Experimental Section

An Example of a Procedure for the Synthesis of Tertiary Amines in Table I. N,N-Dimethylcyclooctylamine.—To a glass-lined[19] high pressure autoclave, arranged for agitation by rocking, was placed 100 g (0.79 mol) of cyclooctanone, 100 g of 90.5% formic acid, and 175 g of dimethylformamide. The autoclave was heated at 190°, under autogenous pressure, for 16 hr. The autoclave was allowed to cool and was vented in a hood.

The pale yellow homogeneous solution was slowly added to a separatory funnel containing 500 ml of a 10% hydrochloric acid solution and the aqueous amine hydrochloride was washed several times with ether.[20] The aqueous phase was treated with a solution of 70 g of sodium hydroxide in 200 ml of water (basic to litmus paper) and the N,N-dimethylcyclooctylamine was recovered by extracting with two 500-ml portions of ethyl ether. The ethereal layer was dried ($MgSO_4$) and the ether was removed under reduced pressure to afford 98 g of crude amine as a light-colored oil.

The amine was distilled under reduced pressure through a short Vigreux column. The product was collected at 63° (3 mm), $n^{25}D$ 1.4710 [lit.[15] bp 79–80 (6 mm), $n^{25}D$ 1.4706].

Cycloheptyltrimethylammonium Iodide.—In a glass-lined high pressure autoclave was placed 56.1 g (0.5 mol) of cycloheptanone, 64 g of 90.5% formic acid, and 110 g of dimethylformamide. The autoclave was heated at 190° for 14 hr and then was cooled to room temperature.

The pale yellow solution was slowly added to a separatory funnel containing 300 ml of 10% hydrochloric acid solution. The aqueous amine hydrochloride was extracted twice with 250-ml portions of ethyl ether. The aqueous layer was cooled and sodium hydroxide was added until the solution was decidedly basic. The N,N-dimethylcycloheptylamine was recovered by extracting with two 250-ml portions of ethyl ether. The ethereal layer was dried ($MgSO_4$) and the solvent was removed, at reduced pressure.

The crude amine was converted into its methiodide without further purification. Methyl iodide (100 g) was added dropwise to a stirred solution of the crude amine in 150 ml of methanol maintained at 0°. The ice bath was removed and the reaction mixture was stirred 3 hr at room temperature. The yellow solution was then poured into 1 l. of ethyl ether, filtered, and washed with ethyl ether to give 101 g (71.3%) of cycloheptyltrimethylammonium iodide that had mp 263.5–264° dec (lit.[21] mp 259°).

Registry No.—I, 15924-18-2; II, 15924-19-3.

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[19] When the reaction was carried out in a stainless steel high-pressure autoclave without the use of a glass liner, the yield of product was greatly reduced and a considerable amount of cyclooctanol was obtained as the major product.

[20] The combined ether layers were dried ($MgSO_4$) and the ether was removed under pressure to afford 21 g of an approximately 1:1 mixture of cyclooctanone and cyclooctanol.

[21] R. Willstatter, *Ann.*, **317**, 204 (1901).

Oxidations of Amines. V. Duality of Mechanism in the Reactions of Aliphatic Amines with Permanganate[1]

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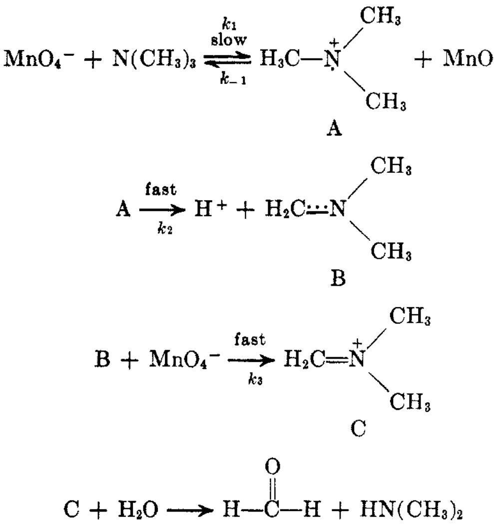
Received September 21, 1967

The mechanism of permanganate oxidation of aliphatic amines, *i.e.*, electron *vs.* hydrogen atom or hydride abstraction in the rate-determining step k_1, as well as the relative reactivities of aliphatic primary, secondary, and tertiary amines with permanganate ion in nearly neutral aqueous solutions are unresolved questions of current interest.[2,3] Whereas one would infer from an early investigation by Vorländer, Blau, and Wallis[4] that the order of reactivity should be tertiary > secondary > primary, Lambert and Jones have quoted the opposite conclusions[2a] from the literature.[2b] This confusion may be the result of a reversal in order of reactivity on change from neutral to acidic permanganate. Stewart[5] has stated that oxidation of trimethylamine by permanganate involves an initial attack on the C–H bond adjacent to the nitrogen.

Recognizing the similarity between permanganate and chlorine dioxide[6] oxidation of aliphatic amines, we tentatively propose, for discussion purposes, the mechanism in Scheme I for permanganate oxidation of trimethylamine. The manganate formed in Scheme I reacts to give manganese dioxide as in eq 1. This

SCHEME I



$$3MnO_4^{2-} + 2H_2O \longrightarrow 2MnO_4^- + MnO_2 + 4OH^- \quad (1)$$

reaction is too fast to enter into the kinetics under the pH conditions chosen for this study.[3] The product, formaldehyde, has been detected. This product is analogous to the benzaldehyde obtained by Wei and Stewart[3] from permanganate oxidation of benzylamine; as was shown by these investigators, the reactive amine species is the free base.

Our experience with chlorine dioxide in amine oxidations[6] led us to believe that both α-hydrogen atom transfer and electron transfer mechanisms can occur simultaneously, depending on the structure of the amine, on the oxidizing species, etc. Indeed, benzylamine, studied by Wei and Stewart,[3] is one of the most likely amines to react by α-hydrogen transfer, both because it is a primary amine (see below) and because

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[1] Paper number IV of this series: W. H. Dennis, Jr., L. A. Hull, and D. H. Rosenblatt, *J. Org. Chem.*, **32**, 3783 (1967).

[2] (a) D. G. Lambert and M. M. Jones, *J. Amer. Chem. Soc.*, **88**, 4615 (1966). (b) H. Schechter, S. S. Rawalay, and M. Tubis, *ibid.*, **86**, 1701 (1964); H. Schechter and S. S. Rawalay, *ibid.*, **86**, 1706 (1964).

[3] M. Wei and R. Stewart, *ibid.*, **88**, 1974 (1966).

[4] D. Vorländer, G. Blau, and T. Wallis, *Ann.*, **345**, 261 (1906).

[5] R. Stewart in "Oxidation in Organic Chemistry," part A, K. B. Wiberg, Ed., Academic Press Inc., New York, N. Y., 1965, p 61.

[6] (a) D. H. Rosenblatt, A. J. Hayes, Jr., B. L. Harrison, R. A. Streaty, and K. A. Moore, *J. Org. Chem.*, **28**, 2790 (1963); (b) D. H. Rosenblatt, L. A. Hull, D. C. DeLuca, G. T. Davis, R. C. Weglein, and H. K. R. Williams, *J. Amer. Chem. Soc.*, **89**, 1158 (1967); (c) L. A. Hull, G. T. Davis, D. H. Rosenblatt, H. K. R. Williams, and R. C. Weglein, *ibid.*, **89**, 1163 (1967).

the free radical formed in the hydrogen transfer process is resonance stabilized by the benzene ring.

We determined kinetic rate constants for the oxidation of trimethylamine and perdeuteriotrimethylamine with permanganate. An isotope effect of 1.84 on the ratio of the true second-order rate constants, k_H/k_D, was observed (Table I). The value of the isotope effect for trimethylamine thus lies in the upper part of the range usually associated with secondary isotope effects (below 2.0).[7] At least two possible explanations may be involved for the somewhat high value. (1) The additive secondary isotope effect of nine α hydrogens, already great by sheer weight of numbers, is enhanced by the nature of the reaction, in that a planar aminium cation radical is formed.[8] (2) Both hydrogen abstraction and electron abstraction are simultaneously operative, with electron abstraction playing a predominant role. Whereas the observation of an isotope effect of 1.84 would not normally rule out rate-determining C–H bond cleavage, we believe that the other evidence supports this view. This evidence is the previous observation by Wei and Stewart[3] of an isotope effect of 7.0 for oxidation of benzylamine by permanganate (thus demonstrating that primary isotope effects of amine oxidation with permanganate tend to be large) and the observation of large secondary isotope effects (1.3 to 1.8)[6] in the formation of aminium cation radicals. (In the latter instance, the mechanism of electron abstraction was corroborated by independent means.) These rationalizations have one element in common, namely that the reaction of permanganate with trimethylamine must involve electron abstraction and cannot be considered exclusively or even predominantly hydrogen transfer.

Table I

Experimental Data

Amine[d]	k,[a] l. mol^{-1} sec^{-1}	pK_a
$(C_2H_5)_3N$	3.08×10^{1}	10.65[b]
$(C_2H_5)_2NH$	9.44×10^{-1}	10.98[b]
$(C_2H_5)NH_2$	8.28×10^{-2}	10.63[b]
$(CH_3)_3N$	3.36	9.92[c]
$(CD_3)_3N$	1.82	10.155[c]

[a] $k = k_{obsd}$ ([H$^+$] + K_a)/K_a(the anal. concn. of amine), $k_1 = 1.5\,k$. [b] H. K. Hall, Jr., *J. Amer. Chem. Soc.*, **78,** 2570 (1956). [c] See ref 6. The pK_a of trimethylamine was determined at 0.49 ionic strength and was found to have the same value that was found at 0.2 ionic strength. [d] Registry no. for these amines follow in descending order: 121-44-8, 109-89-7, 75-04-7, 75-50-3, 13960-80-0.

It should be noted, furthermore, that, in the reaction of ferricyanide[2] and nitrous acid[9] with tertiary amines, electron transfer has been proposed for the former, and hydrogen elimination from an N-nitrosoammonium intermediate has been proposed for the latter in the rate-determining step, but kinetic evidence for the proposed mechanisms (*i.e.*, kinetic isotope studies) is lacking. It is thus even more significant that, in the present case and in the only other case[6c] so far subjected to the kinetic isotope effect test, electron abstraction has been found to play an important mechanistic role, the extent of electron abstraction *vs.* hydrogen abstraction depending on the nature of the amine.

Kinetic rate constants for oxidation of the series triethylamine, diethylamine, and ethylamine by permanganate were determined and it was found that the order of reactivity for this series is tertiary > secondary > primary (Table I). This order of reactivity is not as Lambert and Jones[1] inferred, but conforms to that observed for chlorine dioxide[6] and ferricyanide.[10]

We believe that this order of reactivity will show most pronounced differences when the mechanism is that of pure electron abstraction. However, the same order of reactivity can prevail for the *dual mechanism* of electron abstraction and hydrogen abstraction. As we have previously shown,[6c] benzyl-*t*-butylamine reacts faster with chlorine dioxide than does benzylamine, and the former goes mainly by the electron-abstraction path. The general tendency appears to be that electron abstraction will dominate the reactivities of tertiary amines, but hydrogen abstraction is of increased importance as one goes to secondary and then primary amines. This may be due to the fact that a substituent on the nitrogen atom will affect the electron density of the nitrogen atom to a significantly greater degree than it will affect the bond strength of the α-carbon–hydrogen bond. Therefore, the relative reactivities will mostly reflect the changes in electron density at the nitrogen atom rather than the more remote electronic influences on the α-carbon–hydrogen bond. The value of the rate constant for electron abstraction will thus increase to a greater degree than the value of the hydrogen abstraction rate constant with an increase in aliphatic substitution on the nitrogen. It is entirely reasonable for an oxidation that proceeds principally by hydrogen abstraction for a primary amine to shift to one that is much faster and goes almost exclusively by electron abstraction as the change is made to secondary and then to tertiary amine.

Experimental Section

Kinetics.—The kinetics were followed with a Cary Model 14 spectrophotometer at 525 mμ. An excess of amine (usually about 0.01 M) was permitted to react with 8×10^{-5} M potassium permanganate at 25 ± 1° (0.166 M phosphate buffers, pH 7.5–pH 8.0, and 0.49 ionic strength). These experiments were within the very narrow range of conditions under which the Mn(IV) invariably produced in such oxidations does not come out as a manganese dioxide precipitate[11] until after the permanganate oxidation is complete. Thus it was possible to follow the strictly first-order disappearance of MnO_4^- spectrophotometrically. This was done by plotting $(A - A_\infty)$ against time. The trimethylamine-d_9 hydrochloride was obtained from Volk Radiochemical Co., labeled 99% D.

Isolation of Formaldehyde as the Dimedone Derivative.—In 125 ml of water was placed 0.010 mol of potassium permanganate and 0.015 mol of trimethylamine hydrochloride, and the pH was adjusted to 8. After 5 min, the solution was filtered and 4.21 g of dimedone in 1000 ml of hot water was added at pH 11. After 30 min, the pH was adjusted to 4.0 and the dimedone derivative of formaldehyde, mp 189–190°, was isolated in 19% yield (0.84 g).

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(7) K. B. Wiberg, "Physical Organic Chemistry," John Wiley and Sons, Inc., New York, N. Y., 1964, p 354.

(8) S. I. Miller, *J. Phys. Chem.*, **66,** 978 (1962); A. Streitwieser, Jr., R. H. Jagow, R. C. Fahey, and S. Suzuki, *J. Amer. Chem. Soc.*, **80,** 2326 (1958).

(9) P. A. S. Smith and R. N. Loeppky, *ibid.*, **89,** 1147 (1967).

(10) T. D. Perrine, *J. Org. Chem.*, **16,** 1303 (1951).

(11) The failure of MnO_2 to precipitate for reasonably long periods of time under these reaction conditions is probably due to stabilization of dissolved Mn(IV) by phosphate ions, as noted by R. Stewart ("Oxidation Mechanisms: Applications to Organic Chemistry," W. A. Benjamin, Inc., New York, N. Y., 1964, p 60).