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Deoxygenation of Tertiary Amine Oxides with Carbon Disulfide

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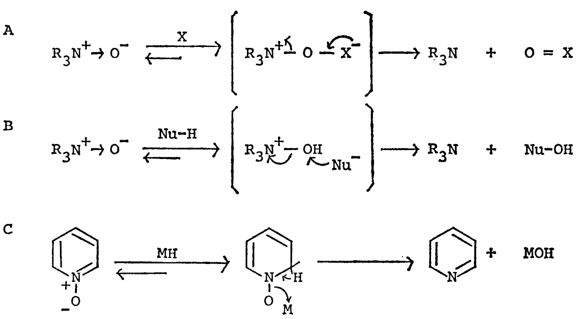
Reduction of various tertiary amine oxides with carbon disulfide was examined and kinetic experiments were carried out. Trialkylamine oxides and *N*,*N*-dialkylarylamine *N*-oxides were readily reduced by CS_2 to give the corresponding tertiary amines in good yields, while heteroaromatic amine *N*-oxides such as picoline *N*-oxide were not affected. The oxygen atom in the *N*-oxide was found to be transferred to CO_2 upon mass spectral analysis of the gas evolved. The kinetic experiments were carried out following the UV spectra of *N*,*N*-dimethylaniline *N*-oxide in CH_3CN containing much excess of CS_2 and the rate was found to be of 2nd order in the *N*-oxide and CS_2. Activation parameters ($\Delta H^{*}=55.7\ \mathrm{kJ\ mol^{-1}}$, $\Delta S^{*}=-78.2\ \mathrm{J\ K^{-1}\ mol^{-1}}$ at 20 °C) are characteristic of a normal bimolecular reaction. The logarithms of the rate constants for para-substituted *N*,*N*-dimethylaniline *N*-oxides are nicely correlated with Hammett σ values and a small negative ρ value ($\rho=-0.2$) was obtained. The rate of reaction was faster in polar aprotic solvents than in nonpolar or protic solvents. These observations seem to suggest that the reaction proceeds via an initial nucleophilic attack of the *N*-oxide oxygen at carbon disulfide followed by the rate-determining N–O bond fission to give the tertiary amine.

Tertiary amine oxides can be reduced back to the corresponding amines by various reducing agents such as trivalent phosphorus compounds, sulfur compounds, carbenes, hexachlorodisilane and metal hydride. These deoxygenation can roughly be classified into the following three types mechanistically.



The mechanism A involves initial electrophilic attack of reagent such as trivalent phosphorus compound,[1] carbens,[2] sulfur dioxide[3] followed by back donation of an electron pair from the central atom of the reducing agent to cleave the N–O bond. Meanwhile, the mechanism B involves the initial coordination of electrophile on *N*-oxide oxygen followed by nucleophilic substitution at oxygen atom like in the reduction with thiols.[4] In the reduction of heteroaromatic *N*-oxides with metal hydride, the reaction proceeds *via* an initial addition of metal hydride to α-carbon and oxygen, followed by elimination of metal hydroxide (mechanism C).[5,6]

Tertiary amine oxides are mild nucleophilic oxidants which can oxidize both disulfides and sulfoxides,[7] whereas carbon disulfide is another dicoordinated sulfur compound which could function as a reducing agent. Indeed, carbon disulfide is known to react with dialkylsulfilimine, which has also a semipolar S–N linkage, eventually affording dialkyl sulfide, the reduction product, and elemental sulfur.[8]

Meanwhile, Hamana *et al.*[9] reported that some tertiary amine oxides reacted with carbon disulfide affording the amines in very poor yields, however, they did not look into the mechanism.

Thus as a part of our systematic studies on the oxidation of organosulfur compounds, it is interesting to investigate the general scope of the reaction and the mechanism of this reduction, since the reaction is presumed to be classified into a modified A type. The reaction was found to be quite general for most aliphatic, aromatic tertiary amine oxides but not heteroaromatic *N*-oxides. This paper describes the scope of the reaction and the kinetic investigation of the reduction of *N*,*N*-dimethylaniline *N*-oxide (**1**) and substituted derivatives with carbon disulfide and the plausible mechanism based on both kinetic and product analyses.

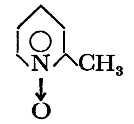
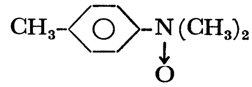
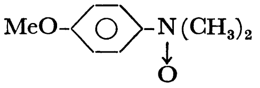
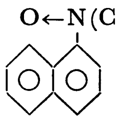
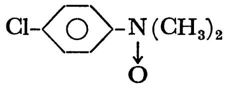
Results and Discussion

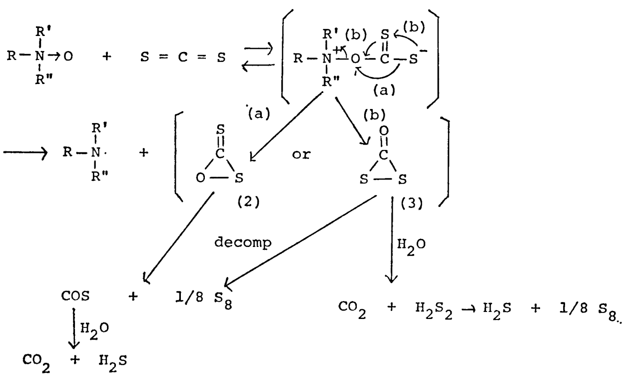
Reaction of Amine Oxides and Carbon Disulfide. The addition of excess carbon disulfide to a stirred solution of a certain amine oxide in chloroform at 0 °C in the presence of anhydrous sodium sulfate[10] afforded the corresponding amine in a good yield. The yield was determined by gas chromatography after confirming by TLC that no amine *N*-oxide remained. As shown in Table 1, picoline *N*-oxide was not reduced at all upon the same treatment with CS_2. All these products were isolated by column chromatography and identified by IR and NMR. A small amount of elemental sulfur (25%) was also obtained when methanol was added to the reaction mixture. The reaction of (**1**) with an equimolar amount of CS_2 under the same conditions for two days also afforded the corresponding amine quantitatively.

When the reaction was carried out under reduced pressure, and gas evolved was analyzed by MS, CO_2 and a trace amount of COS were found. The following mechanism, Scheme, may be conceivable. The reaction is presumed to proceed through the initial nucleophilic attack of the *N*-oxide oxygen to carbon disulfide and subsequent N–O bond cleavage to form the amine and oxathiiranethione (**2**) or dithiiranone (**3**). The intermediate (**2**) is considered to decompose readily to elemental sulfur and COS which would then be hydrolyzed to CO_2 and H_2S. However, in a control experiment, hydrolysis of carbonyl sulfide was found to be very slow in the presence of *N*,*N*-dimethylaniline and water in acetonitrile. Meanwhile, only trace amounts of carbonyl sulfide and hydrogen sulfide were

TABLE 1. REDUCTION OF TERTIARY AMINE OXIDES WITH CARBON DISULFIDE

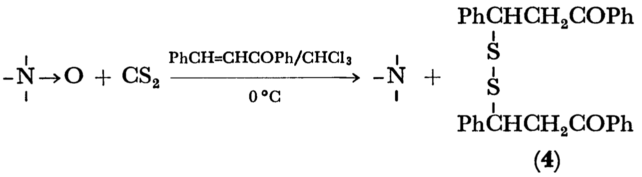
$$\mathrm{RR'R''N{\rightarrow}O \xrightarrow{CS_2} RR'R''N}$$

N-Oxide	Yield of amine/%	N-Oxide	Yield of amine/%
$(n\text{-Bu})_3\mathrm{N{\rightarrow}O}$	69		0
$\underset{\substack{\downarrow\\ \mathrm{O}}}{\mathrm{PhN(CH_3)_2}}$	92		
$\underset{\substack{\downarrow\\ \mathrm{O}}}{\mathrm{PhCH_2N(CH_3)_2}}$	80		73
$\underset{\substack{\downarrow\\ \mathrm{O}}}{\mathrm{PhN(CH_3)CH_2Ph}}$	79		86
	91		77



Scheme

formed in our system. This would suggest that formation of the intermediate (**2**) is quite unlikely. Meanwhile, the intermediate (**3**) might readily be hydrolyzed to CO_2 and H_2S_2 which is then decomposed to elemental sulfur and H_2S. Thus, a trapping experiment of H_2S_2 was carried out. The reduction of trimethylamine N-oxide with carbon disulfide in the presence of benzylidenacetophenone in chloroform at 0 °C afforded the Michael-type adduct of hydrogen disulfide (**4**) in 6% yield together with the usual reduction products. The disulfide (**4**) was identified by com-



$$\mathrm{-\overset{|}{\underset{|}{N}}{\rightarrow}O + CS_2 \xrightarrow[0\,^\circ C]{PhCH{=}CHCOPh/CHCl_3} -\overset{|}{\underset{|}{N}} + PhCHCH_2COPh{-}S{-}S{-}PhCHCH_2COPh}$$

(**4**)

paring its mp, IR, NMR, and elemental analyses with those of the authentic sample.[11] In the reaction of **1** under similar conditions the disulfide was not obtained, however, in the presence of triethylamine as a base the same adduct was obtained in 6% yield. This observation alone may not be enough to suggest the reduction to involve the intermediate (**3**), since there are a few other possibilities for the formation of the adduct.

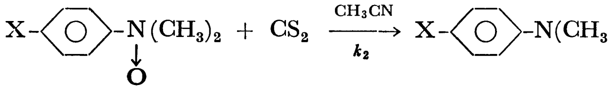
TABLE 2. PSEUDO-FIRST ORDER RATE CONSTANTS OF REDUCTION OF N,N-DIMETHYLANILINE N-OXIDE IN VARIOUS CONCENTRATION OF CARBON DISULFIDE

$[\mathrm{CS_2}]$/M	$10^3\,k/\mathrm{s}^{-1}$
0.166	9.97
0.133	8.17
0.0996	6.46
0.0830	5.23
0.0415	2.67

Hamana *et al.*[9] reported the formation of carbonyl sulfide and elemental sulfur in the reduction of nitrone with carbon disulfide based on their observation of the IR spectra. Meanwhile, the intermediate (**2**) was postulated by Neal *et al.*[12] in the formation of carbonyl sulfide during the oxygenation of carbon disulfide with cytochrome P-450. We have examined the gas evolved from the reaction of N-benzylideneaniline N-oxide with carbon disulfide. Carbonyl sulfide was found to be formed upon mass spectral analysis in agreement with the result of Hamana *et al.* Therefore, the mechanism for the reduction of N-oxide with carbon disulfide should be different from that of the nitrone. In order to clarify the mechanism of the reduction of N-oxides, kinetic experiments have been carried out.

Kinetics. Kinetics of the reaction of N,N-dimethylaniline N-oxide (**1**) with a large excess of carbon disulfide was carried out in acetonitrile at 20 °C by following the UV 250 nm absorption of N,N-dimethylaniline formed in the reaction. The rate of reaction was found to fit with the pseudo first order rate equation. However, it was rather difficult to obtain accurate rate constants in dry acetonitrile since a trace of water affects the rate of reaction. Therefore, acetonitrile containing 2% water was used as the choice solvent. Pseudo-first order rate constants shown in Table 2 were linearly correlated with the concentration of carbon disulfide. From these results, the rate was found to be of first order each with the N-oxide and CS_2 suggesting the mechanism to involve the transition state containing one molecule each of N-oxide

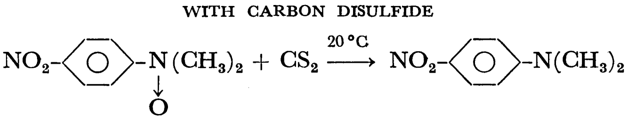
TABLE 3. SECOND ORDER RATE CONSTANTS OF THE REDUCTION OF *p*-SUBSTITUTED *N*,*N*-DIMETHYLANILINE *N*-OXIDES WITH CARBON DISULFIDE



X	Temp/°C	$10^2 k_2$/l mol^{-1} s^{-1}	
H	15	4.28 ± 0.11[a)]	
H	20	6.01 ± 0.05	
H	25	9.23 ± 0.09	$\Delta H^* = 55.6 \pm 2.7$ kJ mo^{-1}
H	30	14.1 ± 0.38	$\Delta S^* = -78.2 \pm 9.2$ J K mol^{-1}
CH_3O	20	6.49 ± 0.02	at 20 °C for mol l^{-1} unit
CH_3	20	5.49 ± 0.01	$\rho = -0.2$ ($\gamma = 0.979$)
Cl	20	4.96 ± 0.01	
NO_2	20	4.14 ± 0.01	

a) Errors shown in the table are standard deviation.

TABLE 4. SOLVENT EFFECT ON THE RATE OF REDUCTION OF *N*,*N*-DIMETHYL-*p*-NITROANILINE *N*-OXIDE WITH CARBON DISULFIDE



Solvent	k_2/l mol^{-1} s^{-1}
DMF	0.372
CH_3CN	0.253
CH_2Cl_2	0.121
$ClCH_2CH_2Cl$	0.0506
$CHCl_3$	$1{\cdot}687 \times 10^{-3}$

and carbon disulfide.

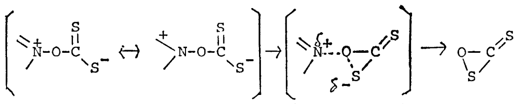
Activation parameters were obtained from Arrhenius plot of the second order rate constants at a temperature range of 15—30 °C as shown in Table 3. Activation parameters ($\Delta H^* = 55.6$ kJ^{-1} mol^{-1}, $\Delta S^* = -78.2$ J K^{-1} mol^{-1} at 20 °C for mol l^{-1} unit) reveal the characteristic feature of the normal bimolecular reaction.

The effect of substituent on the rate of the reactions of para-substituted *N*,*N*-dimethylaniline *N*-oxides and carbon disulfide was examined. The logarithms of these rate constants were nicely correlated with Hammett σ values and a small negative ρ value ($\rho = -0.2$) was obtained. The electron-releasing substituent accelerates the reaction, indicating the importance of the initial nucleophilic attack of the *N*-oxide oxygen to carbon disulfide. However, the ρ-value ($\rho = -0.2$) seems to be too small for the rate-determining initial attack. Perhaps the effect of polar substituent on the initial equilibrium formation of adduct is partially cancelled by the positive ρ-value on the subsequent rate-determining N–O bond cleavage.

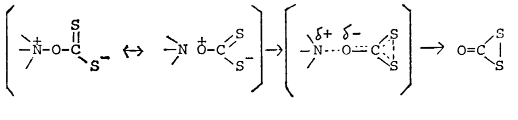
The kinetic experiments in various anhydrous solvents using *N*,*N*-dimethyl-*p*-nitroaniline *N*-oxide were performed by following UV absorption at 390 nm. The results are shown in Table 4. When the reaction was carried out in methanol, the rate of reaction was too low to be measured. The reaction in dry CH_3CN is about six times faster than that in wet CH_3CN (2% H_2O). These results apparently show that hydrogen-bonding of the solvent such as methanol or chloroform to the *N*-oxide oxygen retards the reaction and the solvents, which have strong affinity for water, such as DMF and acetonitrile, accelerate the reaction. The water which hydrates the *N*-oxide is presumably removed partially from the *N*-oxide in DMF or acetonitrile.

Inspection of these experimental results has led us to postulate the mechanism involving the initial equilibrium attack of the *N*-oxide to carbon disulfide, followed by rate-determining N–O bond cleavage to form the corresponding amine and unstable dithiiranone (**3**) which is readily hydrolyzed to give CO_2 and H_2S_2. However, a question still remains, why the reaction of the nitrone with carbon disulfide did afford carbonyl sulfide instead of carbon dioxide.

The reaction of the nitrone is much slower than that of the *N*-oxide. When one compares the structures of the probable intermediates for both reactions, the leaving ability of a Schiff base from the adduct of nitrone is considered to be much poorer than that of the amine in the *N*-oxide, since the delocalization of positive charge on the nitrogen atom of the nitrone adduct would reduce the leaving ability of the Schiff base as compared to that of amine in the *N*-oxide which bears a full positive charge on the nitrogen atom. Therefore, the N–O bond cleavage in the adduct of the nitrone would require an anchimeric assistance of the neighboring thiocarbonate anion. Thus the direct nucleophilic attack of the neighboring thiolate group preferably occurs on the oxygen atom to form (**2**) rather than (**3**) in the reaction of nitrone with carbon disulfide. Whereas, the N–O bond in the adduct of tertiary amine oxide may be sufficiently polarized to allow the S–S bond formation, giving (**3**). Consequently the reduction of the tertiary amine oxide with carbon disulfide would proceed through a modified mechanism A while the reduction of the nitrone with CS_2 presumably proceeds through a modified mechanism B which involves internal nucleophilic attack as described in the introduction section.



(2)



(3)

Experimental

Materials. Most of tertiary amine oxides used were prepared by oxidation of tertiary amines and *p*-substituted *N*,*N*-dimethylanilines[13] with hydrogen peroxide.[14] *N*,*N*-Dimethyl-*p*-nitroaniline *N*-oxide was prepared by oxidation with *m*-CPBA in $CHCl_3$ at room temperature for 1 week and purified by means of silica-gel column chromatography.

Gas Analysis. Carbon disulfide (1 ml) and acetonitrile (2 ml) were condensed in a 20 ml test tube reactor containing, (**1**) (100 mg) at −195 °C (liq. N_2) in a vaccum line. When the temperature was raised slowly to 0 °C, the reaction started evolving gas which was purified three times and subjected to mass spectroscopic analysis. A peak of CO_2 (m/e=44) was observed mainly and COS peak (m/e=60) was only 1% of that of CO_2.

Reaction of N-*Benzylideneaniline* N-*Oxide with Carbon Disulfide.* Carbon disulfide (1 ml) and acetonitrile (2 ml) were condensed in a 20 ml test tube reactor, connected to a vaccum line, containing *N*-benzylideneaniline *N*-oxide (100 mg) at −195 °C (liq. N_2). Then the temperature was raised to room temperature. The solution was kept standing at room temperature for 24 h. Gas evolved was purified three times and its mass spectrum was taken. m/e=44 (40%), 60 (60%).

Hydrolysis of Carbonyl Sulfide. Carbonyl sulfide (10 ml, 1 atom), prepared from NH_4SCN and H_2SO_4 and purified, was condensed in a 20 ml test tube reactor containing *N*,*N*-dimethylaniline (100 mg), H_2O (10 ml) in 2 ml of CH_3CN. The reaction was carried out at room temperature for 3 h. Analysis of the gas showed no CO_2 formation.

The Reaction of N-*Oxides and Carbon Disulfide.* To a stirred solution of an amine oxide (1.0—1.5 mmol) in 3 ml of $CHCl_3$ was added dropwise 3 ml of CS_2 over Na_2SO_4 at 0 °C. After 2 h, the solution was filtered and the filtrate was diluted with 3 ml of CH_3OH. Elemental sulfur was deposited. (Sulfur was confirmed by thin layer chromatography, melting point and liquid chromatography. Amines were identified by thin layer chromatography and gas chromatography). Isolation of amines was carried out with silica gel column chromatography.

Trapping Experiments of H_2S_2. *1)*: To a stirred solution of trimethylamine oxide (0.01 mole) and benzylidenacetophenone (0.01 mole) in 15 ml of $CHCl_3$ was added dropwise over Na_2SO_4 at 0 °C 15 ml of CS_2. White crystals were precipitated in 6% yield. The crystals were identified as bis(1,3-diphenyl-3-oxopropyl) disulfide by comparing its mp, IR, NMR, and elemental analyses with those of the authentic sample.[11]

2): To a stirred solution of (**1**) (1.5 g), chalcone (2.0 g) and triethylamine (2 ml) in 15 ml of $CHCl_3$ was added dropwise over *ca.* 1 g of anhydrous Na_2SO_4 at 0 °C in 15 ml of CS_2. After 2 h reaction, the solution was concentrated. The products were separated by silica-gel column chromatography. The disulfide (**4**) was obtained in 6% yield.

Kinetic Experiments. A solution of carbon disulfide (0.166 M) in CH_3CN–H_2O (2%) (2.5 ml) in a UV cell was incubated at a desired temperature for 30 min. To this was added 12 μl solution of (**1**) (8.23×10^{-5} M) in CH_3CN. UV absorption 250 nm (390 nm for *p*-nitro derivative) of *N*,*N*-dimethylaniline formed was then followed immediately. Pseudo first order rate constants were calculated from the following equation.

$$\ln\frac{A_\infty - A_0}{A_\infty - A_t} = kt \quad A\text{: UV absorption intensity}$$

Solvent Effect. The reaction of *N*,*N*-dimethyl-*p*-nitroaniline *N*-oxides with CS_2 in DMF, CH_2Cl_2, $ClCH_2CH_2Cl$, $CHCl_3$, and dry CH_3CN were followed with UV at 390 nm. All these solvents used were dried and freshly distilled.

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