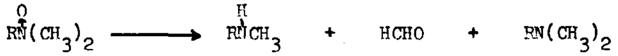
Tetrahedron Letters No.24, pp. 1613-1618, 1964. Pergamon Press Ltd.
Printed in Great Britain.

THE IRON CATALYZED DEMETHYLATION OF TRIMETHYLAMINE OXIDE

James P. Ferris and Roderick Gerwe
Department of Chemistry, The Florida State University,
Tallahassee, Florida

(Received 11 March 1964; in revised form 30 April 1964)

Tertiary amine oxides may be dealkylated by iron salts to yield the corresponding aldehyde and secondary amine along with some tertiary amine. This reaction, first reported by Horning and coworkers (1), is potentially



$$R\overset{O}{\overset{\uparrow}{N}}(CH_3)_2 \longrightarrow R\overset{H}{N}CH_3 + HCHO + RN(CH_3)_2$$

useful for the degradation of alkaloids and the synthesis of aldehydes. A DPN dependent enzyme in mouse liver homogenate will also catalyze this dealkylation reaction (1e,f). Since it has been proposed that the demethylation of amines (1) in biological systems proceeds via the amine oxide, a study of the mechanism of the simpler iron catalyzed reation may provide insight into the reaction in biological systems. Our experimental results also have a direct bearing on recent theories of alkaloid biogenesis which implicate the amine oxide function as an intermediate in the formation of the berberine bridge (2).

We wish to report the results of a study of the demethylation of trimethylamine oxide and to suggest the following reaction sequence that is consistent with our results (Table I) and with previous data (1).

$$(CH_3)_3\overset{+}{N}OH + Fe(II) + H^+ \longrightarrow (CH_3)_3\overset{+}{N}\cdot + Fe(III) + H_2O \qquad (1)$$

$$(CH_3)_3\overset{+}{N}\cdot + Fe(II) + H^+ \longrightarrow (CH_3)_3\overset{+}{N}H + Fe(III) \qquad (2)$$

$$(CH_3)_3\overset{+}{N}\cdot \longrightarrow (CH_3)_2\overset{+}{N}HCH_2\cdot \qquad (3)$$

$$(CH_3)_2\overset{+}{N}HCH_2\cdot + (CH_3)_3\overset{+}{N}OH \longrightarrow (CH_3)_2\overset{+}{N}HCH_2OH + (CH_3)_3\overset{+}{N}\cdot \qquad (4)$$

We have confirmed that iron(III) nitrate in the presence of oxalic, tartaric or citric acid will catalyze the decomposition of trimethylamine oxide to yield formaldehyde (1d). However, when iron(III) nitrate alone is used, we obtained no formaldehyde. Iron(II) alone is an efficient catalyst for this reaction. These data suggest that iron(II) is generated *in situ* when iron(III) and a reducing acid is used as a catalyst. That oxalic acid, tartaric acid, or citric acid will convert iron(III) to iron(II) was confirmed by polarographic analysis after heating a solution of iron(III) and one of these acids at 95-100° for 40 minutes (3).

Trimethylamine and dimethylamine have been identified by vapor phase chromatography (4) as the amines produced in this reaction. It had been suggested previously that the trimethylamine is formed in a side reaction by the reduction of trimethylamine oxide with formaldehyde (1d). However, we find that formaldehyde can be recovered quantitatively after heating with trimethylamine oxide under the reaction conditions. Furthermore, identical yields of formaldehyde and dimethylamine (run 4 - Table I) are obtained from the dealkylation reaction, a result that proves formaldehyde is not consumed in a side reaction with the amine oxide.

It was assumed previously that this reaction proceeds *via* free radical intermediates (1d). The following results confirm this assumption: (a) iron (II) is oxidized to iron(III) during the course of the reaction; (b) cyclohexanone is the product when cyclohexanol is added to the reaction mixture; (c) ethyl methacrylate is polymerized when added to the reaction mixture. The one-electron transfer (a) suggests the presence of a free radical intermediate and this was confirmed by the polymerization of the vinyl monomer. That the formaldehyde is produced only by way of this free radical intermediate was shown by the absence of formaldehyde when cyclohexanol was added to the reaction mixture. The presence of the 2,4-dinitro-

TABLE I

Products from the Reaction of Iron(II) with Trimethylamine Oxide[a]

				Yield[b] (%)		
Run	Iron Salt	Added Salt	Time (hr.)	CH_2O	Fe(III)	Amines
1.	$Fe(ClO_4)_2$	—	0.67	13	—	—
2.	$Fe(ClO_4)_2$	—	24[c]	79	26	92[d]
3.	$FeSO_4$	—	0.67	28	—	—
4.	$FeSO_4$	—	9[c]	65	—	97[e]
5.	$FeSO_4$	—	9.5	—	65	—
6.	$FeSO_4$(3	—	5	39	—	—
7.	$FeSO_4$(10)	—	5	11	—	—
8.	$FeSO_4$	Na_2SO_4[f]	0.67	50	—	—
9.	$FeSO_4$	NaCl[f]	0.67	7	—	—
10.	$FeSO_4$	KH_2PO_4	0.67	11	—	—
11.	$FeSO_4$(2)	KH_2PO_4	0.67[c]	6	—	98
12.	$FeSO_4$(3)	KH_2PO_4	10.5	4	175	—
13.	$FeCl_2$	—	0.67	6	—	—
14.	$FeCl_2$(3)	—	4	—	188	96

[a] Trimethylamine oxide dihydrate (0.009 mole) was refluxed in a nitrogen atmosphere with 0.0133 moles of the iron salt in 200 ml. of 0.49 N acid solution. The anion of the acid and that of the iron salt were always the same. A number in parenthesis next to the iron salt indicates that this multiple of the 0.0133 moles of iron was used. One-tenth mole of added salt was used unless otherwise indicated. The formaldehyde was determined as its 2,4-DNP derivative, the iron(III) by difference after titration of iron(II) with ceric sulfate, the total amines by titration with 0.1 N H_2SO_4 and the relative amounts of dimethylamine and trimethylamine by the method described by J. S. Fritz, "Acid-Base Titrations in Non-aqueous Solvents", The G. F. Smith Chemical Co., Columbus, Ohio 1952, pp. 13-20.

[b] Based on trimethylamine oxide dihydrate

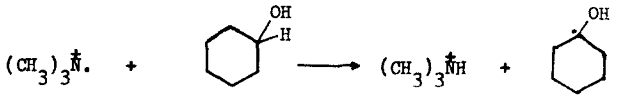
[c] Optimum reaction time

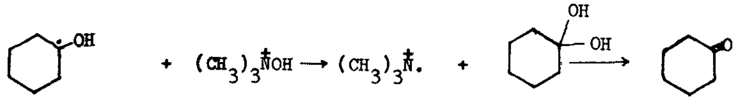
[d] 9 hr. reaction time

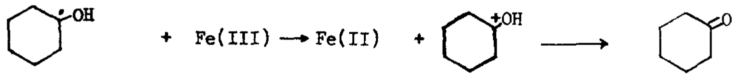
[e] 62 ± 3% dimethylamine and 36 ± 3% trimethylamine. Value determined after 4 hr. reaction time.

[f] 0.16 moles added

phenylhydrazone (2,4-DNP) of cyclohexanone and the absence of the 2,4-DNP of formaldehyde was shown by a comparison of infrared spectra and by thin layer chromatography (5). The yields of cyclohexanone are comparable to the yields of formaldehyde given in Table I. Cyclohexanone must be produced by the reaction of cyclohexanol with some free radical intermediate (see equations 5, 6 and 7) (6).


(5)


(6)


(7)

The reaction rates and product ratios show a marked dependence on the anions present. The reaction rate decreases in the order $PO_4^{\equiv} > SO_4^{=}$, $Cl^- > ClO_4^-$ (compare runs 2, 4, 11). A similar sequence has been observed in other reactions involving the oxidation of iron(II) to iron(III) and has been ascribed to the increased ease with which iron(II) is oxidized in the presence of reagents which coordinate strongly with iron(III) (7). The yield of formaldehyde decreases as the reaction rate increases as a consequence of the acceleration of both reaction 1 and reaction 2 by the co-ordinating agent.[*]

---

[*] A referee has suggested that the observed anion effect may be due to enhanced electron transfer through the mediation of a bridged ion (8). Our studies do not rigorously exclude such a possibility. However the reaction rates follow the stability of the iron(III) complexes so closely that we feel coordination by the anion and not electron mediation by a bridged ion is the source of the anion effect.

The effect of chloride ion may also be due to its oxidation to chlorine by the amminium radical ion and the subsequent reduction of the chlorine to chloride ion, a process which would yield two equivalents of iron(III) and one equivalent of trimethylamine (6). This possibility does not exist for the other anions used in this study.

Finally we observed that the yield of formaldehyde increases to a maximum and then decreases with increasing iron(II) concentration (compare runs 4, 6 and 7. This suggests that the radical intermediate formed is reacting with iron(II) (equation 2) in a reaction that competes with the production of formaldehyde.

Our results may be explained by equations (1-4). The amminium radical ion (equation 1) is the same intermediate formed in the reaction of N-chloramines with iron(II) and other reagents (9). The amminium radical ion is converted to tertiary amine by reduction with iron(II); a step that finds analogy in the Hofmann-Loeffler reaction as well as many others (10, 11). Formaldehyde and dimethylamine are produced in a chain reaction between the amine oxide and a tautomer of the amminium radical ion. Equation 4 is similar to the radical induced decomposition of peroxides and the free radical oxidation of alcohols to ketones (6, 12).

Further studies on this reaction and the chemistry of amines oxides are in progress.

The authors thank Professor C. K. Mann for advise and assistance with the polarographic studies. This work was supported by a grant and a pre-doctoral fellowship (to R. G.) from the U. S. Public Health Service.

REFERENCES

(1) (a) M. S. Fish, N. M. Johnson and E. C. Horning, J. Am. Chem. Soc., 78, 3668 (1956); (b) M. S. Fish, C. C. Sweeley and E. C. Horning, Chem. and Ind. (London), R24 (1956); (c) C. C. Sweeley and E. C. Horning, J. Am. Chem. Soc., 79, 2620 (1957); (d) J. Craig, F. P. Dwyer, A. N. Glazer and E. C. Horning, ibid., 83, 1871 (1961); (e) M. S. Fish, N. M. Johnson, E. P. Lawrence and E. C. Horning, Biochem. Biophys. Acta, 18, 564 (1955); (f) M. S. Fish, C. C. Sweeley, N. M. Johnson, E. P. Lawrence and E. C. Horning, ibid., 21, 196 (1956); (g) M. S. Fish, N. M. Johnson and E. C. Horning, J. Am. Chem. Soc., 77, 5892 (1955).

(2) A. R. Battersby, Proc. Chem. Soc., 189 (1963); D. H. R. Barton, R. H. Hesse and G. W. Kirby, ibid., 267; A. R. Battersby, R. J. Francis, M. Hirst and J. Staunton, ibid., 268.

(3) Citric and tartaric acids have been reported to convert iron(III) to iron(II). L. J. Clark, Anal. Chem., 34, 348 (1962).

(4) R. E. Burks, Jr., E. V. Baker, P. Clark, J. Esslinger and J. C. Lacey, Jr., J. Agr. Food. Chem., 7, 778 (1959).

(5) J. Rosmos and Z. Deyl, J. Chromatog., 6, 187 (1961).

(6) For a related reaction of ethanol, iron(II) and hydrogen peroxide see I. M. Kolthoff and A. I. Medalia, J. Am. Chem. Soc., 71, 3777, 3784 (1949).

(7) R. E. Huffman and N. Davidson, J. Am. Chem. Soc., 78, 4836 (1956); D. A. House, Chem. Rev., 62, 185 (1962); M. Herrmann, Z. Anorg. Chem., 273, 1 (1953). For discussion of this effect with other cations see H. Taube, 77, 4481 (1955).

(8) H. Taube, Advan. Inorg. Chem. Radiochem., 1, 1 (1960).

(9) For a recent review see M. E. Wolff, Chem. Rev., 63, 55 (1963).

(10) C. Walling, "Free Radicals in Solution", John Wiley and Sons, Inc., New York, N. Y., 1957, p. 565.

(11) F. Minisci and P. Galli, Tetrahedron Letters, 167 (1964).

(12) (a) H. E. De La Mare, J. Org. Chem., 25, 2114 (1960); (b) D. B. Denny and H. M. Weiss, ibid., 28, 1415 (1963); (c) W. J. Jackson, 145th meeting of the A. C. S., September 1963, p. 83 O of the abstracts.