5-Mercapto-1,3,4-thiadiazole-2(3H)-thione: Synthesis and Structure of Alkylated Derivatives

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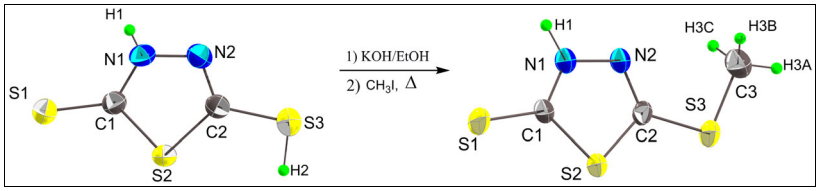

The observed structure of 1,3,4-thiadiazolidine-2,5-dithione (also known as 2,5-dimercapto-1,3,4-thiadiazole) has been previously reported in three different tautomeric forms including —dithiol and—dithione. This report examines the relative stability of each form and also reports synthesis and characterization of the structures of mono-alkylated and di-alkylated forms of 5-mercapto-1,3,4-thiadiazole-2(3H)-thione. The methods of X-ray crystallography, NMR spectroscopy, and *ab initio* electronic structure calculations were combined to understand the reactivity and structure of each compound.

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INTRODUCTION

1,3,4-Thiadiazolidine-2,5-dithione (CAS 1072-71-5) is also known as 2,5-dimercapto-1,3,4-thiadiazole, DMTD or bismuththiol. Its derivatives find application as raw material for various organic syntheses, analytical reagents, fuel additives, lubricant additives, intermediates for other pharmaceutical compounds, chelating compounds for metals, and flash-rust and corrosion inhibitors in coatings.

In our previous work of evaluating, the corrosion inhibition performance of 2,5-bis(thioaceticacid)-1,3,4-thiadiazole (H_2ADTZ) for its use as a potential flash-rust inhibitor and a corrosion inhibitor in coatings [1], the compound 5-mercapto-1,3,4-thiadiazole-2(3H)-thione (MTT) was used as a starting material. The structure of MTT is often reported in the literature in its tautomeric—dithiol form or in the—dithione form. In fact, it has been shown to have three tautomeric structures [2–4], with structure **1** being the most commonly reported in the literature (Fig. 1).

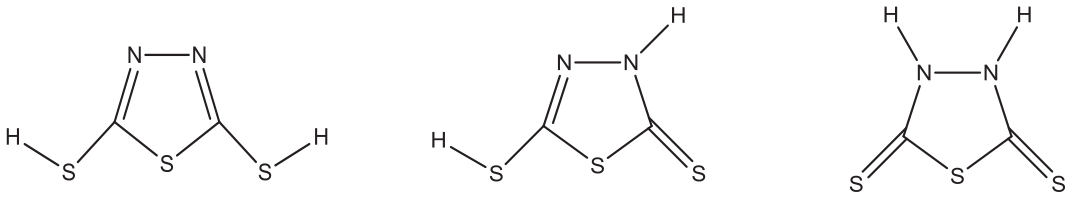
An X-ray crystal structure of MTT was reported in 1976 consistent with structure **2** [5]. Several recent reports refer to the structure of MTT as that of structure **3**[6–8]. In order to synthesize and evaluate the various mono-substituted and di-substituted derivatives of MTT as potential anti-flash-rust and anti-corrosives for coatings, it was important to know and understand the substitution mechanism of this compound and its various derivatives as well as to determine the structures and their stability. This report addresses the structure and various substitution products of MTT by combining results of *ab initio* electronic structure calculations, X-ray crystallography, and NMR spectroscopy to validate and better understand the chemistry of MTT.

RESULTS AND DISCUSSION

MTT as well as the mono-alkylated structure can exist in various tautomeric forms, and the di-alkylated structure can exist in three structurally isomeric forms. The stability of each tautomer was evaluated through *ab initio* electronic structure calculations. These calculations are presented considering MTT first, followed by the alkylated derivatives.

The structure of MMT. Table 1 lists the results of various levels of calculation for the three contending tautomeric forms of MTT. Structure **2** is predicted to be the lowest energy structural isomer by all of the computational methods employed. The highest level explicitly-correlated coupled-cluster (F12) calculations (Table 1) with corrections for solvation in ethanol predict structures **1** and **3** to lie about 4.7 and 5.9 kcal/mol higher in energy, respectively. Finite temperature effects at 298 K were estimated and added to the energies by using harmonic oscillator–rigid rotor approximate free energy corrections obtained from force-field analyses at the B3LYP/aug-cc-pVTZ and MP2/aug-cc-pVTZ levels. Energies for the explicitly correlated F12 methods were combined with thermal corrections from the MP2 calculations. A correction for solvation modeled [polarizable continuum model (PCM)] at the B3LYP/aug-cc-pVTZ level (including geometric relaxation) was added to both the DFT and F12 results. The X-ray crystal structure determined in this study is shown in Fig. 2. Our newly determined structure is in close agreement with that previously reported by J. W. Bats [5].

Mono-alkylation of MTT. The mono-alkylation of MTT can produce four possible structures (**4–7**). Structures **4** and **5**



Structure 1 **Structure 2** **Structure 3**

Figure 1. Three tautomeric forms of MTT.

Table 1

Calculated relative energies (kcal/mol) for structures **1-3** including thermal corrections at 298 K, and the effects of solvation in ethanol [where designated by (s)].

Method	Structure **1**	Structure **2**	Structure **3**
B3LYP/6-31G(d)[a]	8.57	0.00	6.03
B3LYP/AVTZ[a]	7.43	0.00	6.82
B3LYP/AVTZ (s)[a]	8.52	0.00	2.77
MP2/AVDZ[b]	4.48	0.00	9.51
MP2/AVTZ[b]	4.04	0.00	10.08
MP2-F12/VDZ-F12[b]	3.57	0.00	10.50
CCSD(T)-F12a/ VDZ-F12[b]	3.59	0.00	9.92
CCSD(T)-F12b/ VDZ-F12[b]	3.57	0.00	9.99
CCSD(T)-F12a/ VDZ-F12 (s)[b]	4.68	0.00	5.87

All F12 calculations used structures optimized at the MP2/AVTZ level (see text). (s) including implicit PCM solvation model for ethanol.
[a]Thermal corrections computed at B3LYP/AVTZ level.
[b]Thermal corrections computed at MP2/AVTZ level.

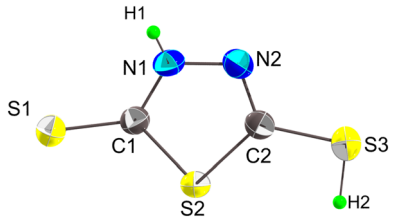


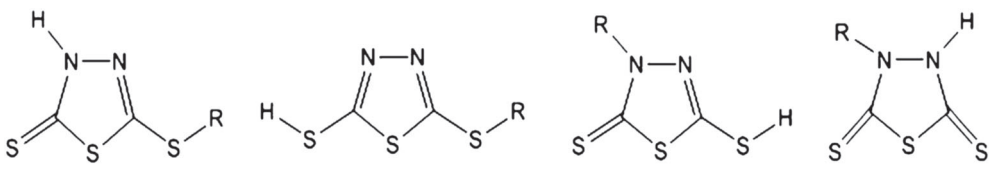
Figure 2. Thermal ellipsoids for MTT as observed through X-ray crystallography. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

derive from S-alkylation, whereas structures **6** and **7** come from N-alkylation (Fig. 3).

The precursors to structures **4–7** are the anions that could exist as either structure **8** or **9**. The highest level *ab initio* calculations for structures **8** and **9** predict that structure **8** is more stable by 7.37 kcal/mol (Table 2), and thus the proton is lost from the sulfur and not the nitrogen during alkylation (Figs. 4 and 5).

S_N2 reaction transition structures (TS) **10** and **11** were located corresponding to methylation of **8** at the S or N positions, respectively, with the use of chloromethane (rather than iodomethane that was used in the experiment to reduce the number of electrons in the calculations) as the alkylating agent. Methylation at the S position is strongly preferred with **10** predicted to be 6.21 kcal/mol lower in free energy than **11** for the highest level calculations (including the preferential solvation of **11**) (Table 3 and Fig. 6).

Methylation of **8** through TS **10** or **11** leads to product structures **12** and **15**, respectively, whereas methylation of disfavored anion **9** at the two positions would lead to structures **13** and **14**. Table 4 compares the calculated energies of all four possible products. Structure **12** is predicted to be the most stable of all four of the methylated structures. Looking at the reaction scheme, structure **12** is strongly favored both kinetically and thermodynamically. The lower energy anion **8** reacts through the lower energy TS **10** to form the most stable product **12**. Not surprisingly, the product of the first methylation step was confirmed by X-ray crystallography (Fig. 7) and ^{13}C NMR spectroscopy to be structure **12**.



Structure 4 **Structure 5** **Structure 6** **Structure 7**

[R = Alkyl]

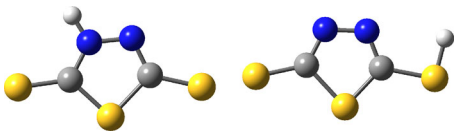
Figure 3. Four possible mono-substituted products of MTT.

Table 2

Calculated relative energies (kcal/mol) for anion structures **8** and **9** including thermal corrections at 298 K, and the effect of solvation in ethanol [where designated by (s)].

Method	Structure **8**	Structure **9**
B3LYP/6-31G(d)[a]	0.00	15.50
B3LYP/AVTZ[a]	0.00	13.68
B3LYP/AVTZ (s)[a]	0.00	10.62
MP2/AVDZ[b]	0.00	11.22
MP2/AVTZ[b]	0.00	10.74
MP2-F12/VDZ-F12[b]	0.00	10.25
CCSD(T)-F12a/VDZ-F12[b]	0.00	10.44
CCSD(T)-F12b/VDZ-F12[b]	0.00	10.44
CCSD(T)-F12a/VDZ-F12 (s)[b]	0.00	7.37

All F12 calculations used structures optimized at the MP2/AVTZ level (see text). (s) including implicit PCM solvation model for ethanol.
[a]Thermal corrections computed at B3LYP/AVTZ level.
[b]Thermal corrections computed at MP2/AVTZ level.



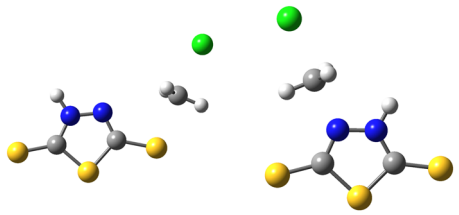
Structure 8 **Structure 9**

Figure 4. Two possible anionic forms of MTT. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

The T_1-diagnostic is around 0.02 for all calculated structures supporting the reliability of single-reference methods to describe these systems. Calculated ^{13}C NMR shifts (relative to TMS) were obtained for structures **12** and **13** by using the GIAO method [9] with B3LYP and the 6-31 G* basis set. Calculated shifts for the ring carbons are 159.6 and 186.0 ppm (structure **12**) and 158.6 and 167.1 ppm (structure **13**). The calculated values for structure **12** agree closely with experimentally recorded values of 159.4 and 187.6 ppm.

Di-alkylation of MTT. The di-alkylation of MTT was analogously investigated. From structure **12** (mono-alkylated MTT), a second alkylation can occur at two possible alkylation sites—either at the sulfur (forming structure **16**) or at the nitrogen (forming structure **17**) (Fig. 8).

Considering the second methylation step starting from **12** and again with the use of chloromethane as the alkylating agent (to simplify the calculations), TS structures **16** and **17** were located connecting **12** with product structures **19** and **20**, respectively. Table 5 compares calculated energies for TSs **16** and **17**. Methylation at the S position appears to be kinetically favored as **16** is predicted to be lower in estimated free energy at 298 K than **17** for the B3LYP and CCSD(T)-F12 calculations. The differences in this case are only 1.0 and 0.6 kcal/mol (B3LYP and CCSD(T)-F12),



Structure 10 **Structure 11**

Figure 5. The S_N2 transition structures for two possible alkylation sites—at the sulfur (structure **10**) or at the nitrogen (structure **11**). [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

Table 3

Calculated relative energies (kcal/mol) for S_N2 transition structures **10** and **11** including thermal corrections at 298 K, and the effect of solvation in ethanol [where designated by (s)].

Method	TS (Structure **10**)	TS (Structure **11**)
B3LYP/AVTZ[a]	0.00	7.44
B3LYP/AVTZ (s)[a]	0.00	5.77
MP2/AVTZ[b]	0.00	7.21
MP2-F12/VDZ-F12[b]	0.00	7.54
CCSD(T)-F12a/VDZ-F12[b]	0.00	7.89
CCSD(T)-F12b/VDZ-F12[b]	0.00	7.89
CCSD(T)-F12a/VDZ-F12 (s)[b]	0.00	6.21

All F12 calculations used structures optimized at the MP2/AVTZ level (see text). (s) including implicit PCM solvation model for ethanol.
[a]Thermal corrections computed at B3LYP/AVTZ level.
[b]Thermal corrections computed at MP2/AVTZ level.

whereas MP2 calculations actually favor **17**. Preferential solvation of **16** contributes the most to the net difference of 1.62 kcal/mol at the CCSD(T)-F12a (s) level. Given the smaller differences in barrier heights (than for the first methylation step) and the discrepancy with the MP2 results, additional DFT calculations were performed with the use of iodomethane and the Quadruple Zeta Valence Polarization (QZVP) basis set. Including solvation by ethanol and thermal corrections at 298 K, the difference in barrier heights increases to 2.91 kcal/mol, making methylation at the S position more strongly kinetically favored. Table 6 compares the energies of di-methylation structures **18–20**. Assuming a concerted 6-membered transition state involving the sodium salt and the alkyl halide, the relative energy was 31.4 kcal/mol higher than TS **16** (Fig. 9).

TSs **16** and **17** connect **12** with **19** and **20**, respectively, whereas **18** is included for comparison. Structure **19** is predicted to be significantly less stable (2.9–3.8 kcal/mol) than **20** yet has been confirmed through X-ray crystallography as the only detectable product structure. The highest level calculations reported here are expected to be quite reliable especially for estimating the relative energies of product structures. The best calculations with the use of chloromethane do predict **19** as the kinetically favored product and DFT calculations for iodomethane favor it

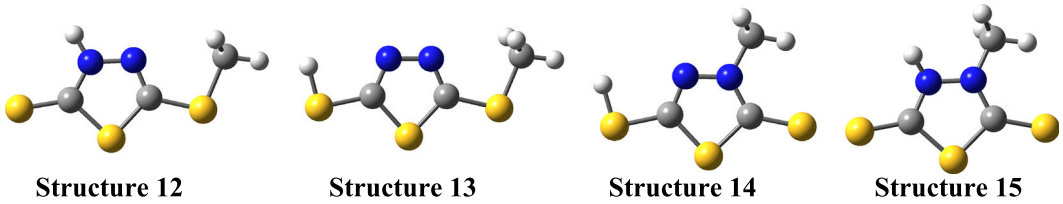


Figure 6. Four potential mono-alkylation structures **12–15**. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

Table 4

Calculated relative energies (kcal/mol) for structures **12–15** including thermal corrections at 298 K, and the effect of solvation in ethanol [where designated by (s)].

Method	Structure **12**	Structure **13**	Structure **14**	Structure **15**
B3LYP/6-31G(d)[a]	0.00	8.33	1.06	6.31
B3LYP/AVTZ[a]	0.00	7.21	1.92	7.72
B3LYP/AVTZ (s)[a]	0.00	8.58	2.72	4.39
MP2/AVDZ[b]	1.56	5.77	0.00	9.23
MP2/AVTZ[b]	0.02	3.83	0.00	9.60
MP2-F12/VDZ-F12[b]	0.00	3.38	0.61	10.55
CCSD(T)-F12a/VDZ-F12[b]	0.00	3.35	1.03	10.25
CCSD(T)-F12b/VDZ-F12[b]	0.00	3.34	1.01	10.30
CCSD(T)-F12a/VDZ-F12 (s)[b]	0.00	4.72	1.83	6.93

All F12 calculations used structures optimized at the MP2/AVTZ level (see text). (s) including implicit PCM solvation model for ethanol.
[a]Thermal corrections computed at B3LYP/AVTZ level.
[b]Thermal corrections computed at MP2/AVTZ level.

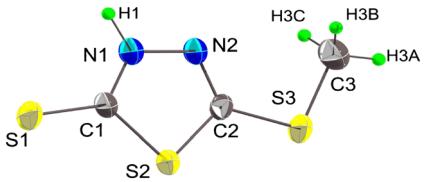


Figure 7. Thermal ellipsoids for Me–MTT as observed through X-ray crystallography. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

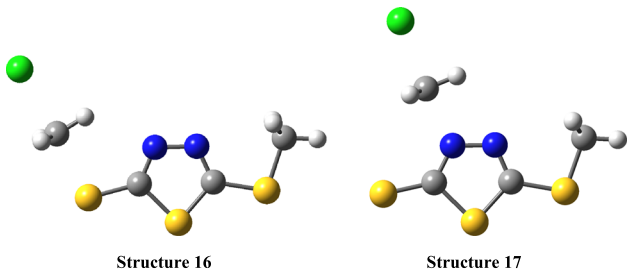


Figure 8. The transition structures for di-alkylation of MTT. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

even more. The barrier for methyl transfer converting **19** into **20** was computed (at the B3LYP/AVTZ level) to be 55.5 kcal/mol, which supports the idea that once **19** is formed, it will not easily convert to the more stable **20**.

Because 2,5-bis(methylthio)-1,3,4-thidiazole-2-thiol is a liquid compound, a crystal structure for the di-alkylation

Table 5

Calculated relative energies (kcal/mol) for S_N2 transition structures **16** and **17** including thermal corrections at 298 K, and the effect of solvation in ethanol [where designated by (s)].

Method	TS (Structure 16)	TS (Structure 17)
B3LYP/AVTZ[a]	0.00	1.04
B3LYP/AVTZ (s)[a]	0.00	2.02
MP2/AVTZ[b]	0.79	0.00
MP2-F12/VDZ-F12[b]	0.40	0.00
CCSD(T)-F12a/VDZ-F12[b]	0.00	0.64
CCSD(T)-F12b/VDZ-F12[b]	0.00	0.61
CCSD(T)-F12a/VDZ-F12 (s)[b]	0.00	1.62
B3LYP/QZVP (s) iodo[c]	0.00	2.91

All F12 calculations used structures optimized at the MP2/AVTZ level (see text). (s) including implicit PCM solvation model for ethanol.
[a]Thermal corrections computed at B3LYP/AVTZ level.
[b]Thermal corrections computed at MP2/AVTZ level.
[c]DFT calculation using iodomethane (see text).

product of MTT, namely H_2ADTZ was obtained to reconfirm the aforementioned results that both of the substitutions occur on sulfur. Both ^{1}H and ^{13}C NMR spectra of dimethylated MTT and H_2ADTZ are consistent with the X-ray determined structure **19**. 2,5-bis(methylthio)-1,3,4-thidiazole-2-thiol (dimethylated MTT) showed ^{13}C peaks in d-DMSO at 165.56 ppm (–N=C–S–Me), and 15.60 (–CH3) and GC–MS parent peak at 177 (isotopic abundance peaks because of sulfur at 178 and 179), and

Table 6

Calculated relative energies (kcal/mol) for structures **18**, **19**, and **20** including thermal corrections at 298 K, and the effect of solvation in ethanol [where designated by (s)].

Method	Structure **18**	Structure **19**	Structure **20**
B3LYP/6-31G(d)[a]	8.89	7.89	0.00
B3LYP/AVTZ[a]	10.34	5.89	0.00
B3LYP/AVTZ (s)[a]	7.09	6.76	0.00
MP2/AVDZ[b]	9.42	6.43	0.00
MP2/AVTZ[b]	11.23	4.45	0.00
MP2-F12/VDZ-F12[b]	12.16	3.40	0.00
CCSD(T)-F12a/VDZ-F12[b]	11.75	2.93	0.00
CCSD(T)-F12b/VDZ-F12[b]	11.82	2.93	0.00
CCSD(T)-F12a/VDZ-F12 (s)[b]	8.50	3.81	0.00

All F12 calculations used structures optimized at the MP2/AVTZ level (see text). (s) including implicit PCM solvation model for ethanol.
[a]Thermal corrections computed at B3LYP/AVTZ level.
[b]Thermal corrections computed at MP2/AVTZ level.

significant *m*/*z* peaks at 146 and 147 (because of the loss of two methyl groups), which confirmed the identity of the compound as 2,5-bis(methylthio)-1,3,4-thiadiazole. H_2ADTZ showed ^{13}C peaks in d-DMSO at 165.56 ppm (–N=C–S–), 169.11 ppm (–COOH), and 35.74 ppm (–CH_2–) (Fig. 10).

CONCLUSION

A combined study by means of X-ray crystallography, ^{13}C NMR spectroscopy and *ab initio* electronic structure calculations was performed, determining the structure of MTT and its substituted derivatives conclusively and explaining the chemistry of its reaction mechanisms (Fig. 11).

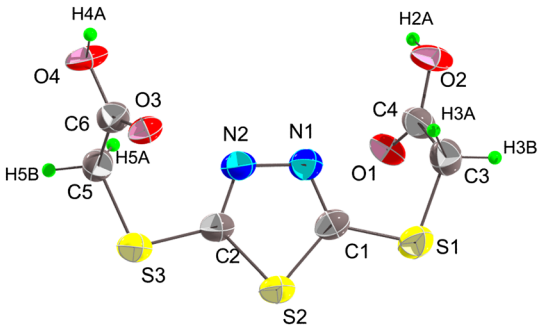
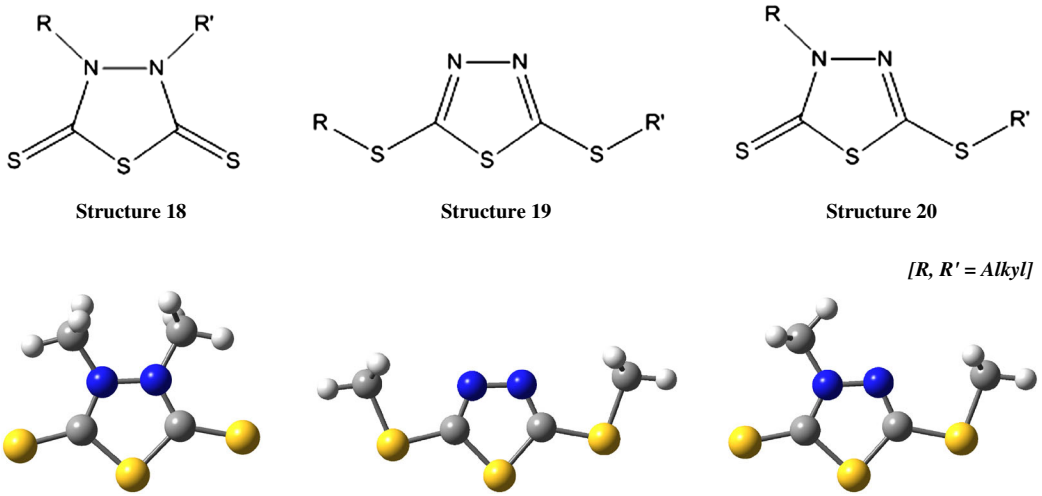


Figure 10. Thermal ellipsoid for 2,5-bis(thioaceticacid)-1,3,4-thiadiazole (H_2ADTZ) as observed through X-ray crystallography. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

EXPERIMENTAL

Materials. The starting material MTT was obtained from R. T. Vanderbilt who lists the chemical as DMTD (Structure **1**) and was re-crystallized from benzene before use. All the solvents were dried and distilled before use unless otherwise specified. All other chemicals were procured from Fisher or Aldrich and used as received.

X-ray crystallography. Intensity data sets for all the compounds were collected on a Bruker Smart Apex diffractometer using SMART software [10]. Suitable crystals were selected and mounted on a glass fiber using epoxy-based glue. The data were collected at room temperature employing a scan of 0.3° in ω with an exposure time of 20 s/frame. The cell refinement and data reduction were carried out with SAINT [11], the program SADABS was used for the absorption correction [11]. The structure was solved by direct methods using SHELXS-97 [12,13] and difference Fourier syntheses. Full-matrix least-squares refinement against $|F^2|$ was carried out by using the SHELXTL-PLUS [12,13] suite of programs. All non-hydrogen atoms were refined anisotropically. Hydrogen atoms were placed geometrically and held in the riding mode during the



Structure 18 **Structure 19** **Structure 20**

Figure 9. Three possible structures of the di-substituted product of MTT. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

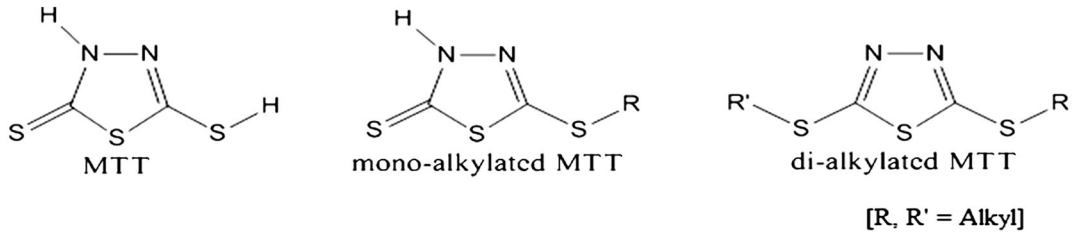


Figure 11. The results of X-ray crystallography, NMR spectroscopy, and *ab initio* electronic structure calculations indicate the preferred structures of MTT, mono-alkylated MTT, and di-alkylated MTT.

final refinement. However, hydrogen atoms on N and S in case of MTT and on N in the case of 5-(methylthio)-1,3,4-thidiazole-2-thiol were well located from the difference Fourier map and refined subsequently.

Crystallographic data (excluding structure factors) for the structures in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication nos. CCDC 883750 [5-mercapto-1,3,4-thiadiazole-2(3H)-thione], CCDC 883751 [5-(methylthio)-1,3,4-thidiazole-2(3H)-thione], and CCDC 883752 [2,5-(S-acetic acid)dimercapto-1,3,4-thiadiazole]. Copies of the data can be obtained, free of charge, on application to CCDC: 12 Union Road, Cambridge CB2 1EZ, UK, (fax: +44-(0)1223-336033 or e-mail: deposit@ccdc.cam.ac.uk).

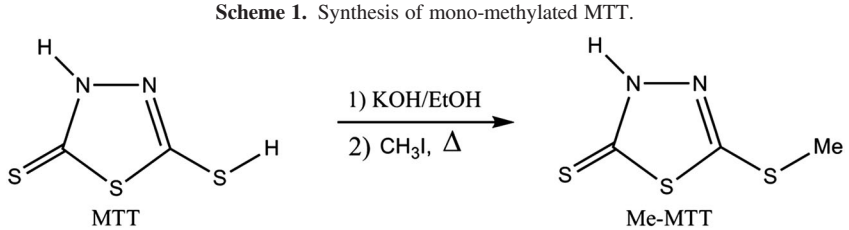
NMR spectroscopy. The instrument used for recording the ^{1}H NMR and ^{13}C NMR data for liquid state NMR was 400 MHz Varian FT/NMR spectrometer. The reference peak used was δ for TMS at 0.0 ppm.

NMR of MTT. The Bruker DRX300 spectrometer with CP-MAS and 7 mm diameter solid rotor was used for the solid state NMR. Measurements were made at 5 kHz spinning and the reference peak used was δ for glycine C=O carbon at 176.03 ppm. MTT showed ^{13}C peaks at 159.60 ppm (–N=C–SH) and 189.07 ppm (–N–C=S). The 400 MHz Varian FT/NMR spectrometer was used for the ^{13}C NMR liquid state NMR with the use of ethanol-D6 as solvent, and the spectra showed ^{13}C peaks at 148.50 ppm (–N=C–SH) and 190.20 ppm (–N–C=S) confirming the structure to be in the thiol–thione form (one H on sulfur and another on nitrogen). MTT was observed to form disulfides in DMSO, and thus DMSO was not considered a suitable solvent for recording the NMR spectra even though some researchers have reported the ^{1}H NMR and ^{13}C NMR spectra of MTT in DMSO-d6 [14].

***Ab initio* electronic structure calculations.** A variety of *abinitio* electronic structure calculations were performed to study candidate starting material structures **1–3**. From the starting material, two consecutive methylation reactions were studied comparing at each stage the relative energies of possible anions formed by deprotonation as well as S_N2 TSs leading to possible product structures. The GAUSSIAN09 [15] and MOLPRO2010 [16] software packages were used for all the calculations reported here. Geometry optimizations and harmonic vibrational frequency calculations were used to locate and confirm minimum energy configurations for each structure. Structures were optimized by using the B3LYP [17] hybrid DFT method with the 6-31 G* and aug-cc-pVTZ basis sets as implemented in the GAUSSIAN program. Additional optimizations were performed with the use of Møller–Plesset second-order perturbation theory (MP2) [18] with Dunning's double and triple-zeta augmented correlation-consistent basis sets (aug-cc-pVDZ and aug-cc-pVTZ) [19]. Some high-level explicitly correlated F12 [20] single-point energy calculations were performed by using the structures previously determined at the MP2/aug-cc-pVTZ level. Peterson's specialized double-zeta F12 basis set VDZ-F12[9] was used to compute energies with the MP2-F12 and CCSD(T)-F12 methods. The MOLPRO program was used for all explicitly correlated F12 calculations. For all structures, the effect of solvation was estimated (allowing structural relaxation) at the B3LYP/aug-cc-pVTZ level by using the implicit PCM solvation model as parameterized for ethanol in the GAUSSIAN09 program [21]. The T_1-diagnostic was recorded to confirm the applicability of the single-reference methods used in this study.

Synthesis of mono-methylated MTT [6] (Structure 12). To a stirred aqueous solution of potassium hydroxide (0.1 mol, 5.61 g) in absolute ethanol (2.17 mol, 99.97 g), MTT (0.1 mol, 15.02 g) was added. The reaction mixture was stirred for half an hour before methyl iodide (0.11 mol, 15.61 g) was added to the mixture and refluxed for 6 h, and then it was cooled and filtered. The filtered product 5-(methylthio)-1,3,4-thidiazole-2(3H)-thione (mol. wt. 164.27) was crystallized from benzene to yield a yellowish needle-shaped precipitates that were dried under vacuum. The yield was 74% (12.15 g). The melting point of the compound was found to be 137–138°C. 5-(methylthio)-1,3,4-thidiazole-2(3H)-thione showed ^{13}C peaks in d-DMSO at 159.39 (–N=C–S–Me), 187.51 (–N–C=S), and 14.67 ppm (–CH3);

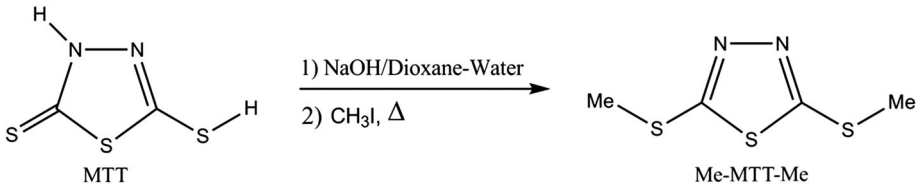
Scheme 1. Synthesis of mono-methylated MTT.



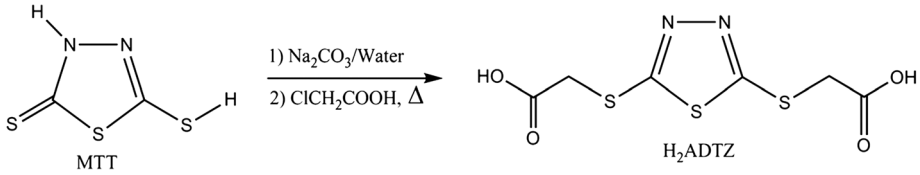
^{1}H peaks in d-DMSO at 2.52 (S–CH_3) and 14.30 ppm (N–H); IR bands at 3050, 1480, 1365, and 1100 cm^{-1}; MS peaks at 164, 91, 88, 73 and 59 *m/z* (Scheme 1).

Synthesis of di-methylated MTT [22] (Structure 19). To a stirred aqueous solution of 100 mL DI/distilled water with sodium hydroxide (0.3 mol, 12 g) in 1,4-dioxane (0.12 mol, 100 mL), MTT (0.1 mol, 15.02 g) was added. The reaction mixture was stirred for 30 min before methyl iodide (0.21 mol, 29.80 g) was added to the mixture and refluxed for 6 h, after which the reaction product was cooled, poured into water, and

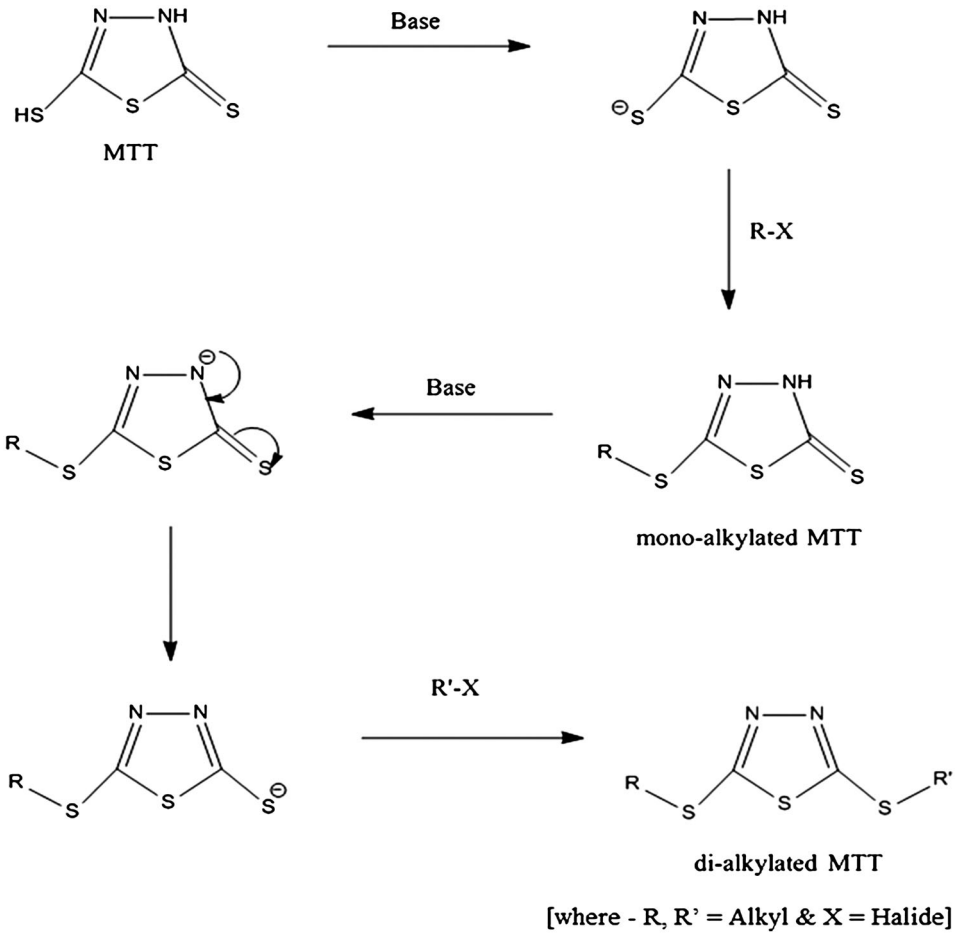
Scheme 2. Synthesis of di-methylated MTT.



Scheme 3. Synthesis of 2,5-bis(thioaceticacid)-1,3,4-thiadiazole (H_2ADTZ).



Scheme 4. Proposed mechanism for reactions of MTT.



extracted twice with diethyl ether, dried over anhydrous sodium sulfate, filtered, and rotavaped to give a yellowish liquid product 2,5-bis(methylthio)-1,3,4-thiadiazole (mol. wt. 178.30). The yield was 79% (14.08 g). The boiling point of the compound was found to be 311–313°C. 2,5-Bis(methylthio)-1,3,4-thidiazole was a yellowish liquid that showed ^{13}C peaks in d-DMSO at 165.56 (–N═C–S–Me) and 15.60 ppm(–CH_3); ^{1}H peaks in d-DMSO at 2.55 ppm (–CH_3), and GC–MS parent peak at 177 (isotopic abundance peaks because of Sulfur at 178 and 179) and significant *m*/*z* peaks at 146 and 147 (because of the loss of 2 methyl groups), which confirmed the identity of the compound as 2,5-bis(methylthio)-1,3,4-thiadiazole.

Di-alkylation of MTT can also be achieved by sequential alkylation of mono-alkylated MTT, but one-pot dimethylation procedure is convenient and therefore preferred. Di-methylated MTT has been synthesized in similar yields by taking mono-methylated MTT in absolute ethanol with potassium hydroxide as the base and iodomethane as the alkylating agent (as per the mono-methylation described earlier) (Scheme 2).

Synthesis of H_2ADTZ [1] (Fig. 10). To a stirred aqueous solution of chloroacetic acid (94.5 g, 1 mol) and sodium carbonate (53 g, 0.5 mol), MTT (75 g, 0.5 mol) was added. The reaction mixture was stirred and refluxed for 3 h, then it was cooled and filtered. Ethanol was added to the reaction mixture, yielding a white precipitate. The product 2,5-(S-acetic acid)-dimercapto-1,3,4-thiadiazole (H_2ADTZ) (mol. wt. 266.32) was then washed with ethanol and dried under vacuum to give a white solid (H_2ADTZ). The yield was 83% (110.51 g). The melting point of the compound was found to be 164–165°C. H_2ADTZ showed ^{13}C peaks in d-DMSO at 164.56 (–N═C–S–), 169.11 (–COOH), and 35.74 ppm (–CH_2–); ^{1}H peaks in d-DMSO at 4.11 (–CH_2) and 11.46 ppm (–OH); IR bands at 3410, 2920, 2830, 1750, and 1600 cm^{-1} (Schemes 3 and 4).

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