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## COMMUNICATION

## Identification of dimethyl sulfide in dimethyl sulfoxide and implications for metal-thiolate disulfide exchange reactions

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Gamage S. P. Garusinghe,<sup>a</sup> S. Max Bessey,<sup>a</sup> Chelsea Boyd,<sup>a</sup> Mostapha Aghamoosa,<sup>a</sup> Brian Frederick,<sup>a,b</sup> Mitchell R. M. Bruce,<sup>\*,a</sup> Alice E. Bruce<sup>\*,a</sup>

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**The concentration of dimethyl sulfide (DMS) in seven different samples of research grade dimethyl sulfoxide (DMSO), including one deuterated sample, was measured by GC-MS. The average concentration of DMS is  $0.48 \pm 0.14$  mM (range: 0.44 – 0.55 mM) and ca. 0.35 mM in DMSO- $d_6$ . The presence of DMS in DMSO is potentially problematic for compounds that are susceptible to reaction with DMS and are present at  $\mu\text{M}$ -mM concentrations. Standard methods of purification of DMSO were unsuccessful in removing DMS.**

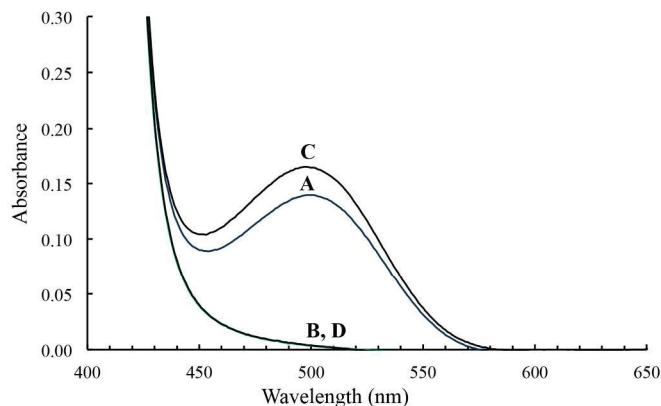
Dimethyl sulfoxide (DMSO) is an aprotic, polar solvent that is widely used in chemistry and biology. It dissolves hydrophobic and hydrophilic solutes,<sup>1-4</sup> is used as a cryoprotectant for biological samples,<sup>5</sup> and is a component in drug delivery.<sup>6</sup> Researchers have taken advantage of the miscibility of DMSO with water, organic solvents, and ionic liquids (IL) to solubilize polymers and enhance reaction chemistry. For example, recent reports describe the beneficial effects of a DMSO:IL co-solvent as a green solvent for hydrolysis of cellulose,<sup>7</sup> and a DMSO:water co-solvent to promote thiol-disulfide dynamic combinatorial chemistry.<sup>8</sup> DMSO can also participate in reactions. Some examples include: playing an essential role as a ligand for transition metal catalysts,<sup>9,10</sup> an oxidant for the oxidation of thiols or alcohols,<sup>11,12</sup> and a participant in the oxidation of gold phosphine complexes.<sup>13</sup>

We have employed DMSO as a solvent in our kinetic studies of the influence of solvent dielectric on metal thiolate-disulfide exchange reactions.<sup>14-16</sup> Our interest lies in comparing metal-mediated thiolate-disulfide exchange to metal-free thiol-disulfide exchange, the latter of which proceeds at a slower rate in high dielectric solvents, such as water or DMSO, than in low dielectric

solvents such as THF or  $\text{CH}_2\text{Cl}_2$ .<sup>17</sup> Since the metal thiolate complexes and disulfides employed in our kinetic studies are not water-soluble, DMSO was selected as a solvent with a high dielectric constant ( $\epsilon = 46.45$ )<sup>1</sup> for these studies. During the course of kinetic investigations, we observed that addition of bis(4-nitrophenyl)disulfide to DMSO, in the absence of any metal thiolate, formed a pale red solution with an absorbance near 500 nm. Bis(4-nitrophenyl)disulfide is isolated as a pale yellow solid after recrystallization from boiling n-butanol. When the disulfide is dissolved in solvents such as  $\text{CH}_2\text{Cl}_2$ ,  $\text{CH}_3\text{CN}$ , acetone, or THF, the solution does not turn red (i.e. there is no absorbance at 500 nm). We suspected that the species responsible for the color in solutions of DMSO was 4-nitrophenylthiolate because addition of base ( $\text{NET}_3$ ) to a DMSO solution of 4-nitrophenylthiol produced a similar red solution with  $\lambda_{\text{max}} = 502$  nm.<sup>18</sup> Over the course of time, we observed that when bis(4-nitrophenyl)disulfide is dissolved in a variety of DMSO solvents obtained from different commercial suppliers, a similar red color was produced. Thus, we hypothesized that an impurity in DMSO reacts with the disulfide to form 4-nitrophenylthiolate. DMSO is an odorless solvent, however a faint odor of sulfide can often be detected even in samples of high purity DMSO (anhydrous, >99.9%, etc.). Since the manufacturing process typically involves oxidation of dimethyl sulfide (DMS), we considered the possibility that our DMSO solvents contained trace amounts of DMS.

We report UV-Vis and GC-MS experiments that confirm the presence of DMS in DMSO samples and provide estimates for the concentration of DMS in seven different samples of high purity DMSO, including a deuterated sample. Further we have found that commonly used methods for purifying DMSO do not, in our hands, completely remove DMS. Our findings are significant for chemists and biologists who use DMSO as a solvent, in particular for dilute solutions (millimolar or less) in which the solutes may be sensitive to reaction with sulfides.

**UV-vis Experiments.** Figure 1A shows the visible spectrum of a red solution prepared by dissolving bis(4-nitrophenyl)disulfide in DMSO (20 mM). The peak at 502 nm, which is assigned as 4-nitrophenylthiolate,<sup>18</sup> photobleaches in room light and disappears over the course of several minutes (Fig. 1B). Addition of an aliquot of neat DMS ( $\approx 50 \mu\text{L}$  in 2 mL) to the photobleached solution regenerates the peak at 502 nm (Fig. 1C). Exposure of this solution to room light again bleaches the color (Fig. 1D). These findings are consistent with the hypothesis that DMS reduces bis(4-nitrophenyl)disulfide to 4-nitrophenylthiolate, which is responsible for the red solution.



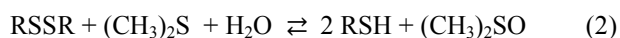
**Figure 1.** UV-vis spectra of 4-nitrophenylthiolate generated by dissolving bis(4-nitrophenyl)disulfide in DMSO. A. 20 mM bis(4-nitrophenyl)disulfide prepared in the dark, B. after exposure of solution A to room light, C. after addition of neat DMS to solution B, D. after exposure of solution C to room light

The photobleaching demonstrated in Figure 1 suggests that the reaction producing 4-nitrophenylthiolate is reversed by exposure to room light. This result is consistent with a literature report of the photo-oxidative coupling of 4-nitrophenylthiol to bis(4-nitrophenyl)disulfide in THF/water solvent mixtures.<sup>19</sup> The yield for disulfide is highest using a wavelength of light at which the thiolate strongly absorbs ( $\lambda_{\text{max}} = 455 \text{ nm}$  in THF/water) and the reaction requires the presence of thiol and thiolate.

DMSO is a useful solvent for the oxidation of thiols (RSH) to disulfides (eq. 1). The reaction is typically carried out at elevated temperatures (80 – 100 °C), with aliphatic thiols requiring a higher temperature than aromatic thiols. The reaction mechanism is proposed to proceed *via* nucleophilic attack of thiolate on protonated DMSO to yield disulfide, DMS and water.<sup>11</sup> Use of chromatographic neutral alumina as a catalyst for DMSO-promoted oxidation of thiols has also been reported.<sup>20</sup>



The reverse of the reaction shown in eq 1. suggests that in the presence of water, DMS may be capable of reducing bis(4-nitrophenyl)disulfide to 4-nitrophenylthiol. Further, since 4-nitrophenylthiol is mildly acidic ( $\text{pK}_a = 5.5$  in DMSO solution<sup>21</sup>) we expect the thiolate to be stabilized in DMSO. This sequence is summarized by equations 2 and 3 (where R = 4-nitrophenyl).



**GC-MS Experiments.** Quantitative analysis using GC-MS was carried out to determine the amount of DMS in seven different samples of DMSO. A standard bracket method was developed, using calibration standards of DMS in dioxane with pentane as internal standard, as described in Electronic Supplementary Information (ESI). Samples were purchased from five different chemical suppliers and included a variety of research grades: ACS reagent, anhydrous, HPLC, high purity ( $\geq 99.99\%$ ), and one deuterated solvent, DMSO- $\text{d}_6$  (chemical purity  $\geq 99.5\%$ ). All the sample bottles were newly opened just prior to testing. According to our results, the average DMS concentration in the nondeuterated DMSO samples is  $0.48 \pm 0.14 \text{ mM}$  and the deuterated sample of DMSO contains ca.  $0.35 \text{ mM}$ .

This concentration of DMS is especially significant when the concentration of solutes, which are sensitive toward reaction with DMS, are millimolar or less. For example, in  $^1\text{H}$  NMR kinetic exchange studies on metal thiolate complexes and bis(4-nitrophenyl)disulfide at concentrations in the 1–4 mM range, the presence of DMS represented 12–48% of the reactant concentrations and significantly complicated kinetic analysis. Further, attempts to employ UV-vis spectroscopy to monitor reaction rates at concentrations in the 25–50  $\mu\text{M}$  range,<sup>15</sup> have proven unreliable because the amount of DMS present in DMSO represents a 10 to 20-fold excess of the reactant disulfide of interest.

**Purification Trials.** Attempts to remove DMS from DMSO by using standard purification procedures were unsuccessful in our hands.<sup>22, 23</sup> These attempts included storing samples of DMSO over  $\text{CaH}_2$ , alumina, anhydrous  $\text{MgSO}_4$ , or 4Å molecular sieves for two weeks, either in a  $\text{N}_2$ -filled dry box or exposed to air; passing DMSO down columns of alumina (acidic and basic) or silica; and distillation of DMSO (at 80°C) under reduced pressure. The various methods for purifying DMSO were qualitatively evaluated by adding several milligrams of recrystallized bis(4-nitrophenyl)disulfide to an aliquot of DMSO (details regarding purification of disulfide are provide in ESI). In each of the attempts described above, a pink color appeared ( $\lambda_{\text{max}} = 502 \text{ nm}$ ), which was interpreted as failure to remove all traces of DMS from DMSO.

Since the reaction of DMS and disulfide to form DMSO and thiolate is a redox reaction, we reasoned that electrochemical oxidation might also remove DMS from DMSO. Oxidation of DMS to DMSO is reported to occur in the potential range of 0.8–1.1 V, while oxidation of DMSO to  $\text{DMSO}_2$  occurs at more positive potentials (ca. 1.6–1.7 V).<sup>24–26</sup> Bulk electrolysis was carried out at 0.7–0.9 V in a two-compartment electrochemical cell on 15 mL of DMSO solution containing 0.1M  $\text{Bu}_4\text{NPF}_6$  as the electrolyte (Pt working and auxiliary electrodes; Ag wire reference). Electrolysis was judged to be complete (after about 2 hours) when addition of bis(4-nitrophenyl)disulfide to the electrolyzed solution did not produce a pink color.<sup>27</sup> Thus it appears that DMS can be removed by electrolysis; however, this process is not ideal as a purification method since it requires long times to purify small volumes, and it also necessitates adding electrolyte, which is counterproductive to producing a higher purity sample of DMSO.

**Disproportionation.** The presence of DMS in a variety of samples of DMSO led us to consider the possibility that disproportionation of DMSO might be contributing to the source of DMS (equation 4). Disproportionation of DMSO is catalyzed by UV



light,<sup>28</sup> or occurs at elevated temperatures for extended periods of time ( $>150^\circ\text{C}$  for 24 hr.).<sup>29</sup> Using National Bureau of Standards thermodynamic parameters, Wood estimated that the disproportionation of DMSO is favorable ( $\Delta G^\circ = -98 \text{ kJ mol}^{-1}$ ).<sup>30</sup> *Ab*

*initio* calculations using B3LYP/6-31G\* theory and basis set in Gaussian 09,<sup>31</sup> also indicate a similar finding, i.e.  $\Delta G^\circ = -57 \text{ kJ mol}^{-1}$  in the gas phase ( $\epsilon=0$ ) and  $\Delta G^\circ = -58 \text{ kJ mol}^{-1}$  in DMSO ( $\epsilon=46.83$ ). While calculations indicate that disproportionation of DMSO is thermodynamically favorable, the relatively low concentration of DMS in a variety of samples of DMSO suggests that it is not kinetically favorable. The presence of DMS may be a consequence of the DMSO manufacturing process. However a longer-term study to monitor the shelf life of DMSO may be needed to shed light on the issue of disproportionation.

## Conclusions

The GC-MS analysis shows that samples of research grade DMSO from a variety of commercial suppliers contain trace amounts of DMS. UV-vis studies in solutions of bis(4-nitrophenyl)disulfide are consistent with presence of DMS in DMSO samples. The average concentration of DMS ( $0.48 \pm 0.14 \text{ mM}$ ) found in DMSO is potentially problematic for reactants that are susceptible to reaction with DMS and are present at  $\mu\text{M}$ - $\text{mM}$  concentrations. Standard methods of purification of DMSO were unsuccessful, in our hands, in removing all traces of DMS.

## Notes and references

<sup>a</sup> Department of Chemistry, Aubert Hall, University of Maine, Orono, Maine 04473

<sup>b</sup> Laboratory for Surface Science and Technology, Barrows Hall, University of Maine, Orono, Maine, USA 04473

† Electronic Supplementary Information (ESI) available: purification and analysis of bis(4-nitrophenyl)-disulfide; experimental details for GC-MS experiments and procedures and tabulated results for Gaussian calculations. See DOI: 10.1039/c000000x/

- C. Reichardt, *Solvents and Solvent Effects in Organic Chemistry*, Wiley-VCH, 2008.
- D. Martin, A. Weise and H. J. Niclas, *Angew. Chem., Int. Ed. Engl.*, 1967, **6**, 318-334.
- T. Clark, J. S. Murray, P. Lane and P. Politzer, *J. Mol. Model.*, 2008, **14**, 689-697.
- Y. Marcus, *The Properties of Solvents*, Wiley, 1998.
- Y. C. Song and D. E. Pegg, *Tissue and Cell Processing: an Essential Guide*, Wiley-Blackwell, 2012.
- A. McKim and G. Kvakovsky, *Spec. Chem. Mag.*, 2009, **29**, 50-52.
- J. Iglesias, J. A. Melero, M. Paniagua, M. Teresa Andreola and E. Barragan, *Biomass Bioenergy*, 2014, **62**, 158-165.
- J. Atcher and I. Alfonso, *RSC Advances*, 2013, **3**, 25605-25608.
- T. Diao, P. White, I. Guzei and S. S. Stahl, *Inorg. Chem.*, 2012, **51**, 11898-11909.
- W. Zierkiewicz and T. Privalov, *Organometallics*, 2005, **24**, 6019-6028.
- W. W. Epstein and F. W. Sweat, *Chemical Reviews (Washington, DC, United States)*, 1967, **67**, 247-260.
- W. Ge, X. Zhu and Y. Wei, *RSC Advances*, 2013, **3**, 10817-10822.
- G. S. P. Garusinghe, S. M. Bessey, M. Aghamoosa, Meaghan McKinnon, A. E. Bruce and M. R. M. Bruce, *Inorganics*, 2015, **3**, 40-54.
- A. Chandrasoma, A. E. Bruce and M. R. Bruce, American Chemical Society, 2010, pp. INOR-494.
- M. Aghamoosa, G. S. Garusinghe, A. E. Bruce and M. R. Bruce, American Chemical Society, 2010, pp. INOR-414.
- G. S. Garusinghe, A. E. Bruce and M. R. Bruce, American Chemical Society, 2010, pp. INOR-171.
- G. S. Garusinghe, M. R. Bruce and A. E. Bruce, American Chemical Society, 2010, pp. INOR-676.
- S. M. Bessey, M. Aghamoosa, G. S. P. Garusinghe, A. Chandrasoma, A. E. Bruce and M. R. M. Bruce, *Inorganica Chimica Acta*, 2010, **363**, 279-282.
- H. J. Kim, J. H. Yoon and S. Yoon, *The Journal of Physical Chemistry A*, 2010, **114**, 12010-12015.
- M. Hirano, S. Yakabe, H. Monobe and T. Morimoto, *Journal of Chemical Research, Synopses*, 1998, 472-473.
- F. G. Bordwell and D. L. Hughes, *J. Org. Chem.*, 1982, **47**, 3224-3232.
- W. L. F. Armarego and D. D. Perrin, *Purification of Laboratory Chemicals, Fourth Edition*, Pergamon, 1997.
- A. J. Gordon and R. A. Ford, *A Chemist's Companion. A Handbook of Practical Data, Techniques, and References*, Wiley-Interscience, 1972.
- I. Radoi and G. Mara, *Bul. Stiint. Teh. Inst. Politeh. Traian Vuia Timisoara, Ser. Chim.*, 1984, **29**, 59-64.
- G. Mara, M. Nemes and I. Radoi, *Rev. Chim. (Bucharest)*, 1987, **38**, 408-411.
- A. V. Bukhtiarov, A. V. Lebedev, A. P. Tomilov and O. V. Kuz'min, *Zh. Obshch. Khim.*, 1988, **58**, 2718-2724.
- Addition of bis(4-nitrophenyl)disulfide to a DMSO solution containing 0.1 M TBAPF<sub>6</sub>, prior to electrolysis, generates the pink color, i.e. excess electrolyte does not suppress formation of thiolate.
- G. R. Harvey and R. F. Lang, *Geophys. Res. Lett.*, 1986, **13**, 49-51.
- Gaylord Chemical, Technical Bulletin Reaction Solvent Dimethyl Sulfoxide (105B DMSO), <http://www.gaylordchemical.com/uploads/images/pdfs/literature/105B.pdf>, Accessed 3/10/2015, 2015.
- P. M. Wood, *FEBS Letters*, 1981, **124**, 11-14.
- G. W. T. M. J. Frisch, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, G. Scalmani, V. Barone, B. Mennucci, ; G. A. Petersson, H. N., M. Caricato, X. Li, H. P. Hratchian, A. F. Izmaylov, J. Bloino, G. Zheng, J. L. Sonnenberg, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, T. Vreven, J. A. Montgomery, Jr., J. E. Peralta, F. Ogliaro, M. Bearpark, J. J. Heyd, E. Brothers, K. N. Kudin, V. N. Staroverov, R. Kobayashi, J. Normand, K. Raghavachari, A. Rendell, J. C. Burant, S. S. Iyengar, J. Tomasi, M. Cossi, N. Rega, J. M. Millam, M. Klene, J. E. Knox, J. B. Cross, V. Bakken, C. Adamo, J. Jaramillo, R. Gomperts, R. E. Stratmann, O. Yazyev, A. J. Austin, R. Cammi, C. Pomelli, J. W. Ochterski, R. L. Martin, K. Morokuma, V. G. Zakrzewski, G. A. Voth, P. Salvador, J. J. Dannenberg, S. Dapprich, A. D. Daniels, O. Farkas, J. B. Foresman, J. V. Ortiz, J. Cioslowski, and D. J. Fox, 2009.