tion 6 implies that hydrogens are transferred within the molecule.

Using steady state assumptions regarding the transient species Rf* and Rf′, we obtain for the quantum yield.

$$\Phi = \left[\frac{k_3}{k_2 + k_3}\right] \frac{k_5(B)^2 + k_w}{k_4 + k_5(Q) + k_6(B)^2 + k_w}$$

where $k_5(Q)$ refers to the contributions by the various quenchers (Rf, DfH_2 and KI) and where the constant k_w is included to account for the acid-base catalytic action of water alone (*i.e.*, finite rate for $B = 0$). From the variation of α with (B) we calculate that $k_6 = 210\ k_w$ liter^2 mole^{-2}. Using the rate at zero buffer concentration we calculate that $k_w = 135$ sec.$^{-1}$.

If Q is taken to be the photochemical product then the concentration of Q is proportional to $E_0 - E$ since the dye obeys Beer's law. If the quenching term is dominant in the denominator of the above theoretical equation, then $\Phi = \alpha/\beta - E$ in conformity with the observed result (Fig. 2). From the experimental data it is found that the quenching for the photoproducts $k_5 = 1.06 \times 10^{10}$ mole^{-1} sec.$^{-1}$.

When KI is added to the system there is competition between iodide ion and photoproduct as quenchers. It follows from the theoretical expression for Φ that for a given degree of retardation the KI concentration must be higher for higher product concentration, that is, for greater extent of reaction. From our retardation studies with KI we calculate a quenching constant of $1.5 \times 10^6\ k_w$ liter mole^{-1} sec.$^{-1}$ when extrapolated to zero time (*i.e.*, no product present). If every encounter between Rf′ and iodide ion led to quenching, then for KI $k_5 = 6.6 \times 10^9$ liter mole^{-1} sec.$^{-1}$ as shown from diffusional arguments[23] so from this argument $k_w = 4.4 \times 10^3$ sec.$^{-1}$. If it is assumed that all singly excited riboflavin molecules which do not fluoresce are converted to long-lived species, then $k_3/(k_2 + k_3)$ is unity minus the fluorescence yield, namely, 0.26. In pure water $\Phi = 0.006$ so the lifetime of the long-lived species $k_4^{-1} = 1.0$ millisec. or about one hundred thousand times longer than the first excited singlet state.[24] The fact that the photoproduct is a more efficient quencher than KI suggests that the former quenches statically possibly as a semiquinone dimer.

Deviations from the above scheme appear after the reaction has proceeded for some time (points not lying on the straight lines of Fig. 2). This may arise from a dark reaction of leuco deuteroflavin with riboflavin: (7) $DfH_2 + Rf \rightleftarrows Df + RfH_2$ followed by the photolysis of deuteroflavin leading, we assume, to lumichrome Lc plus fission products from the side chain:

(8) $Dt \xrightarrow{h\nu} Lc +$ fragments.

When oxygen is admitted, leuco deuteroflavin is oxidized: (9) $DfH_2 + O_2 \rightarrow Df + H_2O_2$. In a similar way RfH_2 is oxidized: (10) $RfH_2 + O_2 \rightarrow Rf + H_2O_2$. These reactions proceed *via* a free radical since the polymerization of vinyl monomers are initiated under these conditions.[15]

Extraction of the faded and then oxidized solution yields lumichrome formed in step 8. Treatment with alkali yields a second chloroform-soluble compound, lumiflavin Lf: (11) $Df + OH^- \rightarrow Lf +$ fragments. The contribution of this reaction is unimportant unless the *p*H is high (about 9) and/or the intensity of light is low.

The rapid anaerobic fading of the reoxidized solution must be ascribed to a new compound Df since the wave length dependence is different from that of the fading of riboflavin.

The leucoflavin can reduce the substrate S (DPIP): (12) $DfH_2 + S \rightarrow Df + SH_2$. Unlike true photosensitizers, however, the sensitizer riboflavin is destroyed in the over-all reaction.

The fact that H_2O_2 has been detected[10] in the faded solution before oxygen is admitted has been taken[25] to be the proof for the water-splitting hypothesis. On the other hand, H_2O_2 could be produced in the reactions leading to lumichrome (step 8) or lumiflavin (step 11) without the envolvement of water.

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Tertiary Amine Oxide Rearrangements. I. Mechanism

BY J. CYMERMAN CRAIG,[1] F. P. DWYER, A. N. GLAZER AND E. C. HORNING

RECEIVED AUGUST 5, 1960

It is proposed that the metal-complex catalyzed rearrangement of trimethylamine N-oxide occurs in two 1-electron steps involving the formation of an intermediate possessing an unpaired electron on a methylene carbon atom which is then attacked by an OH radical to yield the methylolamine known to give dimethylamine and formaldehyde. The N-oxide is bound to the metal through its oxygen, and a hydroxo or aquo group occupies the adjacent (*cis*) coördination position. The necessary ability of the metal complex to exist in a higher oxidation state and to provide the requisite binding sites is satisfied by a number of iron(III), ruthenium(III) and (IV), osmium(III) and (IV) and vanadium(IV) compounds.

Introduction

Although *tert*-amine oxides have been detected in both animals and plants,[2] the smallness of the amounts of these compounds present in biological systems suggests that they are not simply the ter-

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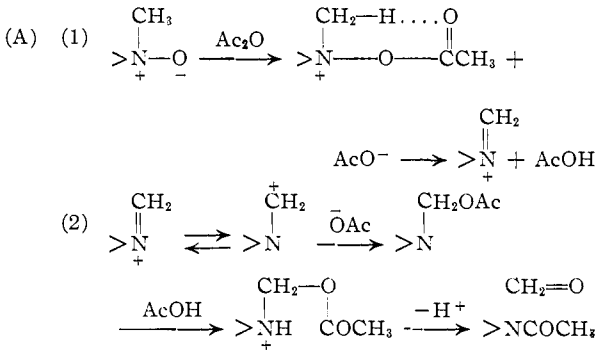
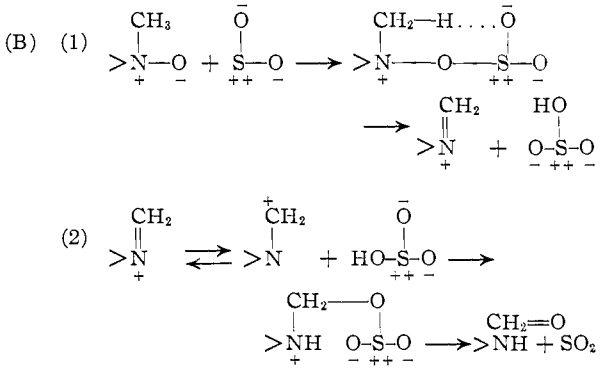
(2) (a) C. C. J. Culvenor, *Rev. Pure Appl. Chem.*, **3**, 84 (1953); (b) M. S. Fish, N. M. Johnson and E. C. Horning, THIS JOURNAL, **77**, 5892 (1955).

minal products of amine oxidation but instead have a function as intermediates in some biochemical reaction sequence.

The Polonovski reaction,[3] whereby *tert*-amine oxides containing at least one N-methyl group are converted by acetic anhydride into *sec*-amines and formaldehyde, suggested that the biological step might be one of oxidative demethylation mediated in the cellular environment by a catalyst capable of lowering the activation energy of the process to a level commensurate with that existing in natural systems.[4]

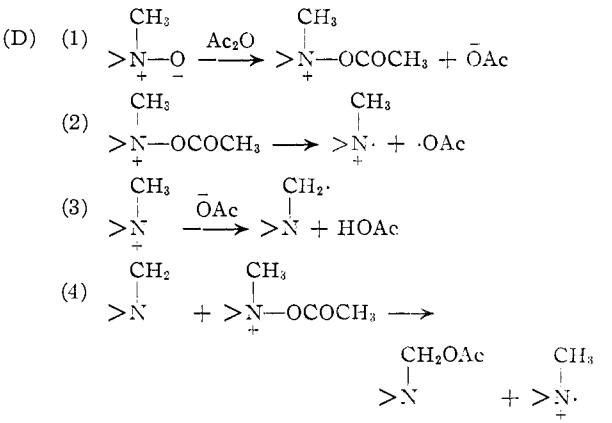
A further instance of such a reaction has been reported by Tsuyuki and co-workers[5] in the transformation of octamethylpyrophosphoramide ("Schradan") to an N-oxide readily hydrolyzed to the heptamethyl compound and formaldehyde, and it was pointed out[2b] that the intermediate in this reaction was probably the N-methylolamine or the equivalent anhydronium base.[6]





A similar reaction is to be found in the ready formation[7] from trimethylamine oxide and sulfur dioxide of a compound $Me_3NO{\cdot}SO_2$ shown to undergo facile decomposition in aqueous solution at 10° into dimethylamine, formaldehyde and sulfur dioxide.

Both the reaction using acetic anhydride and that employing sulfur dioxide may be formulated as closely-related plausible ionic mechanisms A and B. However, recently it has been shown[3b] that the rearrangement of 2-methylpyridine N-oxide with acetic anhydride (which proceeds with a strongly exothermic phase) involves free radical intermediates. (See ref. 3b for this mechanism which we will designate as (C).) Moreover, the rearrangement of triethylamine N-oxide has been found[3b] to give acetaldehyde and N,N-diethylacetamide, and that of diethylaniline N-oxide in boiling benzene was effective in causing the polymerization of styrene.[3b] The Polonovski reaction, also characterized[3a] by its exothermic nature, must therefore proceed by an analogous free-radical sequence, as shown in (D)



It is evident that 2-methylpyridine N-oxide is the vinylog of the aliphatic system in (D) and closely similar behavior is to be expected. In the case of the sulfur dioxide reaction,[7] the available evidence does not permit a decision between an ionic and a free radical mechanism. The stability of the intermediate $R_3NO{\cdot}SO_2$ to solvents other than water suggests that an ionic mechanism may operate, however.

Horning and his co-workers found[8a] that the rearrangement of N,N-dimethyltryptamine oxide, a compound isolated from natural sources, took place in aqueous solution at *p*H 2–7 in the presence of ferric ion under relatively mild conditions to yield N-methyltryptamine and formaldehyde and established that similar rearrangements occurred with bufotenine oxide, hordenine oxide, N,N-dimethyltyrosine oxide[8b–d] and N,N-dimethylglycine oxide.[8e] These authors showed the reaction to require Fe^{3+}, no rearrangement taking place with other metal ions. In the case of dimethylglycine oxide[8e] the reaction was found to proceed in aqueous solution using Fe^{3+} and either oxalic acid (*p*H 1 to 5) or tartaric acid (*p*H 2 to 9) as complexing agent.

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TABLE I

EFFECT OF OXALIC ACID AND Fe^{3+} ON THE DEMETHYLATION OF TRIMETHYLAMINE N-OXIDE[a]

Ratio oxalic acid:Fe	Metal	Chelating agent	pH	Temp., °C.	Yield, % After reduction with Mg + HCl	Yield, % Before reduction with Mg + HCl
1.25:1	$Fe(NO_3)_3 \cdot 9H_2O$, 0.003 mole	Oxalic acid, 0.00375 mole	0.8	100	33	
				90	39	38, 43
				80		12
				75	0	0
				25	0	0
10:1	$Fe(NO_3)_3 \cdot 9H_2O$, 0.003 mole	Oxalic acid, 0.030 mole	0.4	100	19, 17	
3:1		$K_3[Fe(C_2O_4)_3]^{3-}$, 0.003 mole	3.6	90	16	16
				80	0	0
				70	0	0
6:1		$K_3[Fe(C_2O_4)_3]^{3-}$, 0.003 mole +	3.8	90	0	
		$(COONH_4)_2 \cdot H_2O$, 0.01 mole		80	0	0
	$Fe(NO_3)_3 \cdot 9H_2O$, 0.003 mole		1.6	100	37	(160 min.)
					8	
				90	0	
				80	0	(75 min.)
			6.0[b]	100	0	0

[a] All solutions contained 0.001 mole of amine oxide and were kept for 40 min. at the temperature specified, unless otherwise mentioned. [b] Amine oxide alone.

The successive steps E, F and G occurred

(E) $COOHCH_2NMe_2O \longrightarrow [COOHCH_2NMe(CH_2OH)] \longrightarrow COOHCH_2NHMe + CH_2O$

(F) $\bar{C}OOCH_2\overset{+}{N}Me_2(OH) \longrightarrow CO_2 + [CH_2{=}\overset{+}{N}Me_2] \rightleftharpoons [\overset{+}{C}H_2\text{–}NMe_2] + \bar{O}H \longrightarrow [OHCH_2NMe_2] \longrightarrow CH_2O + HNMe_2$

(G) $COOH \cdot CH_2NMe_2O + CH_2O \longrightarrow COOH \cdot CH_2NMe_2 + H \cdot COOH$

The mechanism of the ferric ion-induced demethylation which occurs in aqueous solution is unknown; in order to study the function of the metal ion and of the chelating agent in the demethylation reaction, without the complication of simultaneous decarboxylation, trimethylamine oxide was selected as the test substance. The expected reactions were H and I

(H) $Me_3NO \longrightarrow Me_2NH + CH_2O$

(I) $Me_3NO + CH_2O \longrightarrow Me_3N + H \cdot COOH$

Reaction I results from the reduction of some N-oxide by formaldehyde to give the *tert*-amine and formic acid.

The reaction may be regarded essentially as an internal 2-electron oxidation of the methyl group, at the expense of the nitrogen, and the role of the metal ion catalyst may be in mediating the transfer of electrons to the $\overset{+}{N} — \bar{O}$ portion of the molecule, possibly by a transitory oxidation of the metal chelate to a suitable higher oxidation state. The complexing agents employed[3] indicated the formation of a metal chelate; the oxidation of the methyl group could then be effected either without direct binding of the organic moiety or (more probably) with at least a single-point attachment of the N-oxide to the metal, necessitating the existence of at least one vacant or labile coördination site in the metal chelate. These various possibilities have now been examined using a variety of metal complexes and complexing agents.

Experimental

All reagents were of analytical reagent grade. Trimethylamine oxide was used as the colorless dihydrate of m.p. 96°. Reaction conditions similar to those of Sweeley and Horning[5e] were employed.

Determination of Formaldehyde.—Formaldehyde was determined by direct isolation from the reaction mixture as the 2,4-dinitrophenylhydrazone; the reagent was prepared by dissolving 2 g. of 2,4-dinitrophenylhydrazine in 500 ml. of 2 *N* HCl. The estimation procedure for total formaldehyde and formic acid was: following the heating period, the reaction mixture was placed in an ice-bath and chilled to 0 to 5°. It was then acidified by the addition of 5 ml. of 5 *N* HCl, and then an excess of magnesium shavings. After a reduction period of 25 min. at 0 to 5°, the solution was decanted, or if necessary filtered, from any excess magnesium and 50 ml. of the 2,4-dinitrophenylhydrazine reagent was added. The solution now was shaken vigorously for 2 min. and the 2,4-dinitrophenylhydrazone was filtered, washed with cold water and dried overnight at 70 to 80°. Duplicate determinations gave results reproducible to within 1%. All m.p.'s were checked and mixed m.p.'s taken wherever possible.

In blank experiments it was found that this procedure gave a 97 to 99% recovery of formaldehyde and a 95% recovery of formic acid. In the presence of vanadium salts and with ruthenium and osmium complexes, formic acid was not reduced to formaldehyde under these conditions. A large amount of formaldehyde present was also lost, since in these cases the yield of the dinitrophenylhydrazone was very much decreased after the reduction. It seems probable that the reduction can in some circumstances proceed to methanol. For this reason the efficiency of these catalytic agents is likely to be much higher than the yields of the derivative would indicate.

Catalysis by Iron(III) Chelates. A. Oxalate System.—The reaction mixture containing 0.001 mole of trimethylamine oxide, 0.003 mole of iron(III) nitrate 9-hydrate and 0.00375 mole of oxalic acid in a total volume of 15 ml. (*p*H 0.8) was kept at the desired temperature for 40 min. A few experiments involving longer times indicated that no further increase in formaldehyde formation took place. Other systems examined under the same conditions contained 0.001 mole N-oxide, (a) alone, (b) with 0.003 mole Fe(III) nitrate 9-hydrate and various ratios of oxalic acid (nil to 0.03 mole) or (c) with 0.003 mole of potassium trisoxalatoferrate(III), with and without the presence of 0.01 mole of added oxalate ion. The results are presented in Table I.

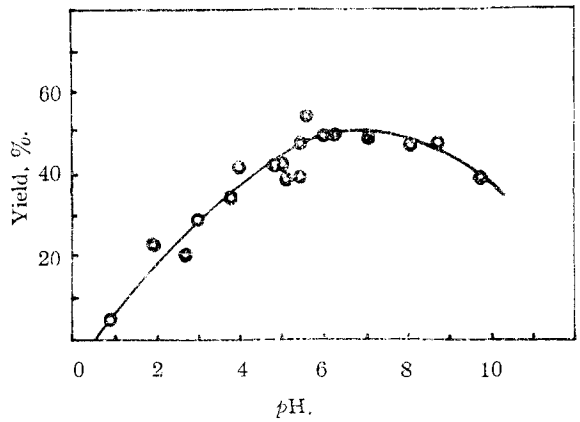

Fig. 1.—Effect of *p*H on combined yield of formaldehyde and formic acid in the demethylation of trimethylamine oxide at 80° for 40 min. with iron(III)–tartrate complex.

B. Citric Acid.—Solutions containing 0.001 mole of trimethylamine oxide were examined (a) with 0.003 mole of Fe^{3+} and various ratios of citric acid (0.003 to 0.03 mole) at *p*H 0.6 to 8.6 and (b) with 0.003 mole of the preformed complex iron(III) ammonium citrate (*p*H 6.6). All solutions were kept at 80° for 40 min. The results are shown in Table II.

TABLE II

EFFECT OF CITRIC ACID ON THE CATALYTIC ACTIVITY OF Fe^{3+} IN THE DEMETHYLATION OF TRIMETHYLAMINE N-OXIDE[a]

Chelating agent	Ratio of citric acid:Fe	*p*H	Yield (%) (CH_2O + HCOOH)
Citric acid (0.03 mole)	10:1	0.6	0
Citric acid (.03 mole)	10:1	5.1	0
Citric acid (.03 mole)	10:1	8.6	0
Citric acid (.015 mole)	5:1	4.4	0
Citric acid (.006 mole)	2:1	0.8	21
Citric acid (.003 mole)	1:1	0.8	23
Ferric ammonium citrate[b] (0.003 mole)	1:1	6.6	0

[a] All solutions contained 0.001 mole of trimethylamine oxide and 0.003 mole of ferric nitrate 9-hydrate and were kept at 80° for 40 min. [b] Preformed complex.

C. Tartaric Acid.—A solution containing 0.001 mole of trimethylamine oxide, 0.003 mole of iron(III) nitrate 9-hydrate and 0.03 mole L(+)-tartaric acid was adjusted to the desired *p*H with the use of saturated sodium carbonate solution. The final volume varied between 25 and 40 ml. The solution was kept at 80° for 40 min., and the experiments were run over the *p*H range 0.5 to 10. The results are presented in Fig. 1. When the formaldehyde was determined in the optimum *p*H range (prior to reduction) at *p*H 6.3, an 18% yield was obtained against a 48% yield after reduction, indicating that reaction I took place to an appreciable extent. No rearrangement occurred at 25°.

On addition of the trimethylamine oxide to the iron(III) tartrate system, color changes dependent on *p*H occurred at room temperature, as:

*p*H 0.5 to 2.5: no change observed.

*p*H 3.0 to 5.5: dark brown color after 1 to 2 min., faded slightly on standing.

*p*H 5.7 to 6.2: very intense immediate dark brown color, fading slowly to that described for the 3.0 to 5.5 range.

*p*H 6.6 to 9.8: no color on mixing; a less intense dark brown color developed on standing.

D. Succinic Acid.—At *p*H 1.2, 0.03 mole of succinic acid in a reaction mixture containing 0.001 mole trimethylamine oxide and 0.003 mole of Fe^{3+} gave only a trace of formaldehyde. Expts. at higher *p*H values could not be carried out owing to the precipitation of iron(III) hydroxide.

E. α-Hydroxy Acids. (a) Malic Acid.—A series of experiments over the *p*H range 0.5 to 8.5 was carried out using a reaction mixture containing 0.001 mole of trimethylamine oxide, 0.003 mole of Fe^{3+} and 0.03 mole of (±)-malic acid. The results are shown in Fig. 2.

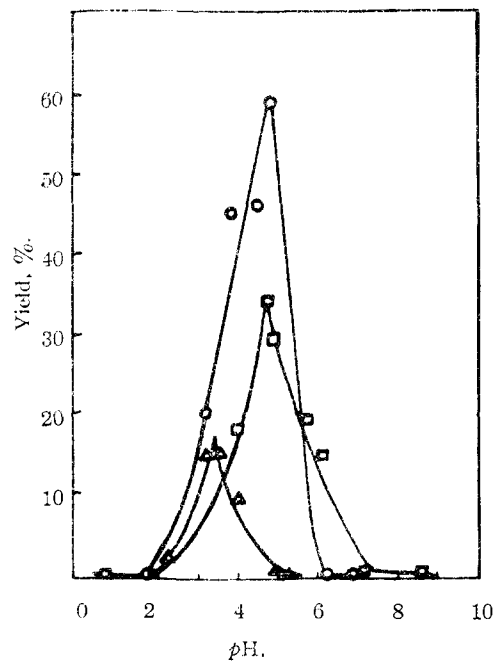

Fig. 2.—Effect of *p*H on combined yield of formaldehyde and formic acid in the demethylation of trimethylamine oxide at 80° for 40 min. with: iron(III)–aspartate complex, O; iron(III)–malate complex, □; iron(III)–glycinate complex, △.

(b) Lactic Acid.—Lactic acid was tested under the optimum tartrate conditions, *i.e.*, in a reaction mixture containing 0.001 mole of trimethylamine oxide, 0.003 mole of Fe^{3+} and 0.03 mole of lactic acid, *p*H 6.3 [sodium-(±)-lactate was used]. A yield of 6% was obtained as compared with 48% for tartaric acid under the same conditions.

(c) Glycolic Acid.—This acid could not be adequately tested as under the optimum tartaric acid conditions glycolic acid was unable to keep the iron in solution. On heating, most of the metal precipitated as the hydroxide.

F. α-Amino Acids. (a) Aspartic Acid.—The (±)-aspartate system was examined over the *p*H range 3 to 7. As shown in Fig. 2, the results were closely analogous to those observed with malic acid. No experiments could be performed below *p*H 3, owing to the reduced chelating capacity of aspartic acid in strongly acid solutions. Above *p*H 6.5 some precipitation of iron(III) hydroxide was observed on heating. An expt. using L-aspartic acid was performed under the optimum (±)-aspartic acid conditions,

i.e., *p*H 4.8. The yield was 58% as compared with 59% for the (±)-acid under the same conditions.

(b) **Glycine.**—The Fe^{3+}–glycine system was examined over the *p*H range 2 to 6, using a reaction mixture with 0.001 mole of trimethylamine oxide and 0.003 mole of glycine. The results obtained were similar to those described above for aspartic and malic acids (Fig. 2).

(c) **Glutamic Acid.**—Experiments involving 0.015 mole of L(+)-glutamic acid, 0.001 mole of trimethylamine oxide and 0.003 mole of Fe^{3+} yielded negative results at *p*H 4.1 and 7.7. The colors given by the Fe^{3+}–glutamate complex were much paler than those from the corresponding aspartate complex at each of the *p*H values examined. Below *p*H 4.1 the glutamic acid precipitated to a large extent, while at *p*H 7.7 precipitation of iron(III) hydroxide was observed.

(d) **Asparagine.**—No reaction occurred in the presence of L-asparagine (0.03 mole) at *p*H 3.2.

Other Chelating Agents.—No reaction occurred after 40 min. at 80° and at various *p*H values with the amine oxide (0.001 mole) and 0.003 mole of Fe^{3+} in the presence of salicylic acid (0.03 mole), 8-hydroxyquinoline (0.015 mole) or ethylenediaminetetraacetic acid (0.03 mole).

Catalysis by Complexes of Cu(II) and Other Metals.—The experiments summarized in Table III were carried out at 80° for 40 min. using Cu^{2+} (0.003 mole) and chelating acid (0.03 mole). Using the optimum conditions for the Fe(III)–tartrate system, no rearrangement could be detected with Zn^{2+}, Mn^{2+}, Ni^{2+} and Al^{3+} ions.

TABLE III

EFFECT OF CHELATING ACID ON THE CATALYTIC ACTIVITY OF Cu^{2+} IN THE DEMETHYLATION OF TRIMETHYLAMINE OXIDE[a]

Chelating agent	*p*H	Yield (HCHO + HCOOH), %
L(+)-Tartrate	6.0	3
(±)-Malate	4.7	2
Oxalate	1.2	Trace
(±)-Aspartate	5.0	3

[a] All solutions contained 0.001 mole of trimethylamine oxide, 0.003 mole of Cu^{2+} and 0.03 mole of chelating acid and were kept at 80° for 40 min.

Catalysis by Complexes of Transitional Metals.—The complexes were used in 0.2% aqueous solution adjusted to the appropriate *p*H value and containing 50 mg. of the amine oxide. No catalytic effort was observed with: (1) aquochlorotetramminecobalt(III) chloride, (2) carbonatobis-(ethylediamine)-cobalt(III)chloride, (3) *cis* and *trans*-dichlorobis-(ethylenediamine)-cobalt(III) chloride, (4) potassium tris-(oxalato)-chromate(III), (5) potassium tris-(oxalato)-cobaltate(III), (6) potassium dioltetra-(oxalato)-cobaltate(III) [Durant's salt] or (7) acetylacetone-bis-(1,-10-phenanthroline)-ruthenium(II) chloride.

The approximate yields (*vide supra*) with other complexes are summarized in Table IV.

Results

The results obtained using the oxalate system (Table I) show that the rearrangement occurred at 80 to 100° with an oxalic acid:Fe ratio of 1.25:1. No reaction took place below 80°. Iron(III) ion showed a small catalytic effect at 100°, while no decomposition occurred with the amine oxide alone even at this temperature. When the oxalic acid:Fe ratio was 10:1, the reaction was largely suppressed, as it was also when the tris-oxalato ferrate(III) complex was employed (ratio 3:1). The need for one or more available binding sites on the complex was further indicated by the effect of adding oxalate ion to the tris-oxalato ferrate-(III) system; the increase in the oxalate:Fe ratio to 6:1 resulted in *complete* suppression of rearrangement.

The same conclusions could be reached from the citrate system (Table II). Here again the highest activity was obtained using a citric acid:Fe ratio of 1:1 at *p*H 0.8; use of a 2:1 ratio reduced the reaction, while no rearrangement occurred with 5:1 or 10:1 ratios. The inactivity of the preformed iron(III) ammonium citrate complex at *p*H 6.6 suggests that, as in the case of oxalic acid, the binding of Fe(III) by the chelating agent is so strong that under practical conditions the equilibrium

$$\mathrm{Fe(III)} + n\mathrm{AH}^+ \rightleftharpoons \mathrm{Fe(III)A}_n + n\mathrm{H}^+$$

lies far to the right except at low *p*H values.

Results obtained with the tartaric acid system (Fig. 1) showed that substantial rearrangement occurred in the *p*H range 5 to 9, with a fall in the combined formaldehyde + formic acid yield on either side of this range. The color changes observed on addition of the amine oxide to the Fe-(III)–tartrato complex suggest the addition of hydroxo- or aquo groups to Fe(III) complexes, and again indicate binding of the N-oxide to the metal complex. The same color changes occurred with malic acid, being most intense at the optimum *p*H for the reaction.

The α-hydroxy- and α-amino-dicarboxylic acids gave interesting results. Both aspartic and malic acids had marked *p*H optima for the rearrangement at about *p*H 5 (Fig. 2). Glycine showed a reduced efficiency, with an optimum at a somewhat lower *p*H.

The lack of reaction with asparagine and glycine under the optimum conditions for aspartic acid may indicate that additional binding by the second carboxyl group was beneficial; the inactivity of glutamic acid may therefore be ascribed to the stereochemistry of the latter acid. For bivalent cations, the stability of the 1:2-glutamic acid complex is appreciably less than that of the 1:2-aspartic acid one and is comparable with the value for glycine.[9] Thus glutamic acid shows a markedly lower affinity for Co(II) at all *p*H values and does not bind the metal significantly below *p*H 7, compared with *p*H 5.5 for aspartic acid.[10]

The results of the experiments employing 8-hydroxyquinoline, ethylenediaminetetraacetic acid and salicylic acid confirmed that the mere retention of iron in solution was insufficient to produce the rearrangement; of other common metal ions examined, only Cu(II) gave slight reaction (Table III) in agreement with the findings[8d] that this metal was slightly effective for the rearrangement of bufotenine oxide.

The necessity for free binding sites on the complex having been established, the negative results obtained with the complexes of the transitional metals listed above indicated further that the mere presence of a metal complex possessing two free or available chelating positions was not in itself

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(10) J. Z. Hearon, D. Burk and A. L. Schade, *J. Natl. Cancer Inst.*, **9**, 337 (1949).

sufficient to induce catalysis of the rearrangement. The positive results summarized in Table IV pointed to the need for the metal complex, in addition to providing the requisite two binding sites, to be able to exist in a suitable higher oxidation state. These findings are discussed below.

TABLE IV

EFFECT OF COMPLEXES OF TRANSITIONAL METALS IN CATALYZING THE DEMETHYLATION OF TRIMETHYLAMINE N-OXIDE

Complex[f]	*p*H	Yield (%) (CH_2O + HCOOH)	Ref.
$K_2Ru(III)Cl_5 \cdot H_2O$	2	20[a]	12
$K_2Ru(III)Cl_5 \cdot H_2O$	1	30[b]	12
$K_2Ru(IV)Cl_5OH$	1	30	12
$K_3Ru(C_2O_4)_3$	3	45[c]	13
$KRuCl_4phen$	3	40[d]	11
$[Rubipy_2Cl \cdot H_2O]Cl$	5	10	11
$(NH_4)_2OsBr_6$	2–4	Trace	14
$[Osphen_2Br_2]$	4	15	11
$[RhCl_3 \cdot 3H_2O]$	2	Trace	16
K_3IrCl_6	2	Trace	15
$VOCl_2$	1.5	50[e]	..

[a] Black ppt. of RuO_2 deposited. [b] Color changed from red to red-brown due to formation of K_2RuCl_5OH. [c] Color changed from green to red brown ($K_2Ru(C_2O_4)_2(H_2O)_2$) as a result of oxidation and hydrolysis. [d] Color changed from yellow to dark brown as a result of hydrolysis and oxidation. [e] Color changed from blue to brown-green, slight brown ppt. (V_2O_5). [f] Phen = 1,10-phenanthroline, bipy = 2,2′-bipyridine.

Discussion

In common with other amine oxides, trimethylamine oxide is an oxidizing agent. The oxidizing action in the cold is slow and irreversible. In hot acid solution (*p*H 1), it rapidly oxidized iron(II) to iron(III) ion,[17] ($E_0 = -0.772$ v.) with precipitation of iron(III) hydroxide and very slowly oxidized bromide ion to bromine[17] ($E_0 = -1.065$ v.) and tris-(2,2′-bipyridine)-iron(II) ion[18] ($E_0 = -1.096$ v.), some decomposition of the latter substance occurring simultaneously in the hot acid solution. It can be inferred that the potential of the reaction $Me_3NO + 2H^+ = CH_3N + H_2O + 2e$ is of the order of -1.1 v. Formaldehyde was found only in the presence of iron(II) ion. Under the standard experimental conditions used with the iron(III) complexes (0.001 mole), traces only could be detected, but at 100° in the presence of high concentrations of iron(II) ion (0.1 mole), large amounts of iron(III) hydroxide separated and substantial rearrangement took place. It is not clear whether the reaction was catalyzed by iron(II) or iron(III) ions since the latter had some activity (Table I).

Consideration of the complexes with catalytic activity (Table IV) shows that all are derived from metals that can exist in a higher oxidation state. This applies also to the iron(III) and Cu(II) complexes to be discussed later. However, mere participation in an oxidation-reduction reaction does not suffice to promote rearrangement. This is illustrated by the chemically stable red substance acetylacetone bis-(1,10-phenanthroline)-ruthenium(II) chloride[11] which is oxidizable to the blue Ru(III) complex ($E_0 = -0.65$ v.), and thence to the brown Ru(IV) complex ($E_0 = -1.3$ v.). Though the blue complex was produced in the reaction, no rearrangement occurred. The vanadyl ion exists in aqueous solution as various hydrated species such as $[VO(H_2O)_5]^{2+}$ and $[V(OH)_2(H_2O)_4]^{2+}$ both of which can attach the N-oxide (probably rather weakly) by the replacement of a molecule of water. The value of the potential[17] of the reaction $VO^+aq. + 2H_2O = V(OH)_4^+aq. + 2H^+ + e^-$, ($E_0 = -1.00$ v.) also seems especially favorable for the rearrangement, because it is evident that two competing reactions are always involved: one leading merely to oxidation of the catalyst and the other of a methyl group of the N-oxide.

Although the potential for the oxidation of chlorobipyridineterpyridine-ruthenium(II) chloride[11] ($E_0 = -0.93$ v.) is close to the V(IV)–V(V) potential, and a point of attachment for the N-oxide can be provided by dissociation of a chlorine atom, the substance had no catalytic effect. This suggests the necessity of an aquo or hydroxy group coordinated to the metal adjacent to the bonding site of the N-oxide. This can be provided with all of the complexes in Table (IV) by dissociation–aquation reactions. There appears to be no functional value in a hydroxy or aquo group in the *trans* position, and in any event other chemical evidence[11] suggests that chloroaquobis-(2,2′-bipyridine)-ruthenium(II) chloride and dibromobis-(1,10 - phenanthroline)-osmium(II) have the *cis* structure. A number of *cis* and *trans* isomeric forms of ruthenium complexes have been described[19] and some proportion at least of the *cis* form can be expected to exist in the solutions of the aquated $[RuCl_5OH]^{2-}$, $[RuCl_5H_2O]^{2-}$ and $[RuphenCl_4]^-$ ions. The tris-oxalatoruthenate(III) ion, though spin-paired, cannot be resolved and yields a precipitate of calcium oxalate if boiled with calcium salt solutions.[13] Dissociation of the oxalate group would yield initially the *cis* diaquo complex which may rearrange.

With the ruthenium and osmium complexes, the higher oxidation states of +4 and +6 are available especially after halogen atoms have been replaced by aquo and hydroxy groups.

Aquation of trichlorotriaquorhodium(III) and hexachloroiridate(III) ions proceeds rather slowly as evidenced by the rate of precipitation of silver halide. The potential[17] of the system Rh^{3+}

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(14) F. P. Dwyer and J. W. Hogarth, *Inorg. Syntheses*, **5**, 204, (1957).

(15) M. Delepine, *Bull. soc. chim.*, **9**, 771 (1911).

(16) J. Meyer and M. Kawezyk, *Z. anorg. Chem.*, **228**, 297 (1936).

(17) W. M. Latimer, "The Oxidation States of the Elements and their Potentials in Aqueous Solutions," Prentice–Hall Book Co., New York, N. Y., 1952, pp. 340–345.

(18) W. W. Brandt, F. P. Dwyer and E. C. Gyarfas, *Chem. Revs.*, **54**, 959 (1954).

(19) N. V. Sidgwick, "The Chemical Elements and their Compounds," Vol. II, Clarendon Press, Oxford, 1950, pp. 1470, 1471.

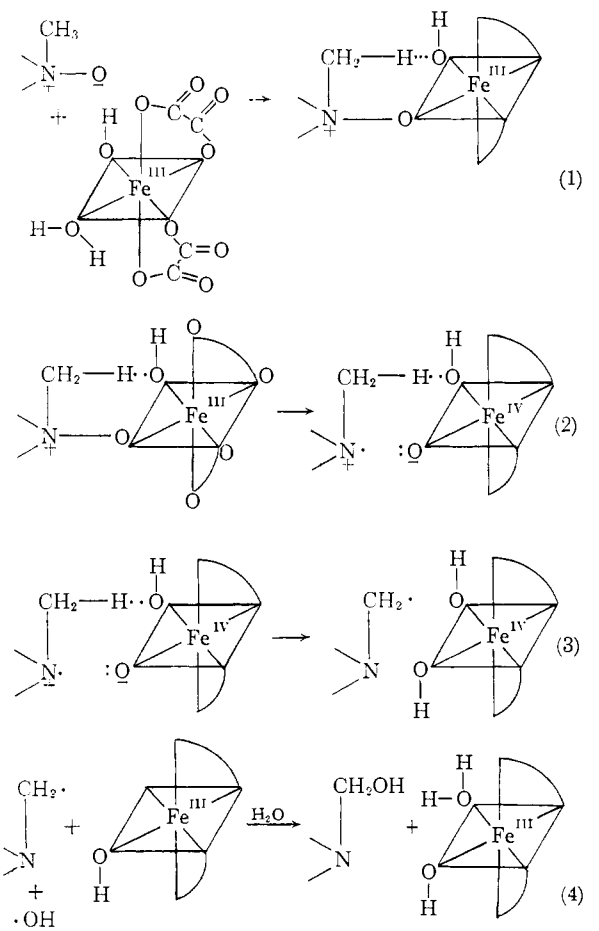
$+ H_2O = RhO^+ + 2H^+$, $E_0 = 1.42$ v. (absence of halide ion) suggests that the N-oxide would be ineffective as an oxidizing agent. On the other hand a lower value ($E_0 = -1.2$ v.) has been adduced[17] for the system $[RhCl_3]^{3-} = [RhCl_6]^{2-} + e^-$. It is possible that the potential of some of the chloro-aquo or hydroxy-chloro-aquo species may be more positive. The potential of the $[IrCl_6]^{3-}$ $[IrCl_6]^{2-}$ system[20] is -1.017 v.

Catalysis by Iron(III) and Copper(II) Complexes.—Coördinately saturated iron(III) complexes such as the tris-(oxalato)-ferrate(III) ion in the presence of excess oxalate ion and the ethylenediaminotetraacetatoferrate(III) ion do not catalyze the rearrangement. Slow rates of equilibration are characteristic of many iron(III) complexes, and mixtures of iron(III) ion and a chelating anion, *e.g.*, oxalate ion, even under favorable *p*H conditions, are transformed to the tris complex fairly slowly. When the iron(III) salt is partly hydrolyzed (above *p*H 3), depolymerization of the complex hydroxo entity markedly reduces the rate of formation of other complexes. For these reasons, it is probable that during some of the rearrangement experiments a mixture of complex species was present.

Since the chelating agents attach in the anion form it is evident that chelation is favored by a relatively high *p*H value, but on the other hand competition by hydroxyl ions for the coördination positions about the metal may then become serious. Investigations of the stability of iron(III) complexes with α-amino acids has shown that at the highest practicable *p*H value (4.7), stable 1:1 complexes are formed.[21] In less acid solution separation of iron(III) hydroxide obscures the possible existence of higher complexes. Water and/or hydroxyl groups presumably occupy other coördination positions in the 1:1 complexes. The iron(III) oxygen complexes usually have two or three molecules of the ligand attached, *e.g.*, $[Fe(C_2O_4)_3]^{3-}$ and $[Fe(C_2O_4)_2(OH_2)_2]^-$. The structures of the complexes and mode of attachment of tartrato and citrato groups is not known with any certainty and hence the high stability in alkaline solution is not understood. The tartrato complex acts as a catalyst up to *p*H 10. Relatively, the oxalato complex would seem to be a better catalyst than the citrato at the same *p*H value. This may well be because the oxalato complex is weaker[22] (log $K = 9.4$ compared with 11.85), *i.e.*, a higher proportion of the bis complex, with appropriate sites, is present. The evidence for the existence of high oxidation states of iron has been summarized by Kleinberg,[23] and in recent articles on the mode of action of catalase,[24] peroxidase[24] and other catalytically active haemoproteins.[25] The ion dichlorobis- [*o*-phenylenebis- (dimethylarsine)]- iron[26] undoubtedly contains tetravalent iron. None of the iron complexes used in this work have ever been oxidized to a higher oxidation state, possibly because no serious attempt has been made. On general principles, oxidation of the bis-(chelate)-diaquo species should be favored since not only is the detachment of electrons facilitated by the negative charge but dissociation of a proton to form a hydroxyl group would tend to stabilize the oxidized form. The catalytic mode of action envisaged requires only a transitory existence of the oxidized form, which might well be more of the nature of a highly polarized state of the iron atom than a discrete oxidation state. The photoactivated state of tris-(2,2′-bipyridine)-iron(II) salts in which negative charge is transferred from metal to ligand constitutes this kind of internal oxidation–reduction system.[27]

The situation regarding the oxidation of Cu(II) complexes is not unlike Fe(III). A complex Cu(III) fluoride[28] is known and also complex periodates,[29] but other Cu(II) complexes have not been oxidized.

Mechanism of Rearrangement.—Trimethylamine N-oxide is a weak base, ($pK_a = 4.6$), existing in acid solution as the cation $[(CH_3)_3$-



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NOH]$^+$. Coördination to a metal must occur, as with arsine oxides,[30] through the oxygen atom. Assuming the usual non-linearity of the oxygen bonds it can be seen readily from models that one hydrogen atom of a methyl group approaches the oxygen atom of an adjacent coördinated OH group or H_2O molecule. When the N–O–M bond angle is about 120°, the atoms are close enough to form a six-membered ring through a hydrogen bond. The rearrangement is then formulated as (J). It is proposed that the metal atom [Fe(III)] loses an electron to the oxygen atom of the N-oxide, thereby becoming oxidized to Fe(IV). The N–O bond, weakened as a result, ruptures, the oxygen atom taking with it one electron from the nitrogen (step 2). [An aquo group (H_2O) in the Fe(III) complex would shed a proton on oxidation to Fe(IV).] In this way the oxygen atom, attached now to the iron atom as an *oxo* group, has been reduced in two 1-electron steps. Attack by a proton detached from the methyl group then transforms it to a hydroxo (OH) group, and the odd electron on the nitrogen atom becomes paired with an electron which has migrated from the carbon atom (step 3). (The proton removed from the methyl group need not necessarily be the one attacking the oxo group, however.) The metal atom accepts an electron from the coördinated hydroxyl group, reverting in the process to its original reduced state [Fe(III)] (step 4), the coördinated hydroxyl group being thereby oxidized to a hydroxyl radical which attacks the unpaired electron on the methylene carbon atom to give the methylolamine. An aquo group fills the vacant site on the complex, regenerating the original Fe(III) chelate.

This mechanism is closely similar to that postulated for the radical-mediated Polonovski reaction, (D) above, and to the reported[3b] free-radical rearrangement of 2-methylpyridine N-oxide, (C) above, and is compatible with the experimental facts. An ionic mechanism would not explain the necessity for a valency change of the complex during the reaction. Further examination of this reaction is in progress.

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