Generalized Synthesis and Physical Properties of Dialkoxy Disulfides

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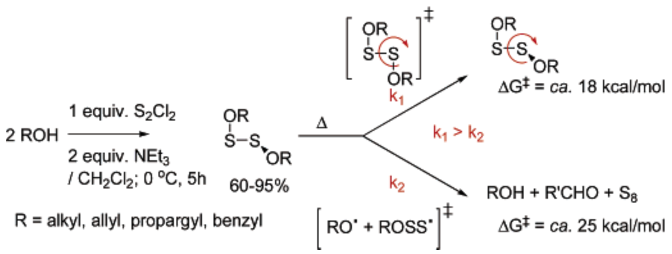
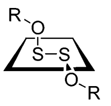


A substrate study was undertaken in order to probe the scope of S_2Cl_2 coupling of alcohols to form dialkoxy disulfides. Compounds **1b** and **1f** are new; along with **1a**, **1c**, **1h**, and **1j**, all of the title compounds are fully characterized, and the yields of **1a** and **1c** have been optimized from previously reported syntheses. The effect of the R-substituent about the OSSO moiety has been carefully probed as yields vary. A substrate and a solvent study of the coalescence behavior of this class was carried out. The origin of the inherently large barrier to rotation and the resultant thermal decomposition pathway is discussed. Both phenomena are shown to be solvent independent; hindered rotation is substrate independent. The decomposition of **1a** is ca. 7 kcal/mol higher than the barrier to rotation about the S−S bond. The combined evidence suggests acyclic unsymmetric homolytic cleavage of the dialkoxy disulfide.

Molecules of the form ROSSOR have been known for over a century.[1] Their connectivity was partially elucidated when Thompson and co-workers[2,3] were able to synthesize and characterize this unbranched polychalcogenide known as a dialkoxy disulfide **1**. Since then, the work conducted generally has been for a specific subset of compounds[4−14] or for theoretical investigations.[15−18]



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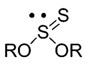

2

Although compounds of form **2** have been characterized,[19−22] the only known systems with this thionosulfite moiety are cyclic.[20−22] Compounds containing the OSSO fragment **1** possibly isomerize into their valence-bond isomeric thionosulfite form (OS(=S)O **2**).[23]

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SCHEME 1. Representation of the Original Concerted Mechanism

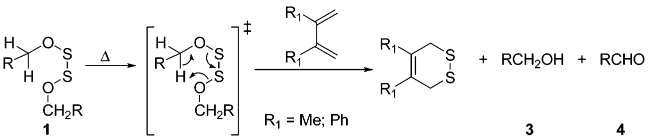

TABLE 1. S−S Torsional Barrier of Some Related Polychalcogens

compd	barrier[a]	ref
MeS−SMe	6.8	55
MeOS−SN(Me)$_2$	14.5	56
EtOS−SOEt	18.4	10

[a] In kcal/mol.

Most intriguingly, Thompson[2] observed that upon heating, **1** decomposed to afford the corresponding aldehyde, alcohol, and elemental sulfur. He hypothesized a six-membered cyclic transition state, similar to that shown in Scheme 1, to account for product formation, though to our knowledge there is no experimental evidence to support this mechanistic conclusion. We have shown that diatomic sulfur can indeed be trapped by dienes in good yield (61−79%) in what was similarly suggested to be a thermal pseudopericyclic reaction; in the absence of a diene trap, S_2 condenses to the more stable S_8 allotrope.[9]

One of the defining and highly unusual properties of **1** is the exceptionally short S−S bond (ca. 1.91 Å)[16,18,24] suggestive of a S−S rotational barrier that is much higher (ca. 18 kcal/mol)[4,10] than that of a normal disulfide (ca. 7 kcal/mol). Restricted rotation in **1** appears to arise entirely from electronic modulation of the S−S σ-bond. Indeed, the degree of this electronic effect manifests itself through electron-withdrawing elements immediately adjacent to the S−S bond (Table 1). Restricted rotation about single bonds[25] is not usually influenced solely through stereoelectronic interactions. For instance, well-documented high torsional barriers in amides,[26−39] thioamides,[36,40,41] sulfenamides,[42] acrylonitriles (DMAAN),[43] and carbamates[44,45] are due in part to resonance-induced double-bond character in these systems.[46] In biphenyls[47,48] and related compounds,[49−52] however, they are due to steric interactions about either an sp^2−sp^2 or an sp^2−sp^3 carbon−carbon bond.[53,54]

SCHEME 2

$$\underset{\mathbf{3}}{2\ \mathrm{ROH}} \xrightarrow[\mathrm{CH_2Cl_2;\ 0\ ^{o}C;\ 3\text{-}5\ h}]{\mathrm{S_2Cl_2\ /\ NEt_3}} \underset{\mathbf{1}}{\mathrm{ROSSOR}}$$

Herein, we report a generalized method for the synthesis of dialkoxy disulfides. We examine the diasterotopic coalescence phenomenon as a function of the substituent as well as the solvent. We also investigate the nature of the thermal decomposition pathway. We used the relatively stable bis(p-nitrobenzyloxy) disulfide **1a** as a representative dialkoxy disulfide in most of these studies.

Results and Discussion

Synthesis. As part of our wider interests in the physical properties of dialkoxy disulfides, we synthesized and characterized several dialkoxy disulfides (derived from the corresponding alcohols **3**) according to a modification of the procedure used by Thompson[2] (Scheme 2, Table 2). Dilute conditions and freshly distilled sulfur monochloride (S_2Cl_2) are key in attaining high yields and purity. This is due to the photolytic instability of S_2Cl_2 over a wide range of wavelengths.[57] Our current synthetic method is effective, with addition times reduced by ca. 90% from earlier preparative methods.[9] Longer reaction

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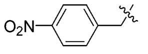
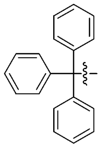
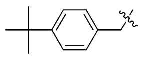
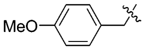
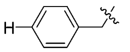
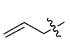
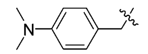
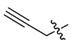
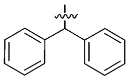
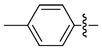
TABLE 2. Yields of Dialkoxy Disulfides

Cmpd	R	Yield (%)	Cmpd	R	Yield (%)
1a		97	**1g**		0^b
1b		90			
1c		93	**1h**		69
1d		83	**1i**		82
1e		0^a	**1j**		57
1f		81	**1k**		0^b

^{a} Complex mixture of products. ^{b} Only starting material detected.

times were sometimes necessary (5 h instead of 3 h), in particular for **1b**−**d**, wherein the para-substituted group was not electron-withdrawing. Initial purification attempts with **1c** resulted in lower yields, as this product was unstable to chromatographic conditions.[9] When R = trityl, as in **1g**, only starting alcohol was obtained.

This series represents a varied substrate study in the synthesis of dialkoxy disulfides, although Thompson prepared several aliphatic examples in his original paper.[2] The coupling of *p*-cresol to form dialkoxy disulfide **1k** and 4-*N*,*N*-dimethylaminobenzyl alcohol to form dialkoxy disulfide **1e** proved to be unsuccessful. Interestingly, only one aromatic dialkoxy disulfide has ever been reported (R = 2,2′-diaminophenoxy).[58,59] Here, there are strong electron-donating groups in the ortho positions that apparently increase the nucleophilicity of the phenolic oxygens enough to drive the reaction forward. It is unclear why **1e** could not be prepared given that dialkoxy disulfides with electron-donating groups such as **1c** can be synthesized and are stable. During the reaction with **1k**, the mixture turns bright green. This is in contrast to the yellow solutions that are usually observed. Direct electrophilic substitution of sulfur monochloride is not unprecedented,[58−60] and the benzene ring may act as a competing nucleophile in this particular case.

Compounds **1a**−**d**, **1f**, and **1h**−**i** were conveniently stored at −10 °C for months with only minor decomposition. Compound **1j** decomposed to a brown solid upon reduced-pressure solvent removal but could be stored in CH_2Cl_2 for weeks. Braverman and co-workers also observed the same solution stability.[61] All the dialkoxy disulfides synthesized possess a sweet, fruity aroma.

It should be noted that the synthesis of **1a**, **1c**, **1d**, and **1h** were all optimized. The preparation of **1b** and **1f** had previously not been reported. Compound **1j** was only recently reported.[61]

TABLE 3. Chemical Shift and Coupling Constant Data for Related ROSSOR^a

entry	compd	J_{AB}	ν_z	$\delta\Delta\nu/J_{AB}$	R
1	**1a**	12.40	4.94	3.84	*p*-NO$_2$-Bn
2	**2d**	11.25	4.84	4.67	Bn
3	**1b**	11.50	4.82	4.81	*p*-*tert*-butyl-Bn
4	**1c**	11.25	4.77	4.54	*p*-MeO-Bn

^{a} J_{AB} in Hz; ν_z in ppm.

Evaluation of Rate Parameters. Although Thompson first concluded that the barrier to rotation was close to that of disulfides (E_a = 8.6 ± 1.7 kcal/mol),[2] such a low value would require an unexpectedly[62] large negative $\Delta S^‡$. Subsequent work has shown that the reported value (8.6 kcal/mol) is erroneous.[4]

Seel[4] demonstrated that such a barrier for MeOSSOMe **1m** was much higher ($\Delta G^‡$ = 17.8 ± 0.1 kcal/mol). Lunazzi and co-workers[10] determined the thermodynamic properties for **1a** in perchloroethene (C_2Cl_4) at 105 °C ($\Delta G^‡$ = 19.0 ± 0.2 kcal/mol, $\Delta H^‡$ = 20 ± 1 kcal/mol, $\Delta S^‡$ = 2 ± 5 eu).

We were first interested in determining whether the barrier height could be modulated by altering the substituent R group of a dialkoxy disulfide. A substituent study (Table 3) of compounds **1a**−**d** reveals a modest but measurable electronic effect on the benzyl proton signals. As the para-substituent is altered from an electron-donating to an electron-withdrawing group, the coupling constant, J_{AB}, increases and the chemical shift of the AB-quartet, ν_z, moves downfield. These two parameters do not change uniformly as noted in their relative ratio (which is a marker of the magnetic environment of the diastereotopic benzyl protons).

Studies of the mutual-site exchange kinetics in DMSO-d_6 provide the torsional barrier about the S−S bond in **1a**−**c**. Complete line-shape analysis (LSA) of the exchange-broadened benzyl signals was accomplished by fitting the experimental data with the computer program WINDNMR[63] (Table 4).[64] Standard activation parameters were obtained from the linear least-squares fit of the experimental rate data to both the Eyring and Arrhenius equations assuming a transmission coefficient of unity. The Pearson regression factor (R^2) for these fits was greater than 0.98 as shown in Figure 1. The error limits in Table 4 assume only random errors. It is unclear why **1a** decomposed in previous studies[9,18] though the cleavage of dialkoxy disulfides is both acid-[2,5] and base-sensitive.[2,65−67]

Clearly the electronic effect shown in Table 3 did not affect the barrier to rotation (see $\Delta G^‡_{298}$, Table 4). Thus, the high barrier in dialkoxy disulfides is a function not of the electronics of the R group but intrinsically that of the OS−SO moiety.

Compound **1a** is organic-soluble, crystalline, stable, and nicely suited for the evaluation of the influence of solvent polarity on the torsional barrier. The MP2/6-

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TABLE 4. Substrate Study of the Activation Parameters for 1a–c

	activation parameters^{a}						
compd	$\Delta H^{\ddagger}$ (kcal/mol)	$\Delta S^{\ddagger}$ (eu)	$\Delta G^{\ddagger}_{298}$ (kcal/mol)	$\Delta G^{\ddagger}_{Tc}{}^{b}$ (kcal/mol)	E_A (kcal/mol)	log A (s^{-1})	T_c (K) ± 0.5
1a	12.9 ± 0.9	−14.9 ± 2.7	17.4 ± 1.2	18.3 ± 1.3	13.6 ± 0.9	23.1 ± 1.4	360.7
1b	16.6 ± 1.0	−4.9 ± 2.9	18.1 ± 1.3	18.4 ± 1.4	17.2 ± 1.0	28.0 ± 1.5	362.7
1c	13.7 ± 0.6	−12.4 ± 1.8	17.4 ± 0.8	18.2 ± 0.9	14.3 ± 0.6	24.2 ± 0.9	362.7

[a] Errors, as given here, represent a 68% confidence interval in the least squares deviation calculation. [b] $\Delta G^{\ddagger}$ determined at the T_c for each compound.

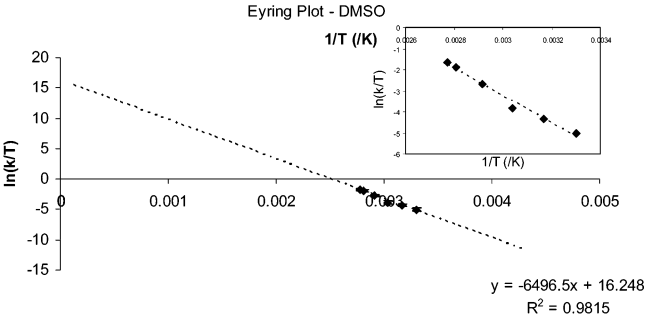

FIGURE 1. Eyring plot of the rotation about the S–S bond in **1a** in DMSO-d_6.

311G(3d)[68–70] dipole moments of the optimized gauche ground state and the trans transition state for MeOSSOMe **1m** (2.4 and 0 D, respectively) suggest a significant difference potentially responsive to a substantial variation in solvent polarity. Examination of the torsional potential of **1a** in different solvents complements the work by Lunazzi[10] and co-workers, who evaluated simple dialkoxy disulfides revealing little or no influence on barrier height with respect to the origin of the R group.

As shown in Figure 2, the two doublets of the AB system eventually coalesce into a single line since fast rotation about the S–S creates a dynamic plane of symmetry that makes the benzyl protons enantiotopic. The Pearson regression factor (R^2) for the linear fits to the Eyring and Arrhenius equations ranged from 0.96 to 0.99, indicating that the simulations are in good agreement with the obtained spectra. The free energies of activation scaled to a common temperature (298 K) for six solvents with empirical solvent polarity parameter (E_T) values[71] ranging from 33 to 45 exhibit no apparent medium effect (Table 5). The spread of $\Delta G^{\ddagger}_{298}$ is a diminutive 0.7 kcal/mol that is essentially flat with respect to solvent polarity as illustrated by plots of activation free energy against the empirical solvent polarity parameter, E_T, and the Onsager[72,73] dielectric constant function, defined as $(\epsilon - 1)/(2\epsilon + 1)$, where ϵ is the dielectric constant (Figures 3 and 4). The lack of solvent correlation with the Onsager reaction field model is at first surprising, as energy differences[74] in gauche and trans conformers and the rotational barriers[75] of 1,2-dichloroethane are well correlated. This lack in correlation may be due to the limited choice of solvents, most of which are aromatic; solvents must be relatively high-boiling for this study.

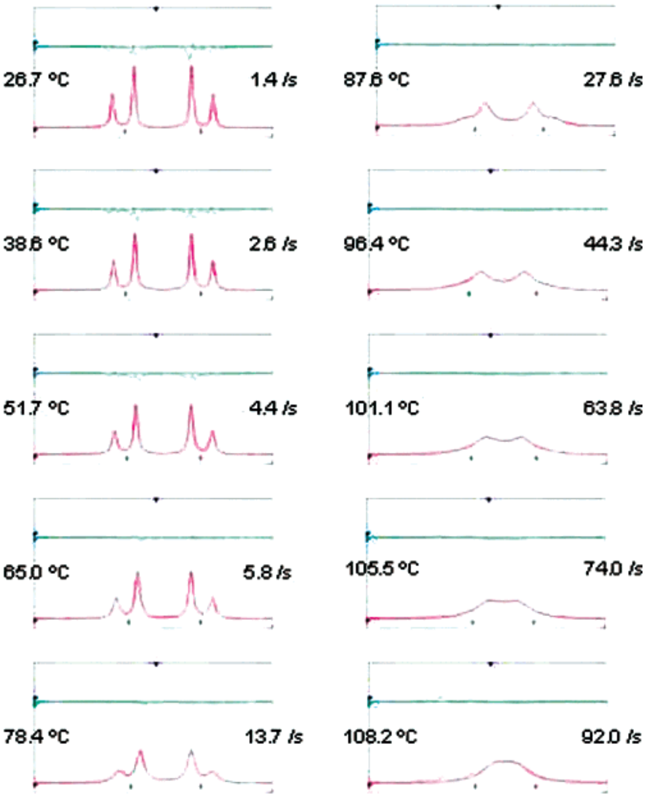

FIGURE 2. Temperature dependence of the benzyl CH_2 signal of **1a** (500 MHz in DMF-d_7). Superimposed on each spectrum is the display of each computer simulation obtained with the rate constants (in s^{-1}) indicated. Above each spectrum is a difference spectrum indicating the goodness of fit of the simulation.

$$k_c = \frac{\pi}{\sqrt{2}}\sqrt{\Delta\nu^2 + 6J_{AB}{}^2} \tag{1}$$

$$\Delta G^{\ddagger} = RT_c\left[\ln\left(\frac{k_B}{h}\right) - \ln\left(\frac{k_c}{T_c}\right)\right] \tag{2}$$

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[68] Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Gill, P. M. W.; Johnson, B. G.; Robb, M. A.; Cheeseman, J. R.; Keith, T.; Petersson, G. A.; Montgomery, J. A.; Raghavachari, K.; Al-Laham, M. A.; Zakrzewski, V. G.; Ortiz, J. V.; Foresman, J. B.; Cioslowski, J.; Stefanov, B. B.; Nanayakkara, A.; Challacombe, M.; Peng, C. Y.; Ayala, P. Y.; Chen, W.; Wong, M. W.; Andres, J. L.; Replogle, E. S.; Gomperts, R.; Martin, R. L.; Fox, D. J.; Binkley, J. S.; Defrees, D. J.; Baker, J.; Stewart, J. P.; Head-Gordon, M.; Gonzalez, C.; Pople, J. A. *Gaussian 94*, revision D.4; Gaussian, Inc.: Pittsburgh, PA, 1995.

[69] Møller, C.; Plesset, M. S. *Phys. Rev.* **1934**, *46*, 618.

[70] Head-Gordon, M.; Pople, J. A.; Frisch, M. J. *Chem. Phys. Lett.* **1988**, *153*, 503.

[71] Reichardt, C. *Chem. Rev.* **1994**, *94*, 2319.

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[73] *The Handbook of Chemistry and Physics*, 3rd ed.; CRC Press: Boca Raton, FL, 2001.

[74] Wiberg, K. B.; Murcko, M. A. *J. Phys. Chem.* **1987**, *91*, 3616.

[75] Wong, M. W.; Frisch, M. J.; Wiberg, K. B. *J. Am. Chem. Soc.* **1991**, *113*, 4776.

TABLE 5. NMR-Derived Activation Parameters for Coalescence of the Diastereotopic Methylene Protons of 1a Obtained by Line Shape Analysis; S−S Bond Rotation, 298 K[a]

solvent	$\Delta H^\ddagger$ (kcal/mol)	$\Delta S^\ddagger$ (eu)	$\Delta G^\ddagger_{298}$ (kcal/mol)	E_a (kcal/mol)	log A (s^{-1})	k_c (s^{-1}) ± 10	$E_T(30)$[b] (kcal/mol)	J_{AB}[c] (Hz)	$\Delta\nu$[d] (Hz)	T_c (K) ± 0.5
C_2Cl_4[e]	20.0 ± 1	2 ± 5					32.1	−12.5	37.5	378.2
p-xylene	8.6 ± 0.5	−28.1 ± 1.4	17.0 ± 0.7	9.3 ± 0.5	16.4 ± 0.7	87	33.1	−12.5	75.0	383.2
pyridine	15.4 ± 1.3	−7.7 ± 4.0	17.7 ± 1.8	16.1 ± 1.3	26.7 ± 2.0	103	33.3	−13.0	54.5	365.1
toluene	13.1 ± 0.5	−15.4 ± 1.4	17.7 ± 0.6	13.7 ± 0.5	22.8 ± 0.7	127	33.9	−12.3	69.7	378.6
chlorobenzene	10.4 ± 0.7	−23.5 ± 2.1	17.5 ± 1.0	11.1 ± 0.8	18.8 ± 1.1	145	39.1	−12.7	67.6	394.7
DMF	11.1 ± 0.7	−21.5 ± 2.1	17.5 ± 1.0	11.7 ± 0.7	19.7 ± 1.1	92	43.8	−12.5	45.8	381.3
DMSO	12.9 ± 0.9	−14.9 ± 2.7	17.4 ± 1.2	13.6 ± 0.9	23.1 ± 1.4	68	45.0	−13.0	39.9	360.7

[a] Errors, as given here, are assumed to be only random and represent a 68% confidence interval in the least squares deviation calculation. [b] From ref.[71] [c] Two bond couplings assigned a negative value consistent with the general rule for geminal couplings. [d] Chemical shift difference at slow exchange (500 MHz at 23 °C) except for C_2Cl_4 (300 MHz at 22 °C). [e] From ref,[10] $\Delta G^\ddagger$ determined at 105 °C.

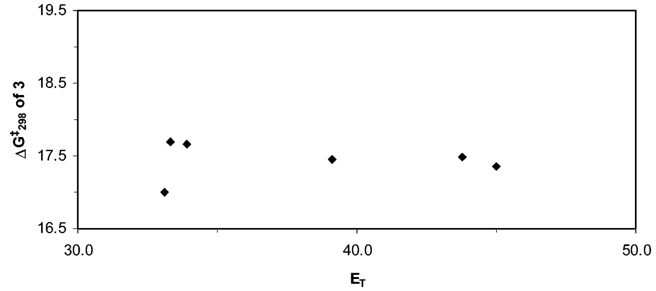

FIGURE 3. Relationship between the observed rotational barriers of **1a** and the Dimroth−Reichardt solvent polarity parameter, E_T.[71]

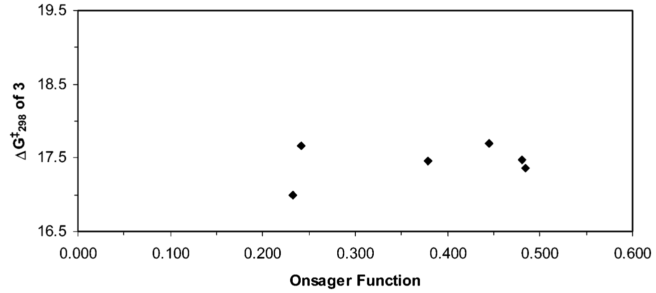

FIGURE 4. Relationship between the observed rotational barriers of **1a** and the Onsager function $(\epsilon - 1)/(2\epsilon + 1)$, where ϵ is the dielectric constant.[73]

Rate constants k_c and free energies of activation $\Delta G^\ddagger$ at the coalescence temperature T_c were also calculated using the Gutowski−Holm[76] approximation equations 1 and 2 following Raban and co-workers.[77] For each solvent, the coupling constant, J_{AB}, the chemical shift difference, $\Delta\nu$, and the full-width-at-half-height (fwhh) were obtained directly from the frequency separation of the appropriate peaks in the slow exchange region ($k_c \ll \Delta\nu$), in the present cases at least 70 °C below each individual T_c.

The LSA free energies from Table 5 recalculated at the corresponding coalescence temperatures (Table 6) are within 0.4 kcal/mol on average from those derived from T_c, indicating that both free energy assessment methods provide comparable values. In this context, the $\Delta G^\ddagger_{T_c}$ values span the slightly larger range of 1.5 kcal/mol, but once again show no correlation with solvent polarity. Unlike amides,[34,35,37] acrylonitriles,[43] 2-alkoxy-3-halobutanes, and 2-acetoxy-3-halobutanes,[78] which all exhibit a detectable solvent dependence on the barrier to rotation, rotation in **1a** appears to be indifferent to medium influences (Scheme 3).

The solvent effects observed for amide rotation[79] depend on a reduction in dipole moment during the dynamic process.[80] For amides, the decrease amounts to ca. 0.2 or 1.8 D, depending on the nature of the torsional transition state (DMA, Figure 5).[30,31,35,37,39]

A polar solvent preferentially stabilizes the charge separation in the more polar ground state relative to the less polar transition states;[34] the lack of a solvent effect in carbamates has been attributed in part to the presence of increased charge separation in the transition state[44] and the relatively smaller dipole moments of carbamates as compared to analogous amides.[45] As implied above for MeOSSOMe **1m**, the dipole moment difference for dialkoxy disulfides is significant. To evaluate the situation for **1a**, the X-ray[10] structure and the corresponding trans transition state were optimized with the MM3* force field[81] and subsequently subjected to single-point calculations with density functional theory using the B3LYP/6-311G* method.[82−84] While the transition state model is essentially nonpolar ($\mu_{calcd} = 0.03$ D), the enantiomeric ground states are estimated to sustain a substantial dipole moment ($\mu_{calcd} = 5.9$ D). Since the ground state-transition state difference is of the same order of magnitude as that for amides, a solvent dependence is expected. It should be noted, however, that for non-hydrogen-bonding solvents similar to those used in the

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(76) Gutowsky, H. S.; Holm, C. H. *J. Chem. Phys.* **1943**, *25*, 1228.
(77) Kost, D.; Carlson, E. H.; Raban, M. *Chem. Commun.* **1971**, 656.
(78) $\Delta G^\ddagger$ varies by ca. 0.2 kcal/mol over two solvents (CH_2CHCl and $CBrF_3$) for a series of 2-alkoxy-3-halobutanes and 2-acetoxy-3-halobutanes. See: Wang, C. Y.; Bushweller, C. H. *J. Am. Chem. Soc.* **1977**, *99*, 313.
(79) $\Delta G^\ddagger$ can increase by as much as 3 kcal/mol upon changing from an apolar solvent to water. Drakenberg, T.; Dahlqvist, K.-I.; Forsén, S. *J. Phys. Chem.* **1972**, *76*, 2178.
(80) Some have attributed the observed solvent effect in the rotation about the C−N amide bond to internal pressure and the increased volume requirements of the transition state structure in comparison to the ground-state structure. See for instance: Suarez, C.; Lemaster, C. B.; Lemaster, C. L.; Tafazzoli, M.; True, N. S. *J. Phys. Chem.* **1990**, *94*, 6679. It should be noted that in the case of dialkoxy disulfides, the transition state does not demand greater steric requirements compared to the ground state. Thus, any increase in the barrier in the liquid phase compared to the gas-phase cannot be due to this reasoning.
(81) Mohamadi, F.; Richards, N. G. J.; Guida, W. C.; Liskamp, R.; Lipton, M.; Caufield, C.; Chang, G.; Hendrickson, T.; Still, W. C. *J. Comput. Chem.* **1990**, *4*, 440. We have modified the MM3* force field to include new atom types and parameters to better handle the OSSO and OS(S)O functionalities.
(82) Becke, A. D. *J. Chem. Phys.* **1993**, *98*, 5648.
(83) Lee, C.; Yang, W.; Parr, R. G. *Phys. Rev. B* **1988**, *37*, 785.
(84) Miehlich, B.; Savin, A.; Stoll, H.; Preuss, H. *Chem. Phys. Lett.* **1989**, *157*, 200.

TABLE 6. Comparison of S−S Torsion Barriers for 1a Derived from Complete Line Shape Analysis (LSA) and the T_c Method of Equations 1 and 2 at T_c

	LSA[a]	T_c method[b]		discrepancy		
solvent	$\Delta G^{\ddagger}_{T_c}$[c] (kcal/mol)	k_c (s^{-1}) ± 60	$\Delta G^{\ddagger}_{T_c}$[c] (kcal/mol)	k_c(s^{-1}) ± 61	$\Delta G^{\ddagger}$ (kcal/mol)	$E_T(30)$[d] (kcal/mol)
C_2Cl_4[e]	19.0 ± 0.2					32.1
p-xylene	19.4 ± 0.7	180	18.7 ± 0.3	−93	0.7 ± 0.8	33.1
pyridine	18.2 ± 2.0	140	17.9 ± 0.3	−37	0.3 ± 2.0	33.3
toluene	18.9 ± 0.7	169	18.5 ± 0.3	−41	0.4 ± 0.8	33.9
chlorobenzene	19.7 ± 1.1	165	19.3 ± 0.3	−20	0.4 ± 1.2	39.1
DMF	19.3 ± 1.1	122	18.9 ± 0.4	−30	0.4 ± 1.2	43.8
DMSO	18.3 ± 1.3	113	17.9 ± 0.4	−45	0.4 ± 1.4	45.0

[a] $\Delta G^{\ddagger}$ was determined using LSA. [b] Comparison of $\Delta G^{\ddagger}$ was made at T_c for each of the solvents. [c] $\Delta G^{\ddagger}$ determined at the T_c of **1a** in each respective solvent. [d] From ref.[71] [e] From ref,[10] $\Delta G^{\ddagger}$ determined at 105 °C.

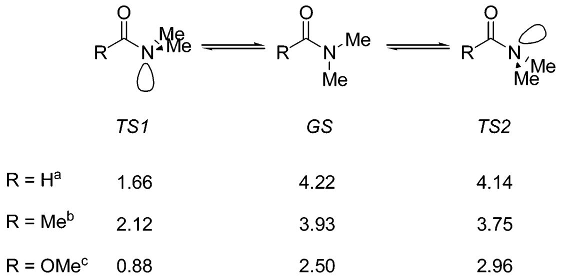
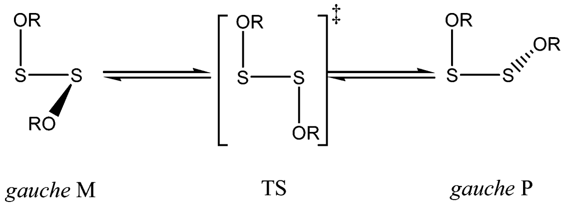


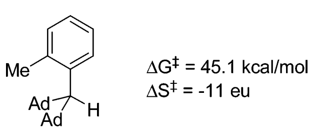
FIGURE 5. Gas-phase ground- and transition-state dipoles (D) for amide and carbamate isomerization. (a) Dipole moments calculated at HF/6-31++G**. Here, rotation through TS1 is preferred by 3.5 kcal/mol.[37] (b) Dipole moments calculated at HF/6-31G*. Here, TS1 is to be more stable than TS2 by 4.1 kcal/mol.[39] (c) Dipole moments calculated at HF/6-311G**. Here, TS1 is more stable than TS2 by 0.6 kcal/mol.[44]

SCHEME 3. Interconversion of Enantiomers of 1



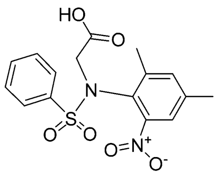
present work, the solvent-induced activation free energy variation for amides is relatively small (0.5−1.5 kcal/mol). If the NMR measurements incorporate an error of ± 0.5 kcal/mol, such an effect would therefore not be observed. While the random errors for **1a** are only on the order of ± 0.3 kcal/mol, complementary errors due in part to temperature control and acquisition procedures appear to have raised the accumulated errors beyond the threshold where a small medium effect can be observed.

The $\Delta H^{\ddagger}$ values are smaller than those cited by Lunazzi,[10] whereas the $\Delta S^{\ddagger}$ values are much larger and negative. Though rotation about single bonds is usually characterized by $\Delta S^{\ddagger}$ values of ca. 0 eu,[85−87] large negative $\Delta S^{\ddagger}$ values of the same order of magnitude as our values are not unprecedented as with *anti-o*-tolyldi(1-adamantyl)methane[88] **7** and related alcohols[89,90] and hydrocarbons.[89]



7

Unimolecular isomerization of carbamates in protic solvents also display a significant negative $\Delta S^{\ddagger}$.[44] In this case, the negative $\Delta S^{\ddagger}$ observed may be associated with stronger solvation of the more polar transition state (TS2 in Figure 5) as compared to the ground state, resulting in it being the more favored transition state in water.



8

The racemization of *N*-benzenesulfonyl-*N*-carboxymethyl-2,4-dimethyl-6-nitroanaline **8** in 26 different solvents consistently displays a large negative entropy of activation.[91] Systems where torsional motion is severely restricted are inherently entropically unfavorable.[92,93] This is the case with **1a**. A possible interpretation of our observed large $\Delta S^{\ddagger}$ is simply a reflection of the degree of rigidity afforded by the OSSO functionality.

Our torsional barrier values of $\Delta G^{\ddagger}$ are between 18 and 19 kcal/mol and are consistent with previous work[18] and the efforts of Lunazzi[10] with both small and large R

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(85) Experimentally determined $\Delta S^{\ddagger}$ for the rotation about the carbon−nitrogen single bond in *tert*-butylamine is 1.3 eu. See: Bushweller, C. H.; O'Neil, J. W.; Bilofsky, H. S. *J. Am. Chem. Soc.* **1970**, *92*, 6349.

(86) Experimentally determined $\Delta S^{\ddagger}$ values ranged from −1 to −5 eu for a series of polychalogenated ethane derivatives. See: Brunelle, J. A.; Letendre, L. J.; Weltin, E. E.; Brown, J. H.; Bushweller, C. H. *J. Phys. Chem.* **1992**, *96*, 9225.

(87) Though not strictly rotation about a single bond, due to resonance stabilization afforded by the benzene ring, $\Delta S^{\ddagger}$ ranges between 0 and −3 eu over three aprotic solvents for *p*-trifluoromethanesulfonylbenzyltriflone carbanion. See: Gromova, M.; Béguin, C. G.; Goumont, R.; Faucher, N.; Tordeux, M.; Terrier, F. *Magn. Reson. Chem.* **2000**, *38*, 655.

(88) Lomas, J. S.; Anderson, J. E. *J. Org. Chem.* **1995**, *60*, 3246.

(89) Lomas, J. S.; Bru-Caodeville, V. *J. Chem. Soc., Perkin. Trans. 2* **1994**, 459.

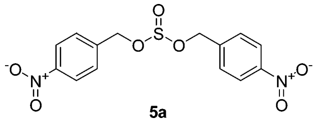
(90) Lomas, J. S.; Dubois, J. E. *Tetrahedron* **1981**, *37*, 2273.

(91) McKelvey, D. R.; Kraig, R. P.; Zimmerman, K.; Ault, A.; Perfetti, R. *J. Org. Chem.* **1973**, *38*, 3610.

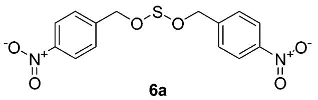
(92) For a review on methodology that gives estimates and trends concerning torsional entropy about single bonds, see: Mammen, M.; Shakhnovich, E. I.; Whitesides, G. M. *J. Org. Chem.* **1998**, *63*, 3168 and references therein.

(93) For a commentary on the definition of torsional entropy, see: Ercolani, G. *J. Org. Chem.* **1999**, *64*, 3350.

TABLE 7. Photolytic and Thermolytic Activity Experiments for 1a



5a



6a

	conditions							^{1}H NMR product yield distribution (%)^d			
entry^b	dark	UV	air	N_2	solid state	$CDCl_3$	temp (°C)^c	**1a**	**3a**	**4a**	**5a**
1	x		x		x		27	86	10	0	4
2		x	x			x	27	87	9	1	3
3		x		x		x	27	89	8	0	3
4^a		x	x			x	27	74	21	1	3
5^a		x		x		x	27	83	14	1	2
6		x	x		x		27	85	10	0	4
7		x		x	x		27	88	9	0	3
8		x	x		x		60	21	45	1	10
9		x		x	x		50	0	85	0	0
10		x	x			x	60	81	15	1	3
11		x		x		x	50	85	15	0	0

[a] Silica added. [b] Reaction time was 20−26 h. [c] No change in relative integrations at 37 °C. [d] ^{1}H NMR yields ± 5%.

substituents. Both the absolute values and the 1 kcal/mol range are entirely compatible with the data of Tables 4−6. Clearly, neither substituent size, electronics, nor medium effects significantly perturb the energetics of the S−S rotation barrier. The magnitude of the S−S rotation barrier for dialkoxy disulfides is of interest, as it is related to the barrier of thermal cleavage outlined next.

Evaluation of the Thermal and Photolytic Stability of Dialkoxy Disulfides. Although acid- and base-catalyzed[2,5,65−67] decomposition of dialkoxy disulfides has been briefly investigated, only one report exists on their photochemistry.[94] The authors were able to detect the presence of radicals both at high temperatures as well as under photolytic conditions. We initially examined the photolytic decomposition of **1a** both in the solid state as well as in solution ($CDCl_3$), in air, and under an inert atmosphere. In addition, we probed the effect of silica on the decomposition mechanism after observing that the corresponding sulfite byproduct **5a** is produced during flash chromatography. The results are summarized in Table 7.

After ca. 24 h at 27 °C, no matter whether in solution (entries 2−4) or not (entries 6, 7) or under an inert atmosphere (entries 2, 6) or not (entries 3, 7), little change was detected in the product ratios of **1a** as compared to a control sample (entry 1) that was left at room-temperature exposed to the atmosphere (but shielded from light). The addition of silica catalyzed a slight decomposition to the corresponding alcohol **3a** while exposed to air (entry 4) or under an inert atmosphere (entry 5). However, when **1a** was heated to temperatures greater than 37 °C under an inert atmosphere while in the solid state (entry 9), it decomposed completely to form the alcohol **3a** and trace amounts of other unidentified decomposition products.

Upon heating **1a** in the solid state (exposed to the atmosphere (entry 8), the corresponding aldehyde **4a** as well as the sulfite **5a** were observed as decomposition products. Except for this particular case, only traces of sulfite **5a** and no sulfoxylate **6a** were ever detected. The decomposition observed in the solid state at elevated temperatures did not translate to the solution state (entries 10, 11). In fact, decomposition in solution was only observed at much higher temperatures (ca. 100−140 °C). It should be noted that in all thermolysis experiments, there was consistently detected a much greater amount of alcohol **3a** than aldehyde **4a**. Such a product distribution inequality argues against a concerted mechanism; these results suggest that these compounds are much more UV stable than previously reported.[94] No rearrangement products such as those observed by Braverman[13,61] were observed because the *p*-nitrobenzyl group is not prone to undergo such [2,3]-sigmatropic rearrangements. In addition, no isomerization to the thionosulfite was observed.

Decomposition to the corresponding alcohol and aldehyde in a non 1:1 ratio (vide infra) was also observed at elevated temperatures in all the solvents used in the determination of the rotational barrier. Qualitative observations revealed that **1a** was much less stable and decomposed much more readily in pyridine relative to the other solvents tested. This is most likely due to the nucleophilic nitrogen of the solvent catalyzing the process.[6,12] We undertook a quantitative solvent study in order to elucidate this decomposition pathway. The rate constant of decomposition of **1a**, over a temperature range of 40 °C, was extrapolated from a series of ^{1}H NMR spectra taken at regular intervals, each containing an internal standard.

We chose three solvents that span a large polarity range. Upon least-squares fitting of the resulting data, we determined that the rate of decomposition of the reaction was first order in **1a**, rate = k_d[**1a**] (e.g., Figure 6).[95]

From these data, through the use of Eyring transition state theory, the following activation parameters were obtained (Table 8). It should be noted that although the individual decomposition kinetics were linear, the corresponding Eyring plots yielded relatively poor linear fits (R^2 ranged from 0.47 to 0.67), which is reflected by the

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(94) Borghi, R.; Lunazzi, L.; Placucci, G.; Cerioni, G.; Plumitallo, A. *J. Org. Chem.* **1996**, *61*, 3327.

(95) Average R^2 value for the linear fits was ca. 0.97.

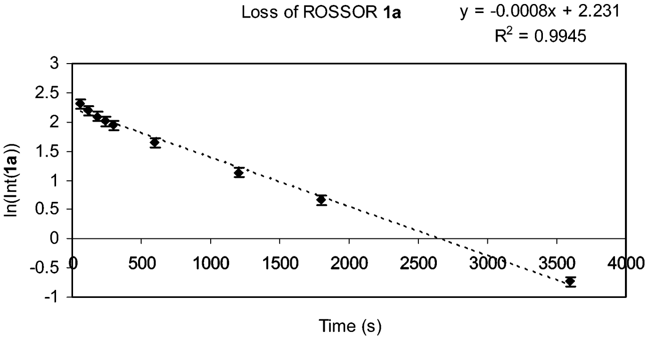


FIGURE 6. First-order rate plot of the decomposition of **1a** at 105.7 °C in DMSO-d_6. Errors as shown here represent a 68% confidence interval in the linear fit of the data.

TABLE 8. Activation Parameters for the Decomposition of 1a[a]

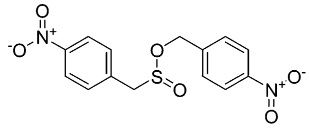
solvent	$\Delta H^\ddagger$ (kcal/mol)	$\Delta S^\ddagger$ (eu)	$\Delta G^\ddagger_{298}$ (kcal/mol)	$E_T(30)$[b] (kcal/mol)
p-xylene	10 ± 4	−46 ± 10	24 ± 5	33.1
chlorobenzene	11 ± 6	−45 ± 15	24 ± 7	39.1
DMSO	13 ± 5	−38 ± 12	25 ± 6	45.0

[a] Errors, as given here, represent a 68% confidence interval in the least squares deviation calculation. [b] From ref.[71]

large errors in Table **8**. The large $\Delta S^\ddagger$ values indicate a highly ordered and associative mechanism. The negative entropies are also comparable with other processes that have nonpolar transition states, though these examples relate to concerted reactions.[96−102] While more positive entropies of activation were expected (vide infra), negative $\Delta S^\ddagger$ values are not unusual in certain parallel reactions.

A nonpolar transition state is suggested, as there seems to be little solvent dependency ($\Delta G^\ddagger$ ranges by ca. 1 kcal/mol over the three solvents). Lunazzi[94] demonstrated the trapping of aliphatic sulfenyl and sulfonyl radicals in the photolysis (−20 °C) of the corresponding dialkoxy disulfide EtOSSOEt **1n**. The latter of these two radicals resulted from oxidation of the former, ostensibly in the presence of the radical trap. The Lunazzi group attributed the formation of the sulfenyl radical through S−S scission. GC-MS analysis of the products derived from the photolysis of **1n** in benzene resulted in the corresponding sulfite (EtOS(O)OEt **5n**) and sulfoxylate (EtOSOEt **6n**), as well as elemental sulfur.

Such a product distribution could be envisioned to occur from the coupling of alkoxyl radicals with the sulfur-centered radicals; these alkoxyl radicals could originate from S−O scission. There were only trace amounts of the analogous sulfite **5a** and no sulfoxylate **6a** or sulfinate **9a** in the photolysis of **1a**; the latter compound likely resulted from the room-temperature isomerization of **6a**. Interestingly, room-temperature photolysis of di-*tert*-butyloxy disulfide **1o** in the presence of DMPO (4-*N*,*N*-dimethylpyridine-*N*-oxide) yielded an ESR spectrum[103] characteristic of the presence of the *t*-butoxyl radical (*t*-BuO•). Photolysis of **1d** in the presence of C_{60}-fullerene yielded a single adduct, indicating benzyloxyl radical formation.



9a

The Lunazzi group also trapped an alkoxyl radical under moderately elevated temperatures (50−70 °C). Their thermolysis of **1d** yielded a spectrum similar to that of its photolysis; in addition, formation of the corresponding benzyl adduct was detected.

To account for our results, we propose the following unsymmetric diradical decomposition mechanism, Scheme 4. This pathway is consistent not only with the radical trapping experiments summarized above but also with the decomposition kinetics and product decomposition ratios obtained during the thermally induced homolysis of dialkoxy disulfides (vide supra, Tables 7 and 8). Diradical pathways have also been implicated in the photolysis[104−106] and thermolysis of cinnamyl-4-nitrobenzene sulfenate and related compounds to their corresponding sulfoxides.[107−109] It should be noted that the concerted mechanism originally proposed by Thompson (Scheme 1) is not consistent with the data.

It is reasonable that the benzylic radicals that the Lunazzi group observed might arise from C−O scission to form highly chalcogenated radical $RCH_2OSSO^\bullet$ followed by SO loss to afford the sulfenyl radical **14a**. This mechanism is somewhat supported through the HRMS of decomposition products of bis(*p*-MeO-benzyloxy) disulfide **1c** wherein SO was lost (HRMS of a second decomposition product wherein SO_2 was lost was also observed). Indeed, the loss of SO was noted in the MS of all of the dialkoxy disulfides. Of significance is that no decomposition products of the form **1a**−SO or **1a**−SO_2 were ever detected by ^{1}H NMR during either photolysis or thermolysis experiments as compared with authentic samples such as sulfide **10a** or sulfoxide **11a**; related sulfone **12a** was also never detected. Though we did not detect any benzyl-derived products resulting from C−O cleavage such as *p*-nitrobibenzyl, we nevertheless observed benzyl radical cations by EI MS. C−O homolysis in **1a** might have been expected given the origin of the para nitro group. The presence of this electron-withdrawing group effectively raises the electronegativity of the

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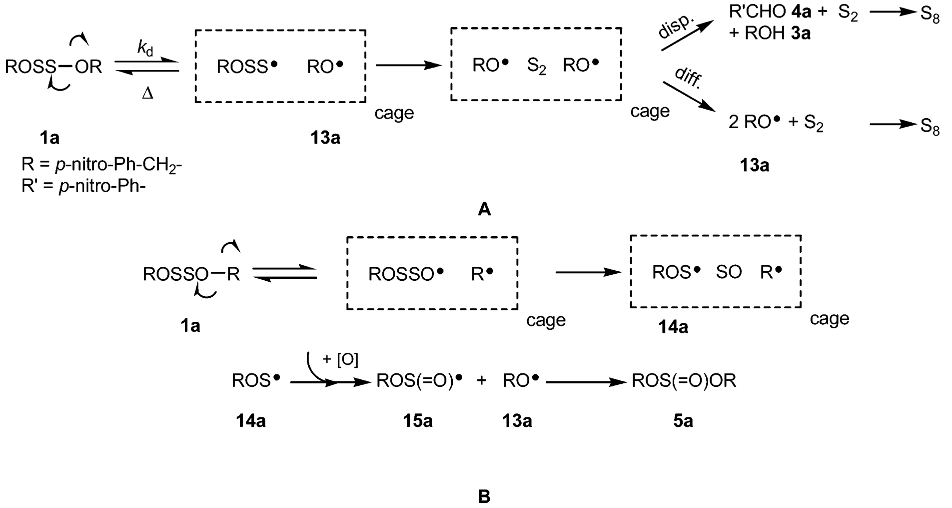
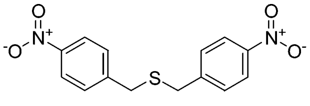
SCHEME 4. Thermally Induced Radical Decomposition Mechanism of 1a[a]

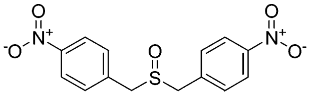


[a] Disp. = disproportionation; diff. = diffusion.

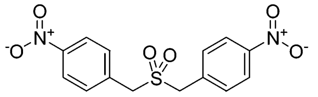
benzylic carbon, thus decreasing the electronegativity difference and thus the BDE between it and the adjoining oxygen atom.[110]



10a



11a



12a

In our scheme, alkoxyl radicals (**13a**) would arise from initial caged S–O bond scission; a second caged S–O bond cleavage is also possible. Pasto[111] has shown in a related H–S–S–O–H system that S–S cleavage is only slightly more favored than S–O cleavage. The preference for S–S cleavage over S–O cleavage was shown to be highly dependent on the stabilities of the radicals formed. Additionally, for nondiaryl disulfides, C–S homolysis is slightly more favorable than symmetric S–S bond breakage.[112] The presence of the benzyl group, containing conjugated π-electrons, exerts a bond weakening effect upon the S–O bond.[113]

Finally, the cage could then disproportionate (via a remote hydrogen abstraction[106] of either of the alkoxyl radicals **13a** or the solvent by the other alkoxyl radical) to yield the alcohol **3a** that was the major product observed in our thermolysis experiments. If the source of the hydrogen atom abstraction is another alkoxyl radical or if β-scission of **13a** occurs, then this would afford observed aldehyde **4a**. Diatomic sulfur is the final disproportionation product, which would immediately concatenate to form the more stable S_8 allotrope in the absence of a diene trap. This stepwise type of decomposition mechanism is not unprecedented. Indeed tetroxides[114–117] and hyponitrites[118–122] have been shown to decompose by analogous mechanisms; some have suggested symmetric homolytic cleavage as the first step,[123,124] but it is only the asymmetric cleavage of tetroxides that leads to product formation. Formation of minor amounts of sulfite **5a** is outlined in Scheme 3B.[125] The presence of only small amounts of sulfite **5a** suggests that in our system, the propensity for in situ oxidation of radical species such as **14a** is low.

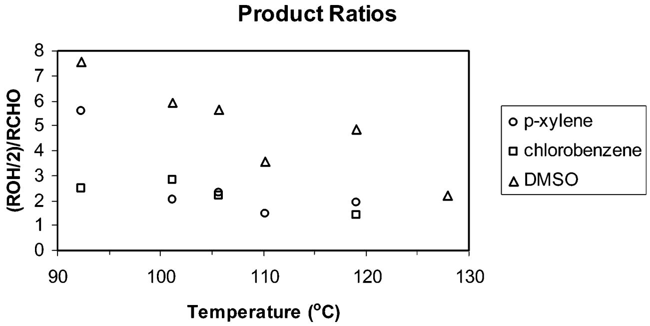


FIGURE 7. Ratio of the integration of *p*-nitrobenzyl alcohol **3a** to *p*-nitrobenzaldehyde **4a** per mole of integratable protons.

The observed product ratios during the high-temperature decomposition kinetics experiments are shown in Figure 7 and further support a stepwise decomposition

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(125) Formation of sulfenyl radical **13** via homolysis of the S–S bond cannot be ruled out.

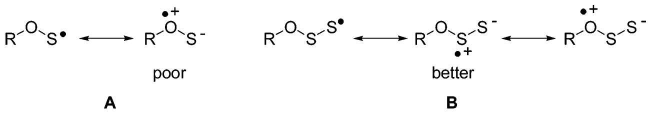

FIGURE 8. Resonance form of ROS$^{\bullet}$ vs ROSS$^{\bullet}$.

mechanism. The average **3a**:**4a** (ROH:RCHO) ratio is ca. 2:1 for chlorobenzene and *p*-xylene. There is consistently considerably more alcohol formed in DMSO. The non 1:1 ratio of decomposition products can usually[120,121] be ascribed to alkoxyl radicals **13a** diffusing from the cage and subsequently abstracting hydrogens from the environment. In hydroxylic solvents, a 1,2-H shift from carbon to oxygen has also been suggested as a viable possibility;[126] this shift is solvent-assisted and would occur due to increased radical stabilization (benzylic radical formation).[127] The relative excess of alcohol observed in DMSO may be due to the presence of water in the solvent, which might promote the fast 1,2-H shift.[122] It should be noted that invoking a concerted mechanism (Scheme 1) implies a 1:1 ratio of ROH:RCHO.

To our knowledge, the S−O and S−S bond dissociation energies for dialkoxy disulfides have not been reported. Estimating them is problematic due to the formation of highly chalcogenated radicals. Nevertheless, the BDEs are related by equation 3.

$$\mathrm{BDE(ROSS{-}OR)} = \Delta H_f^{\circ}(\mathrm{ROSS}^{\bullet}) + \Delta H_f^{\circ}(\mathrm{RO}^{\bullet}) - 2\Delta H_f^{\circ}(\mathrm{ROS}^{\bullet}) - \mathrm{BDE(ROS{-}SOR)} \quad (3)$$

In peroxides (RO−OR), the lone pair repulsion between oxygen atoms is believed to be responsible for the weakening of the O−O bond.[128] In disulfides, the lone pairs are more diffuse, and therefore the S−S bond is stronger. The BDE of sulfenates (RO−SR) is intermediate between peroxides and disulfides. This is evidenced by their relative BDEs: BDE(MeO−OMe) = 38 ± 2 kcal/mol,[129] BDE(MeS−OMe) = 53 ± 10 kcal/mol,[107] BDE(MeS−SMe) = 65 ± 1 kcal/mol.[130] Analogously, we would expect S−O bond cleavage to be easier than S−S bond cleavage in dialkoxy disulfides **1**. Additionally, the formed ROSS$^{\bullet}$ radical is able to be better stabilized through a three-electron π-system with enhanced hyperconjugation compared to ROS$^{\bullet}$,[131] which would result from S−S scission. This is qualitatively shown in Figure 8. As oxygen is more electronegative than sulfur, dipolar structure **A** in Figure 8 is likely to be a poor contributor to the overall stability of the sulfenyl radical. Sulfur is also more polarizable than oxygen, so charge-separated species as in Figure 8B would be seen as more viable resonance contributors. In fact, quantitatively, Gregory and Jenks[132] have shown the ROS$^{\bullet}$ radical to be quite unstable: $\Delta H_f^{\circ} = 1.4$ kcal/mol for MeOS$^{\bullet}$ at the G2(MP2,-SVP) level. The bond dissociation energy for FS−SF is 61 ± 4 kcal/mol,[113] which is slightly less than that reported for MeS−SMe. Thus, it is also reasonable to conclude that the BDE(ROS−SOR) would approximate this value. The ΔH_f° for *t*-BuO$^{\bullet}$ = −22.8 kcal/mol;[133] this is a good estimate for other alkoxyl radicals. Thus, in order for BDE(ROSS−OR) to be less than BDE(ROS−SOR), the contribution of $\Delta H_f^{\circ}(\mathrm{ROSS}^{\bullet}) + \Delta H_f^{\circ}(\mathrm{RO}^{\bullet}) - 2\,\Delta H_f^{\circ}(\mathrm{ROS}^{\bullet})$ has to be negative in magnitude. Given a large negative value for $\Delta H_f^{\circ}(\mathrm{RO}^{\bullet})$ and a small positive value for $\Delta H_f^{\circ}(\mathrm{ROS}^{\bullet})$, as well as rationales in the stabilization of ROSS$^{\bullet}$ (vide supra), it is reasonable to expect that the S−O bond would be the weaker bond and thus more prone to homolysis than the S−S bond in ROSSOR **1**.

It appears that the two observable processes (decomposition and coalescence) are each *solvent-insensitive*. Moreover, the decomposition phenomenon is ca. 6−8 kcal/mol higher. This is in accordance with our qualitative observations; if the decomposition phenomenon were more energetically favored, then one would not be able to observe coalescence.

Conclusion

We have optimized a generalized synthetic procedure for the synthesis of acyclic dialkoxy disulfides. We have shown that this synthesis can be effectively applied with a variety of substrates. We carried out a substituent and solvent study on their ability to influence the S−S torsional barrier. Our data indicates that there exists no significant substituent or solvent effect. The latter point may seem incongruent given our calculated dipoles for the ground and trans transition states, but the observed $\Delta\Delta G^{\ddagger}$ has been rationalized as being too small to detect within experimental error (vide supra). In addition, we propose a mechanism to account for the observed thermal decomposition of **1a**. Our experimentally determined activation parameters for this process indicate that **1a** decomposes under first-order kinetics and that there also does not seem to exist any appreciable solvent effect. Decomposition appears to proceed via initial S−O bond homolysis and is ca. 6−8 kcal/mol more thermally demanding than overcoming the internal S−S rotation barrier. To our knowledge, this represents the first study to account for the mechanism of decomposition of this highly unusual class of compounds.

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Supporting Information Available: Experimental procedures and characterization for selected compounds and experimental procedures for dynamic NMR and thermal decomposition experiments. This material is available free of charge via the Internet at http://pubs.acs.org.

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