, 34 h	–	–	93	–

[a] All reactions were carried out as 0.01 M solutions of **13** or **14** in degassed solvent. [b] Yield of isolated product after column chromatography.

The structure of *cis vic*-disulfoxide **14** was confirmed by X-ray crystallographic analysis (Figure 2).[14,16] The S–S bond length in **14** (2.2356(9) Å) is slightly longer than in **13**, and is perhaps due to the dipolar repulsion of the sulfinyl bonds. In contrast to **13** these bonds are far from being coplanar, with the O(1)-S(1)-S(2)-O(2) torsion angle being 29.09(14)°. Calculations by Gregory and Jenks on *meso*-MeS(O)–S(O)Me have shown that conformations with O-S-S-O torsion angles of 0° are unstable, high energy maxima.[8]

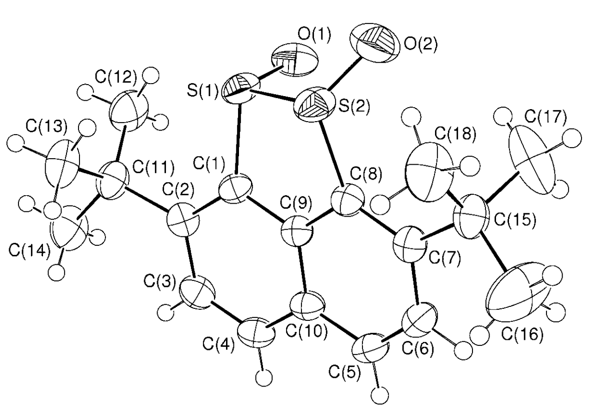
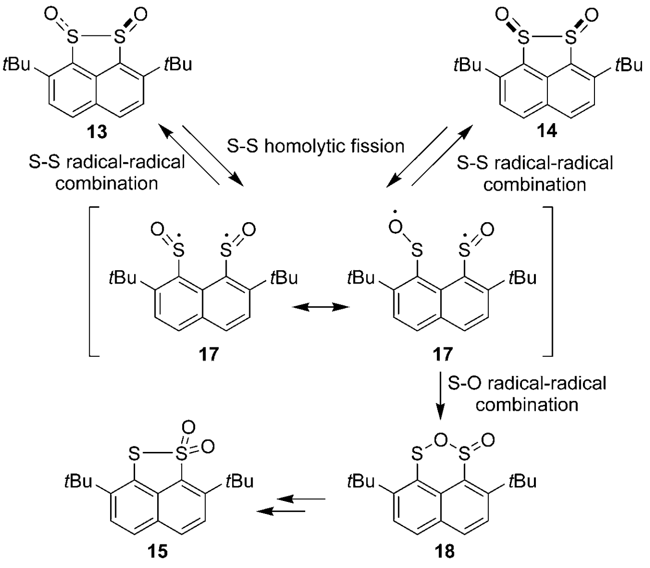


Figure 2. X-ray crystal structure of **14**. Thermal ellipsoids are drawn at the 50 % probability level.

Again, the 1,2-dithiolane ring is twisted relative to the plane of the naphthalene ring, with the C(1)-S(1)-S(2)-C(8) torsion angle being 23.59(11)° and the average distance between the sulfur atoms and the least squares planes through C(1)-C(10) being 0.37 Å.

The thermal stability of *cis vic*-disulfoxide **14** is comparable with *trans*-**13**. After 38 hours at 80°C, the major compound isolated was **14** along with small amounts of *trans*-**13** and thiosulfonate **15** (Table 1, entry 6). At higher temperatures trioxide **16** was again observed (Table 1, entries 7 and 8). Complete conversion into the thiosulfonate **15** was again achieved in mesitylene at reflux in a comparable reaction time (Table 1, entry 9).

The formation of *cis* and *trans vic*-disulfoxides under thermal conditions is consistent with the general mechanism for *vic*-disulfoxide breakdown. After homolytic fission of the S–S bond, the resulting bis(sufinyl)radical **17** can recombine to form *trans vic*-disulfoxide or *cis vic*-disulfoxide through C–S bond rotation (Scheme 3). *O,S*-Sulfenyl sulfinate **18**, a plausible intermediate in the formation of thiosulfonate **15**, can be formed through an alternative S–O bond formation in **17**. We have not isolated **18**, perhaps unsurprisingly since the *peri*-fused six-membered ring is expected to suffer from an increased steric clash with the flanking tertiary butyl groups compared with its five-membered precursor. This steric clash can be relieved through subsequent rearrangement to the thiosulfonate **15**.



Scheme 3. Formation and reactions of bis(sulfinyl)radical **17**.

At present we do not have a satisfactory explanation for the formation of **16**, which is thermally stable in degassed mesitylene and chlorobenzene at reflux, thus suggesting it is not an intermediate in the formation of **15**. Sulfinyl sulfones have been observed in the disproportionation of certain acyclic *vic*-disulfoxides, although the proposed intermolecular mechanistic pathways are unlikely in the case of **13** and **14**.[17] Thiosulfinate **12** was not observed in the reaction mixture, thus suggesting **16** does not arise through disproportionation of **15**.

Diastereomeric *vic*-disulfoxides **13** and **14** were also found to undergo photomediated epimerization at room temperature under irradiation with a 500 W halogen lamp. This apparent equilibration resulted in an approximate 1:1 ratio of *trans*-**13** and *cis*-**14** after around 14 hours of irradiation, starting from either pure **13** or **14**, along with small amounts of thiosulfonate **15** (Table S1 in the Supporting Information). The rate of equilibration and the final ratio of products was essentially independent of solvent ($CDCl_3$, $ClCH_2CH_2Cl$, MeCN, benzene, MeOH). Although these data are also consistent with a mechanism involving cleavage and reformation of a S–S bond after bond rotation in an intermediate bis(sulfinyl)radical **17**, we cannot at this stage exclude other possibilities based on studies on the photomediated racemization of sulfoxides.[18]

In addition to **13** and **14**, we have carried out X-ray crystallographic analyses for oxides **9**, **12**, **15** and **16** to make a comparison with known data for disulfides **8** and **11** and the unsubstituted sulfinyl sulfone naphtho[1,8-*cd*][1,2]dithiole 1,1,2-trioxide (**19**; Table 2).[14,19] In all cases, the sulfur–sulfur bond lengths for the 2,7-di-*tert*-butyl derivatives are shorter than those for the unsubstituted compounds, thus suggesting the *ortho tert*-butyl groups have a significant buttressing effect on the S–S bond. With increasing oxidation level, there is an increase in bond length, however the trend is not linear. The presence of a sulfinyl group (thiosulfinates, *vic*-disulfoxides, sulfinyl sulfones) leads to longer sulfur–sulfur bonds, which correlates with the generally observed increase in reactivity of these functionalities within the organosulfur chemistry of disulfides and their oxides.[1b] The longest S–S bonds are for the *vic*-disulfoxides **13** and **14**.

Table 2: Sulfur–sulfur bond lengths (Å) in 1,8-naphthalene disulfide derivatives from X-ray crystallographic analysis.

Compound class	Unsubstituted derivatives [Å]		2,7-Di-*tert*-butyl derivatives [Å]	
disulfide	**8**	2.0879(8)[a] [2.096(3)][b]	**11**	2.0580(13)[a]
thiosulfinate	**9**	2.138(4) [2.141(4)][b]	**12**	2.0890(9)
vic-disulfoxide	–	–	*trans*-**13**	2.1983(9)[c]
	–	–	*cis*-**14**	2.2356(9)
thiosulfonate	**10**	2.1143(14)[a]	**15**	2.0764(14)[c]
sulfinyl sulfone	**19**	2.2520(13)[a]	**16**	2.179(4)[c]

[a] Data taken from reference [19]. [b] Where there are two crystallographically independent molecules in the unit cell the value for the second molecule is given in parentheses. [c] In structures **13**, **15**, and **16** the groups containing sulfur and oxygen atoms are disordered over two positions at occupancy ratios of 87:13 for **13** and **14** and 86:14 for **16**. The sulfur–sulfur bond lengths could not be determined as accurately for the minor components due to their low occupancies and so only values from the major components have been reported.

In conclusion, the presence of bulky *ortho tert*-butyl groups on the naphthalene ring allows for the isolation of the first *peri*-substituted *vic*-disulfoxides, which contain the shortest (O)S–S(O) bond reported for this traditionally elusive functionality. The *trans* diastereomer **13** can be accessed directly through oxidation of the parent disulfide, whereas the *cis* isomer **14** is prepared through an unprecedented *vic*-disulfoxide photoepimerization reaction. We anticipate the high thermal stability of **13** and **14** will further facilitate study into the mechanism of rearrangement of *vic*-disulfoxides, and their possible application in synthesis.[20]

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Keywords: isomerization · oxidation · rearrangement · substituent effects · sulfur heterocycles

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[13] Analytical data for **13**: $R_f = 0.31$ (8:2 *n*-hexane/EtOAc); m.p. 178–180 °C (EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.70$ (s, 18H; $C(CH_3)_3$), 7.81 (d, $^3J(H,H) = 8.6$ Hz, 2H; ArH), 8.05 ppm (d, $^3J(H,H) = 8.6$ Hz, 2H; ArH); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 33.2$ (CH_3), 38.0 (C), 127.4 (CH), 132.2 (CH), 132.7 (C), 138.7 (C), 139.5 (C) 155.1 ppm (C); IR (KBr): $\tilde{\nu} = 2959$, 1367, 1117, 1067, 1040 cm^{-1}; HRMS (EI) calcd for $C_{18}H_{22}O_2S_2$ (M^+):334.1061; found: 334.1045. Crystallographic data for **13**: $C_{18}H_{22}O_2S_2$, $M_r = 334.48$, $T = 200(2)$ K, $\lambda = 0.67030$ Å, triclinic, $P\bar{1}$, $a = 8.7247(16)$ Å, $b = 9.4724(18)$ Å, $c = 10.642(2)$ Å, $\alpha = 97.649(3)°$, $\beta = 107.070(2)°$, $\gamma = 92.469(3)°$, $V = 830.1(3)$ Å^3, $Z = 2$, $\sigma_{cal} = 1.338$ Mg m^{-3}, $\mu = 0.325$ mm^{-1}, crystal size = $0.10 \times 0.10 \times 0.05$ mm^3, $\theta_{max} = 30.06°$, reflections collected = 10683, independent reflections = 5577, $R(int) = 0.0680$, final $R1$ $[I > 2\sigma(I)] = 0.0711$, final $wR2$ $[I > 2\sigma(I)] = 0.1793$, R1 (all data) = 0.0964, wR2 (all data) = 0.2017, residual electron density = 0.595 e Å^{-3}. The S_2O_2 site shows disorder with 87/13 % occupancy for O(1)-S(1)-S(2)-O(2)/O(1a)-S(1a)-S(2a)-O(2a).

[14] CCDC 714447 (**9**), 714448 (**19**), 714449 (**12**), 714450 (**15**), 714451 (**13**), 714452 (**14**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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[16] Analytical data for **14**: R_f 0.15 (8:2 60–80 petroleum ether/EtOAc); m.p. 172–174 °C; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.76$ (s, 18H; $C(CH_3)_3$), 7.81 (d, $^3J(H,H) = 8.7$ Hz, 2H; ArH), 7.98 ppm (d, $^3J(H,H) = 8.7$ Hz, 2H; ArH); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 33.0$ (CH_3), 38.3 (C), 127.3 (CH), 131.7 (CH), 131.8 (C), 135.9 (C), 137.4 (C), 154.9 ppm (C); IR (KBr): $\tilde{\nu} = 2961$, 2925, 1116, 1099, 1068, 1042 cm^{-1}; HRMS (EI) calcd for $C_{18}H_{22}O_2S_2$ (M^+):334.1061; found: 334.1066. Crystallographic data for **14**: $C_{18}H_{22}O_2S_2$, $M_r = 334.48$, $T = 296(2)$ K, $\lambda = 1.54178$ Å, triclinic, $P\bar{1}$, $a = 8.6970(4)$ Å, $b = 9.5037(4)$ Å, $c = 10.6581(4)$ Å, $\alpha = 97.635(3)°$, $\beta = 107.551(2)°$, $\gamma = 91.727(3)°$, $V = 830.18(6)$ Å^3, $Z = 2$, $\sigma_{cal} = 1.338$ Mg m^{-3}, $\mu = 2.934$ mm^{-1}, crystal size = $0.30 \times 0.20 \times 0.20$ mm^3, $\theta_{max} = 65.74°$, reflections collected = 5460, independent reflections = 2557, $R(int) = 0.0267$, final $R1$ $[I > 2\sigma(I)] = 0.0429$, final $wR2$ $[I > 2\sigma(I)] = 0.1148$, R1 (all data) = 0.0469, $wR2$ (all data) = 0.1183, residual electron density = 0.752 e Å^{-3}.

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