A Convenient Method for Determination of Tetramethylthiuram Disulphide

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Submitted in honour of the sixtieth birthday of my (S.Å.) teacher, Professor *Arne Fredga*

A new method for the determination of small amounts of tetra-methylthiuram disulphide (TMTD) is described. The method is applicable to other tetrasubstituted thiuramdisulphides. The reproducibility of the determination of TMTD is ± 2 %.
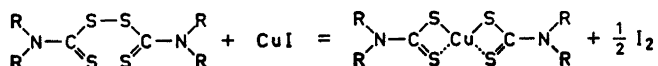
Dithiocarbamates and thiuramdisulphides find a variety of applications as plant fungicides, bactericides, analytical reagents, accelerators in the rubber industry and collectors in the flotation of minerals.

During the last ten years many papers concerning these compounds have been published and an increasing need of rapid and exact methods for their determination has arisen.

One of the present authors is studying the inhibition of growth and photo-synthesis in submerged plants with tetramethylthiuram disulphide (TMTD) [1]. Further, in some pharmaceutical preparations used in dermatology, *e.g.* Nobecutane, TMTD is the bactericidal and fungicidal component. In such cases a sensitive method for determining TMTD concentrations is required.

As early as 1949 Fredga [2] developed a method for the determination of tetraethylthiuram disulphide (antabuse), which at that time was used for the treatment of chronic alcoholism. Some years later Linderholm and Berg [3] used this method for the determination of small amounts of antabuse in blood and urine. The method is applicable to other tetraalkyl-substituted
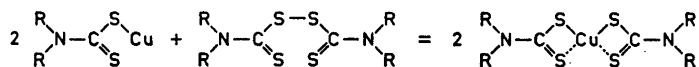
thiuramdisulphides and is based on a reduction of the thiuramdisulphide with copper(I) iodide and a spectrophotometric determination of the intensely coloured copper(II) complex formed.

$$\underset{R}{\overset{R}{>}}N-C\underset{S}{\overset{S-S}{<}}C-N\underset{R}{\overset{R}{<}} + CuI = \underset{R}{\overset{R}{>}}N-C\underset{S}{\overset{S}{<}}Cu\underset{S}{\overset{S}{<}}C-N\underset{R}{\overset{R}{<}} + \tfrac{1}{2}I_2$$

Scheele and Gensch [4] determined TMTD with copper(II) sulphate in the presence of hydroquinone. The same workers [5] also transformed the thiuramdisulphide into the corresponding monosulphide with potassium cyanide and titrated the formed potassium thiocyanate with silver nitrate. Iijima and Eguchi [6] reduced TMTD with sodium thiosulphate to the dithiocarbamate. With copper(II) sulphate this gives the copper(II) N,N-dimethyldithiocarbamate which is then determined spectrophotometrically. Iijima [7] also reduced TMTD with aqueous sodium sulphide and decomposed the dithiocarbamate with acid, the carbon disulphide produced being titrated as the xanthate. Firestone and Vollmer [8] used an infrared spectrophotometric method and Kalasheva [9] developed a polarographic method for TMTD determination. Stepanova [10] has determined TMTD in rubber mixtures and vulcanizates by a photocolorimetric procedure based on the colour reaction of TMTD with cobalt(II) chloride in an ethanol-benzene medium. Salvesen and Domange [11] have determined disulfiram (TMTD) by a colorimetric method. Keppel [12] isolated TMTD by extraction with chloroform. Copper(II) chlorides was then added and the formed complex determined spectrophotometrically at 420 mμ. Barr, Clark and Jacks [13] have worked out a micromethod for the determination of TMTD and dimethyldithiocarbamate based on acid decomposition followed by steam distillation of the formed dimethylamine in excess alkali. The amine is then determined as copper(II) N,N-dimethyldithiocarbamate. In a recent method Lowen [14] titrated TMTD potentiometrically with sodium sulphide in the presence of ferbam (iron(III) N,N-dimethyldithiocarbamate).

None of these methods can be considered as better or simpler than that of Fredga.

The principle of the present method may schematically be written as follows:

$$2\; \underset{R}{\overset{R}{>}}N-C\underset{S}{\overset{S}{<}}Cu + \underset{R}{\overset{R}{>}}N-C\underset{S}{\overset{S-S}{<}}C-N\underset{R}{\overset{R}{<}} = 2\; \underset{R}{\overset{R}{>}}N-C\underset{S}{\overset{S}{<}}Cu\underset{S}{\overset{S}{<}}C-N\underset{R}{\overset{R}{<}}$$

The reaction between the copper(I) compound and the TMTD occurs rapidly and quantitatively. The intensely coloured copper(II) complex formed is determined spectrophotometrically [15,16]. For the determination of TMTD copper(I) N,N-diethyldithiocarbamate was chosen in preference to the corresponding copper(I) N,N-dimethyldithiocarbamate as the solubility of the latter in all common organic solvents is too low. One probably obtains a mixture of the compounds given below owing to the complex constants of the formed copper(II) complexes.
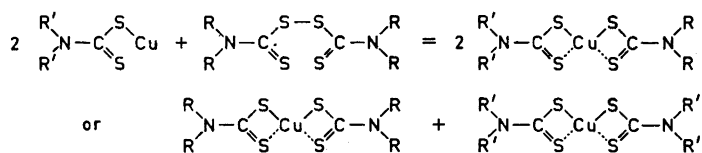
As the extinction coefficients of the copper(II) complexes given below
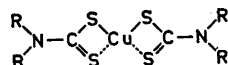
R = methyl, ethyl, propyl, isopropyl.

are the same (within ± 2 % at the absorption maximum of the compounds), this method can also be used for the determination of other tetraalkyl-substituted thiuramdisulphides. For the higher homologues one may also use the corresponding copper(I) N,N-dialkyldithiocarbamate.

In some cases it is necessary to determine dithiocarbamate and thiuramdisulphide in a mixture. For example, TMTD and N,N-dimethyldithiocarbamate ion (DMDT⁻) can be determined in water. The solution, made weakly alkaline, is extracted with chloroform. The TMTD in the chloroform phase is treated with copper(I) N,N-diethyldithiocarbamate and the intensely coloured complex formed is determined spectrophotometrically. The water phase is treated with copper(II) sulphate at another pH and after extraction of the formed copper(II) complex, the amount of dithiocarbamate is determined spectrophotometrically.

<p style="text-align:center">EXPERIMENTAL</p>

<p style="text-align:center">Instruments, solvent and reagents</p>

Beckman Spectrophotometer, Model B.
1-cm glass transmission cells.
Chloroform (*pro analysi*), copper(I) N,N-diethyldithiocarbamate [16], tetramethylthiuram disulphide, and copper(II) sulphate pentahydrate.

<p style="text-align:center">Procedure I</p>

A sample containing 0.1 — 0.3 mg of TMTD is weighed in and diluted with chloroform to 50 ml (*a*). About 3 ml of this solution is required for the zero-adjusting of the spectrophotometer. To the rest of the solution 1 — 10 mg of copper(I) N,N-diethyldithiocarbamate is added (*b*) and shaken well for 10 sec. The optical density of the solution is measured at 433 mμ (*c*).

$$\% \ \text{TMTD} = \frac{s \cdot 100}{w}$$

E = optical density
s = mg of TMTD per 50 ml of solution read off from a calibration curve.
w = amount of sample in mg.

Notes. a) For spray packages of Nobecutane (containing 0.016 % of TMTD) 1—1.5 g is sprayed directly into a 50 ml calibrated flask and diluted with chloroform to the mark.

b) Larger quantities than 10 mg should be avoided as the reagent exhibits a slight absorption at the wave-length in question.

c) Measurement of the optical density should be done within 2—5 min. If the solution is allowed to stand too long the copper(I) N,N-diethyldithiocarbamate is autooxidized leading to an increasing extinction giving a TMTD value which is too high. An error of the same kind could also arise if the sample contains some oxidizing agents, extractable with chloroform and able to oxidize copper(I) N,N-diethyldithiocarbamate.

Table 1. Analyses of spray packages of Nobecutane by procedure I.

Nobecutane			
w	*E*	*s*	% TMTD
2212	0.778	0.378	0.0171
1634	0.572	0.276	0.0169
1530	0.545	0.261	0.0171
574	0.205	0.0981	0.0171

Procedure II

Determination of TMTD. A sample of the water solution (20.0 ml) is adjusted to pH 7.6—9.0 (*d*) and the TMTD extracted with three portions of chloroform, each of which is shaken for about 5 sec. The combined extracts are filtered into a 20 ml calibrated flask containing 1 ml of copper(I) N,N-diethyldithiocarbamate solution (*e*). After washing the filter paper and filling the flask with chloroform the optical density of this solution (E_T) is read at 433 mμ using 1 ml of the copper(I) N,N-diethyldithiocarbamate solution diluted with chloroform to 20 ml as reference.

The molecular extinction coefficient of the formed copper(II) complexes is (1.25$\pm$ 0.02) $\times$ 10^4 liter.mole^{-1} . cm^{-1} (Ref.[16]). The concentration of TMTD in the water solution is then given by the expression

Table 2. Analyses of TMTD in water solutions by procedure II.

Solvent	E_T (433 mμ)	$C_{TMTD} \times 10^{-5}$ moles per litre
Tap water	1.808	7.23
	1.798	7.19
	1.780	7.12
Sea water	1.343	5.37
	1.346	5.38
	1.340	5.36
Medium	1.362	5.45
AN1-Sp	1.350	5.40
(*g*)	1.350	5.40

Note *g*). This medium is based chiefly on sea water and has been used in manometric photosynthesis experiments [1].

Table 3. Analyses of solutions of TMTD by procedure II. The solutions are diluted with the solvent (AN1-Sp, cf. Table 2) from a standard solution.

Extent of dilution	E_T (433 mμ)	$C_{TMTD} \times 10^{-5}$ moles per litre	Recovery per cent
0 % (standard solution)	1.092	4.37	—
50 %	0.547	2.19	100
75 %	0.284	1.14	104

$$C_{TMTD} = \frac{E_T}{1.25 \times 10^4 \times 2 \times 1} = 4\ E_T \times 10^{-5} \text{ moles per litre.}$$

The reproducibility of this procedure has been tested by repeated analyses (Table 2) and by determination of the recovery from solutions of known dilution (Table 3).

Determination of DMDT⁻. To the solution remaining after the extraction of TMTD is pipetted 1 ml 0.3 % copper(II) sulphate solution (*f*) and the estimated quantity of diluted hydrochloric acid for adjusting the pH to 5−7. The copper(II) complex formed is extracted with three portions of chloroform, each of which is shaken for about 5 sec. The combined extracts are filtered into a 20 ml calibrated flask containing no reagent. After washing the filter paper and filling the flask with chloroform, the optical density of the solution (E_D) is read at 433 mμ with chloroform as reference.

With the molecular extinction coefficient mentioned above, the concentration of DMDT⁻ is given by the expression

$$C_{DMDT} = \frac{E_D}{1.25 \times 10^4 \times 0.5 \times 1} = 16 E_D \times 10^5 \text{ moles per litre.}$$

Values from such analyses are given in Table 4.

Table 4. Analyses of both TMTD and DMDT⁻ by procedure II. The solutions have been prepared from TMTD or sodium dimethyldithiocarbamate (Na-DMDT) with AN1-Sp (cf. Table 2).

Solution prepared with	E_T	E_D	C_{TMTD}	C_{DMDT^-}
	(433 mμ)		in 10^{-5} moles per litre	
Na-DMDT	0.003	0.287	0.01	4.59
	0.005	0.292	0.02	4.67
Na-DMDT	0.009	0.097	0.04	1.55
	0.012	0.096	0.05	1.54
TMTD	0.513	0.003	2.05	0.05
	0.510	0.001	2.04	0.02
TMTD	0.870	0.004	3.48	0.06
	0.885	0.003	3.54	0.05

Notes. d) The amount of diluted hydrochloric acid or sodium hydroxide, required to adjust the pH to within the range 7.6 — 9.0 in the sample should be previously estimated.

e) Copper(I) N,N-diethyldithiocarbamate (7 — 10 mg) is dissolved in 10 ml chloroform. The slow autooxidation of Cu(I) to Cu(II) darkens this solution and after about 2 h at room temperature a fresh solution should be prepared. See also note (c).

f) As in note *d*), the amount of acid or base required to adjust the pH to within the range 5 — 7 should be previously estimated.

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