

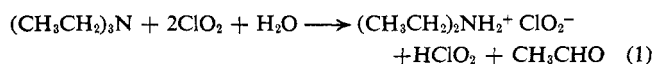
Oxidations of Amines. II. Substituent Effects in Chlorine Dioxide Oxidations^{1,2}

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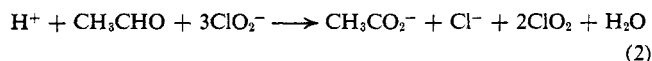
Contribution from the Research Laboratories, U. S. Army Edgewood Arsenal, Edgewood Arsenal, Maryland 21010. Received September 6, 1966

Abstract: Reaction of chlorine dioxide with a series of *meta*- and *para*-substituted benzyldimethylamines was studied at 26.95° in aqueous solution at constant ionic strength. Nonthermodynamic dissociation constants were determined at the same ionic strength for the series of amines. Several of the amines were shown to give significant yields of cleavage products corresponding to both of the possible directions for oxidative dealkylation. Despite the product complexity observed, rate constants for the reaction series were correlated by a Brønsted linear free energy relationship with $\alpha = +0.812$. The reactivities were also correlated by a Hammett plot, with $\rho = -0.924$, as were the amine dissociation constants ($\rho = -1.14$). The significance of these observations is discussed as it relates to the mechanism.

The reaction of triethylamine with chlorine dioxide to give acetaldehyde, diethylamine, and chlorite ion (eq 1) in aqueous solution has been examined



from several points of view in a previous study² of kinetics, stoichiometry, and organic and inorganic products. A complicating reaction which occurs at lower pH values is given by eq 2.² It was suggested,²



on the basis of the over-all second-order kinetics (first order in chlorine dioxide and first order in amine) and the stoichiometry of 2 moles of chlorine dioxide per mole of amine consumed, that an intermediate free radical is produced in this reaction. Such an intermediate could result either from a hydrogen abstraction mechanism or from the transfer of one electron from the nitrogen atom of the amine to chlorine dioxide.

The present study is the first published work, to our knowledge, on quantitative structure-reactivity relationships in the oxidation of aliphatic amines³ by a chemical oxidant.

By means of these correlations light was shed on the problem of distinguishing between the alternatives of attack at the hydrogen of the α carbon and attack at the electrons of the nitrogen atom. In addition, some indication was also obtained of the wide degree to which oxidants may vary in their behavior toward amines.

Results

The pK_a values for amines and kinetic rate constants for their reaction with aqueous chlorine dioxide determined in the progress of this work are presented in Table I. The pK_a values for the dimethylbenzylamines

gave an excellent correlation with ordinary Hammett σ constants⁴ (Figure 1). The least-squares value found for ρ was -1.14 ($pK_a = (9.053 \pm 0.020) - (1.145 \pm 0.059)\sigma$, with correlation coefficient 0.991).

Good first-order plots were obtained for most of the experiments in this study. Only when kinetic determinations were attempted below pH 5 was curvature encountered, as explained in the Discussion.

Treatment of the data for the system chlorine dioxide-benzyldimethylamines by the Brønsted linear free energy relationship⁵ gave an excellent linear regression, with correlation coefficient 0.991 (Figure 2). The data could be fitted to the following least-squares equation: $\log k = (2.899 \pm 0.16) + (0.812 \pm 0.040)pK_a$. Moreover, the trimethylamine rate constant² fell on this plot. The Hammett plot, $\log k = (4.451 \pm 0.027) - (0.924 \pm 0.078)$ (Figure 3), gave a ρ value of -0.924 with correlation coefficient 0.976. In additional kinetic experiments (Table I), a variety of tertiary,

Table I. Reaction of Diverse Amines with Chlorine Dioxide at 25°^a

Amine	pK_a	$k_2, M^{-1} \text{ sec}^{-1}$
<i>p</i> -Methoxybenzyldimethylamine	9.32	$4.94 \pm 0.78 \times 10^4$
<i>p</i> -Methylbenzyldimethylamine	9.22	$3.52 \pm 0.27 \times 10^4$
<i>p</i> -Fluorobenzyldimethylamine	8.94	$1.98 \pm 0.18 \times 10^4$
Benzyldimethylamine	9.03	$2.74 \pm 0.24 \times 10^4$
<i>m</i> -Nitrobenzyldimethylamine	8.195	$6.15 \pm 0.56 \times 10^3$
<i>p</i> -Nitrobenzyldimethylamine	8.14	$4.48 \pm 0.17 \times 10^3$
<i>m</i> -Chlorobenzyldimethylamine	8.67	$1.59 \pm 0.14 \times 10^4$
<i>p</i> -Chlorobenzyldimethylamine	8.83	$1.99 \pm 0.21 \times 10^4$
<i>m</i> -Methoxybenzyldimethylamine	9.04	$2.86 \pm 0.04 \times 10^4$
<i>p</i> -Methoxy-N-methylbenzylamine	9.97	$2.703 \pm 0.061 \times 10^2$
Benzylisopropylamine	9.69	$9.05 \pm 0.29 \times 10$
Diisopropylamine	11.01	$3.48 \pm 0.21 \times 10^2$
Benzyl- <i>t</i> -butylamine	10.19	$2.81 \pm 0.29 \times 10$
Benzylamine	9.60	3.934×10^{-2}
β -Hydroxyethylamine ^b	9.44 ^b	1.444×10^2
Dimethyl- <i>t</i> -butylamine	10.69	$2.346 \pm 0.819 \times 10^5$
N-Methylpiperidine	10.38	$8.71 \pm 1.79 \times 10^4$
Piperidine	11.20	$2.407 \pm 0.028 \times 10^3$
N- <i>t</i> -Butylpyrrolidine	11.13	$1.261 \pm 0.093 \times 10^6$

^a Ionic strength = 0.20. ^b S. Glasstone and A. F. Schram, *J. Am. Chem. Soc.*, **69**, 1213 (1947).

(4) H. H. Jaffé, *Chem. Rev.*, **53**, 191 (1953).

(5) R. P. Bell, "Acid-Base Catalysis," Oxford University Press, London, 1941, p 77.

(1) This paper was presented at the 148th National Meeting of the American Chemical Society, Chicago, Ill., Sept 1964.

(2) Paper I of this series: D. H. Rosenblatt, A. J. Hayes, Jr., B. L. Harrison, R. A. Sreaty, and K. A. Moore, *J. Org. Chem.*, **28**, 2790 (1963).

(3) Previous work has appeared which succeeded in correlating the reactions of a series of aromatic amines with the oxidant diphenylpicrylhydrazyl. See J. C. McGowan, T. Powell, and R. Raw, *J. Chem. Soc.*, 3103 (1959).

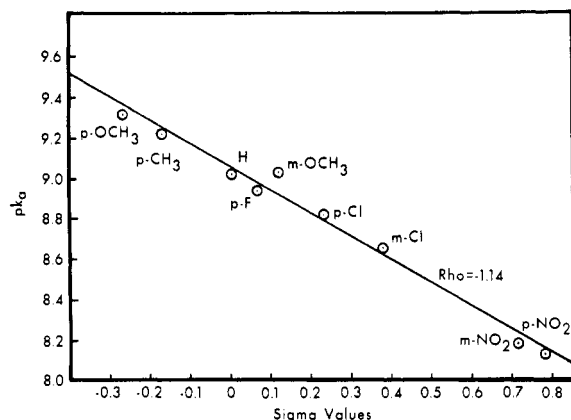


Figure 1. Hammett relationship for dissociation constants of substituted benzyldimethylamines at 25°, $\mu = 0.20$.

secondary, and primary amines, gave rates less than those of benzyldimethylamines of corresponding pK_a . The over-all tendency was tertiary > secondary > primary.

Both of the two possible modes of cleavage occurred, as evidenced by product isolation and by vapor phase chromatographic analysis of the products. In Table II are presented the results of product isolation for four of the amines studied. Products were identified by melting point or (Table III) by elemental analysis. Quantitative determination of the product ratios was hampered by (a) the interfering reaction between formaldehyde and chlorite⁶ to regenerate chlorine dioxide, and (b) the fact that mixtures of chlorite and formaldehyde (Table IV) do not react with amines to give the same ratio of cleavage products (benzyl to methyl cleavage) as obtained with externally generated chlorine dioxide. At high pH, where chlorite and formaldehyde do not react, both *p*-chlorobenzyldimethylamine and *p*-methoxybenzyldimethylamine gave the same ratio of benzyl to methyl cleavage by chlorine dioxide, 0.25 (Table IV).

Table II. Product Isolation and Identification

Substituent X	ArCHO ^a		ArCH ₂ NHCH ₃ ^b		
	% yield	Mp, °C ^{c,d}	% yield	Mp, °C ^c	Method ^f
H	50	235.5–237.5 dec	33	56.5–57	B
<i>p</i> -Cl	42	270–270.5	43	87.5–89	A
<i>p</i> -NO ₂	42	>300 ^e	25	137–138.5	C
<i>p</i> -OCH ₃	46	253–254.5	53	74–74.5	A

^a Yield of crude 2,4-dinitrophenylhydrazones. ^b Yield of crude benzenesulfonamide. ^c Melting point for recrystallized product.

^d Reference 31, pp 283–284: for H, 237°; *p*-Cl, 270°; *p*-OCH₃, 254°. ^e Identification made by elemental analysis. ^f See Experimental Section for methods.

Because of the known possible interferences by chlorite-aldehyde reactions,² kinetics of reactions of three aldehydes with chlorite ion were briefly examined at pH 6.6. The order of reactivities was established as for-

(6) Such reaction would tend to give abnormally high conversion of tertiary amine when the amine is employed in excess, as in our experiments. On the other hand, loss of chlorine dioxide by volatilization from the concentrated solutions used would tend to give low yields of products.

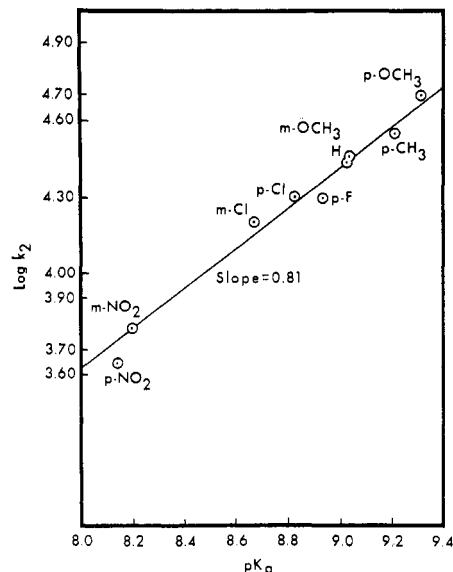


Figure 2. Brønsted relationship for reaction of chlorine dioxide with substituted benzyldimethylamines at 27°, $\mu = 0.20$.

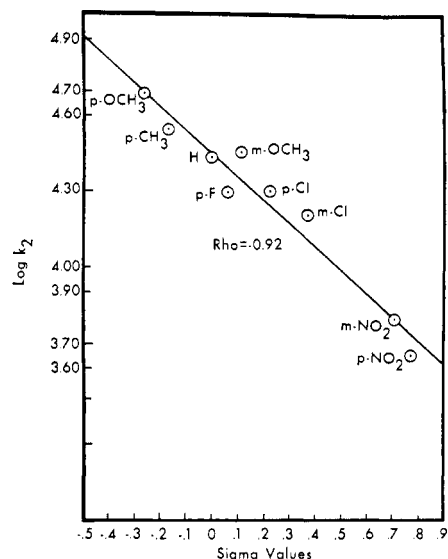


Figure 3. Hammett relationship for reaction of chlorine dioxide with substituted benzyldimethylamines at 27°, $\mu = 0.20$.

maldehyde > acetaldehyde >> benzaldehyde (the latter immeasurably slow under the conditions used).

Discussion

Several *meta*- and *para*-substituted benzyldimethylamines were chosen for the main linear free energy series, these having a sufficient pK_a range to permit correlations with a high degree of reliability. Owing to the activated benzylic position, these compounds might show an unusual disposition toward α -hydrogen attack, but this could not be avoided without introducing an additional methylene group, with the attendant large fall-off in substituent effects. Benzyldimethylamines were selected, rather than benzylamines with larger N-alkyl substituents, to avoid potential solubility problems. In this choice there was inherent the possibility of serious interference with the kinetic determinations through the interaction of the products

Table III. Analytical Results for Product Identification and Previously Unreported Amines^a

Compound	Calcd, %					Found, %				
	C	H	S	N	Cl	C	H	S	N	Cl
I. <i>p</i> -Nitro	54.9	4.6	...	9.1	...	54.4	4.7	...	9.3	...
<i>p</i> -Chloro	56.8	4.8	10.8	57.0	4.9	10.9
<i>p</i> -Methoxy	61.8	5.9	11.0	61.7	5.8	11.0
II. <i>p</i> -Fluoro	57.0	6.9	18.7	56.9	6.9	19.2
<i>m</i> -Chloro	52.5	6.4	34.4	52.5	6.3	34.5

^a I, *N*-methyl-*N*-(*X*-benzyl)benzenesulfonamides; II, *X*-benzyl-*N,N*-dimethylamine hydrochlorides (melting points in Experimental Section).

Table IV. Vapor Phase Chromatographic Determination of Product Ratios for *p*-*X*-Benzyl dimethylamines

Amine	pH	% benzyl cleavage ^a	% alkyl cleavage ^a	Total % ^a	Ratio benzyl: alkyl cleavage
<i>p</i> -Cl	8.9-9.0	14.0	57.1	71.1	0.246
	7.9-8.0	18.1	92.3	110.4	0.249
	6.4	35.7	26.5	62.2	1.35
	6.4	87.5	59.2	146.7	1.48
	6.4	80.7	67.2	147.9	1.20
	6.6 ^b	9.35 ^b
	6.6 ^c	1.78 ^c
<i>p</i> -OCH ₃	8.0	13.2	53.0	66.2	0.249
	6.4	80.8	67.2	148.0	1.25
	6.4	55.7	46.6	102.3	1.20
	6.4	59.2	50.2	109.4	1.18

^a These percentages were calculated cleavage yields based on the limiting reagent chlorine dioxide and the type of stoichiometry shown in eq 1. ^b Ratio produced by action of formaldehyde-chlorite mixture (see Experimental Section) on amine. ^c Ratio from action of hypochlorous acid on amine (see Experimental Section).

formaldehyde and chlorite ion (*cf.* eq 2). This interaction could regenerate chlorine dioxide as demonstrated by the kinetic experiments (see Experimental Section) at pH 6.6, which compared the reactivities of formaldehyde, acetaldehyde, and benzaldehyde with excess chlorite. Ethyl groups would have occasioned less cyclic regeneration of chlorine dioxide than methyl groups. However, the effect of the latter was avoided, in fact, by working at low concentration and pH⁷ above 5.

An additional reason for running the experiments at sufficiently high pH derives from the hitherto unexpected effect of pH on the ratios of methyl to benzyl cleavage.

Although the Hammett plot also gave excellent linear correlation, the Brønsted plot, in the present instance, represented a more direct and fundamental relationship between the variables. (The substituent effects on the nitrogen in the ground state are, of course, identical for amines acting as bases toward protons or as reducing agents for chlorine dioxide. The Brønsted plot utilizes the direct correspondence; by contrast, the Hammett relationship, in essence, *predicts* the basicities of the amines and relates the *predicted* values with the reactivities toward chlorine dioxide.) Thus, substituent interaction mechanisms in the protonated amine were directly compared with those of the transition state. Had these interaction mechanisms been identical, a Brønsted slope of $\alpha = 1.00$ would have been obtained.

(7) The decrease in reaction rate of benzaldehyde and chlorite ion with increasing pH is documented by H. F. Launer and Y. Tomimatsu, *Anal. Chem.*, **31**, 1385 (1959).

The actual value obtained was 0.812, probably indicating a close similarity between the transition state and the protonated amine. The Hammett ρ value of -0.924 is reasonable, by comparison with other systems having similar geometry (in aqueous systems at 25°)⁴ in which the principal interaction mechanism is caused by approximately one unit charge.

The identical ratio (0.25) of benzyl to methyl cleavage for two amines (Table III) by chlorine dioxide, under conditions of noninterference by the chlorite-aldehyde reaction, is close to the value predicted for a statistical attack on the available α protons. This result indicates that the product-determining step is nonselective. The strikingly different ratio (9.35) obtained with a chlorite-formaldehyde mixture is evidence that this combination of reagents is able to produce an oxidant (presumably precursor to chlorine dioxide) which reacts in a manner different from that of chlorine dioxide. It was established by independent experiment (Table IV) that the intermediate oxidant could not have been hypochlorous acid. Oxidation by the latter species gave a product ratio intermediate between that for chlorine dioxide and that for the formaldehyde-chlorite reagent. Furthermore, hypochlorous acid is comparatively sluggish in action, under the conditions employed (see Experimental Section), as indicated by the very low yield of oxidized products obtained.

The over-all tendency for amine reactivity observed, tertiary > secondary > primary, has been previously obtained for amine oxidations.^{3,8} *t*-Butylamine does not react with chlorine dioxide, and this parallels the observation of McGowan and co-workers³ in their studies with diphenylpicrylhydrazyl. However, this amine is not completely unreactive toward all oxidants, as shown by the studies of Kornblum and Clutter,⁹ who observed relatively facile oxidation of *t*-butylamine by permanganate and by alkaline hydrogen peroxide to give *t*-nitrobutane.

Our results for the benzyl dimethylamine series are best interpreted as supporting initial rate-determining attack at the nitrogen lone pair. Phenyl activation of the α carbon should give preponderant attack at the α position if hydrogen abstraction (to give a carbon radical) were the rate-determining step. However, our results do not substantiate preferential benzyl cleavage. In fact, attack is slightly biased in favor of methyl cleavage. In addition, the lack of selectivity exemplified by the product ratios obtained points to a product-determining step with a low activation energy. Apparently an intermediate of relatively high energy is

(8) D. Vorlander, G. Blau, and T. Wallis, *Ann.*, **345**, 261 (1906); G. J. Papariello and M. A. M. Janish, *Anal. Chem.*, **37**, 899 (1965); C. K. Mann, *ibid.*, **36**, 2424 (1964).

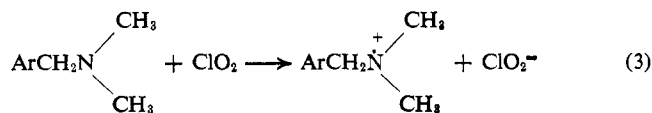
(9) N. Kornblum and R. J. Clutter, *J. Am. Chem. Soc.*, **76**, 4494 (1954).

produced, which reacts further, with a very low activation energy, to determine the product's nonselectively.¹⁰ This nonselective step cannot be the rate-determining step, inasmuch as our value for the activation energy, 13 kcal, is a substantial figure (see Experimental Section). This "normal" activation energy contrasts with the very low apparent activation energy derivable from the data of McGowan and co-workers³ on their experiments on reactivity of aliphatic amines with diphenylpicrylhydrazyl in carbon tetrachloride. Furthermore, correlation of the rates with ordinary Hammett σ values argues against hydrogen abstraction as a rate-determining step, since the literature is biased in favor of σ^+ correlations for reactions producing benzyl radicals.¹¹ Apparently, conjugation¹² of such radicals with the aromatic ring imparts some carbonium ion character to the reaction site.

Since attack appears to be at the nitrogen atom, the intermediate species produced is postulated to be an aminium cation radical. Support for the choice of this intermediate is easily obtained. Several examples of stable aminium cations have been reported in the literature.¹³

In addition to the aminium species stabilized by aromatic substitution cited above, aminium radicals not stabilized by such substitution have recently been reported^{14,15} or postulated as intermediates in the oxidation of amines.¹⁶⁻¹⁸

The mechanism presently favored by us for oxidation of amines by chlorine dioxide is represented for the series of benzyldimethylamines in the case of benzyl cleavage as follows.



(10) E. S. Gould, "Mechanism and Structure in Organic Chemistry," Henry Holt and Co., New York, N. Y., 1959, p 699.

(11) A. Streitwieser, Jr., and C. Perrin, *J. Am. Chem. Soc.*, **86**, 4938 (1964); G. A. Russell and R. C. Williamson, Jr., *ibid.*, **86**, 2357 (1964); J. A. Howard and K. U. Ingold, *Can. J. Chem.*, **41**, 1744 (1963).

(12) We attempted to evaluate conjugative substituent effects on delocalization where X is H, Cl, F, and OCH₃ in the model $p\text{-X-C}_6\text{H}_4\text{-CH=N}^+\text{C}(\text{CH}_3)_2$, employing the crude Hückel molecular orbital approach in the heteroatom model for substituents, using $h_N = 2$, $k_N = 1$, $h_F = 3$, $k_F = 0.7$, $h_{Cl} = 2$, $k_{Cl} = 0.4$, $h_O = 2$, and $k_O = 0.8$, with auxiliary inductive parameters, $0.1h_X$. Significant differences for substituents were not obtained (DE : H = 0.667 β , Cl = 0.725 β , F = 0.729 β , and CH₃ = 0.723 β), but some conjugative stabilization by the phenyl group was indicated. The MO calculations were carried out according to A. Streitwieser, Jr., "Molecular Orbital Theory for Organic Chemists," John Wiley and Sons, Inc., New York, N. Y., 1961, Chapter 5. The bond is represented with a three-electron π bond rather than as a simple $>\text{C}-\text{N}^+<$ classical system. A referee has requested clarification of this preference. It is felt that chemical evidence of preferred oxidation of the α -carbon atom in amines requires extra stabilization of the intermediates derived from this attack relative to the simple classical carbon radical. Otherwise, there would be no advantage to attack at the α position over any other similarly accessible position.

(13) R. I. Walter, *J. Am. Chem. Soc.*, **77**, 5999 (1955); K. Kuwata and D. H. Geske, *ibid.*, **86**, 2101 (1964).

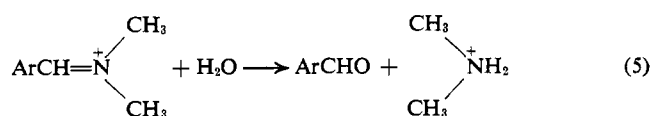
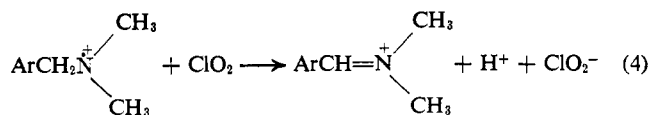
(14) A. J. Tench, *J. Chem. Phys.*, **38**, 593 (1963); T. Cole, *ibid.*, **35**, 1169 (1961).

(15) T. M. McKinney and D. H. Geske, *J. Am. Chem. Soc.*, **87**, 3013 (1965).

(16) L. Horner and W. Kirmse, *Ann.*, **597**, 48 (1955); L. Horner and B. Anders, *Chem. Ber.*, **95**, 2470 (1962).

(17) H. J. Dauben, Jr., and L. L. McCoy, *J. Am. Chem. Soc.*, **81**, 4863 (1959).

(18) C. D. Russell, *Anal. Chem.*, **35**, 1291 (1963); R. F. Dapo and C. K. Mann, *ibid.*, **35**, 677 (1963).



The initial slow step 3 is followed by one or more fast steps (for simplicity represented as (4)) in which the intermediate cation radical is converted to a quaternary Schiff's base. The latter intermediate is rapidly hydrolyzed to the isolable products, aromatic aldehyde and dimethylamine. The same general mechanism would also apply to cleavage of a methyl group.

Experimental Section

Chlorine dioxide solutions were prepared in triple-distilled water (distilled water redistilled from alkaline permanganate followed by redistillation from dilute sulfuric acid in an all-glass apparatus. The specific conductivity of one sample of such water was $1.286 \times 10^{-8} \text{ ohm}^{-1} \text{ cm}^{-1}$). The method for generation and storage was previously described.²

Amines and amine hydrochlorides were prepared by standard procedures or simple modifications thereof. All amines were obtained at least 99.8% pure by vapor phase chromatographic criteria. The purified hydrochlorides were used for kinetics, as they are more easily stored and weighed than the free bases. The melting points of the X-substituted benzyldimethylamine hydrochlorides are as follows, literature values being in parentheses: H, 175.1° (170°, 175°²⁰); $p\text{-OCH}_3$, 157.9° (157°²¹); $p\text{-NO}_2$, 191–192° (188°²²); $p\text{-Cl}$, 213.5–214.5° (212–213°²³); $p\text{-CH}_3$, (bp) 196–198° (bp 195–198°, lit.²⁴ bp 196–197°); $m\text{-NO}_2$, 235–237° (230°²²); $m\text{-OCH}_3$, 176–177° (173°²²); $p\text{-F}$, 205–206°, $m\text{-Cl}$, 203–204°.

The melting points of other hydrochlorides utilized were: diisopropylamine, 214.5–216° (216.5–217°²⁵); $N\text{-}t\text{-butylpyrrolidine}$, 228–229° (bp 145–147°, lit.²⁶ 146–147°); dimethyl- t -butylamine, 254–255° (238–239°²⁷); piperidine, 246–247° (244.5–246°²⁸); dibenzylamine, 264.5–265.5° (258°²⁹); benzyl- t -butylamine, 246.5–247.5 dec (240°³⁰); benzylamine, 264.5–265.5° (255.5–258°³¹); $N\text{-methylpiperidine}$, 201–202° (209–210°³²); and $p\text{-methoxybenzylmethylamine}$, 172–174° (166°²¹). Commercial t -butylamine was used after redistillation from potassium hydroxide.

Product Isolation and Identification. **Method A.** Into a 500-ml reaction flask equipped with two dropping funnels, pH electrodes, and magnetic stirrer was placed 2.06 g (10 mmoles) of p -chlorobenzyl- N,N -dimethylamine hydrochloride in about 25 ml of water. With stirring, 200 ml of 0.100 M (20 mmoles) chlorine dioxide and 103 ml (20 mmoles) of sodium hydroxide were added simultaneously, maintaining the pH at 6.9–7.9. On raising the pH to 8.2–8.3, the yellow color disappeared, and the pH was further adjusted to 12.2 by addition of 2 M sodium hydroxide. After extraction with four 100-ml portions of ether, the ether extracts were washed with several portions of 0.1 N hydrochloric acid (250 ml total) followed by 50 ml of water. The washings were then extracted with 50 ml of ether, and the ether solution was added to the original ether extracts. The aqueous acidic solution was warmed to expel

(19) J. Van Overbeke and C. Glacet, *Bull. Soc. Chim. France*, 933 (1962).

(20) M. Tiffeneau and K. Fuhrer, *ibid.*, **15**, 169 (1914).

(21) M. Tiffeneau, *ibid.*, **9**, 825 (1911).

(22) E. Stedman, *J. Chem. Soc.*, 1904 (1927).

(23) R. Baltzly and P. B. Russell, *J. Am. Chem. Soc.*, **72**, 3410 (1950).

(24) E. Eliel, *et al.*, *J. Org. Chem.*, **19**, 1693 (1954).

(25) K. A. Taipale, *Compt. Rend.*, 903 (1924).

(26) A. T. Bottini and J. D. Roberts, *J. Am. Chem. Soc.*, **80**, 5203 (1958).

(27) A. Ya Khorlin, L. A. Vorotnikova, and N. K. Kochetkov, *Zh. Obsch. Khim.*, **31**, 1827 (1961).

(28) T. B. Grave, *J. Am. Chem. Soc.*, **46**, 1467 (1924).

(29) J. V. von Braun, M. Kühn, and O. Goll, *Ber.*, **59**, 2335 (1926).

(30) B. L. Emling, *et al.*, *J. Org. Chem.*, **24**, 657 (1959).

(31) S. Hoogewuff and W. A. Van Dorp, *Rec. Trav. Chim.*, **5**, 253 (1887).

(32) H. W. Magnusson and E. R. Schierz, *Wyoming Univ. Publ.*, **7**, 1 (1940).

ether and treated with 2.00 g of benzenesulfonyl chloride and sufficient 3 *M* sodium hydroxide to make the solution cloudy. After shaking and standing for about 1.75 hr, a yield of 43% of *N*-methyl-*N*-*p*-chlorobenzenesulfonamide was obtained, mp 80–84.5°, raised to 87.5–89° by recrystallization.

Evaporation of the dried ether solution followed by treatment of the residue with 2,4-dinitrophenylhydrazine solution containing 2.00 g of reagent³³ gave 42% of *p*-chlorobenzaldehyde 2,4-dinitrophenylhydrazone, mp 204–216.5°, raised to 270–270.5° by recrystallization.

Method B differed from A only in that the organic products were steam distilled out of the reaction mixture prior to the extraction step.

Method C differed from A only in the use of chloroform as extractant instead of ether.

Determination of Amine Dissociation Constants. A potentiometric titration method was employed. Commercial buffers of pH 7.00 and pH 10.00 were used for standardization of a Beckman Model GS pH meter or a Beckman Research Model pH meter. The pH meters were equipped with glass and calomel fiber junction electrodes. A semimicroburet was used to dispense carbonate-free, standardized sodium hydroxide solution. The titrations were performed in a cell thermostated at 25.0 ± 0.2° under a nitrogen atmosphere.

A 100-ml sample of accurately prepared amine hydrochloride solution, dissolved in triply distilled, carbon dioxide free water and adjusted to 0.200 ionic strength by addition of sodium chloride, was titrated with standardized sodium hydroxide of 0.05–0.5 *M*. Sodium ion corrections were made where applicable. A parallel titration of the same quantity of medium in the absence of amine hydrochloride was then performed, and the sodium hydroxide consumed for a given pH was subtracted from the base consumed in titrating the amine hydrochloride to the same pH. These corrected values were used in determining the ratio of free amine to amine hydrochloride. Plots of pH vs. log ([B]/[BH⁺]) gave straight lines with slopes near 1.0, corresponding to the equation

$$\text{pH} = \text{p}K_a + \log ([B]/[BH^+])$$

where [B] = concentration of free amine, [BH⁺] = concentration of protonated amine.

Agreement with the theoretical slope of 1.00 was satisfactory in all cases. The *pK_a* was obtained by inspection of the graph at the point where the expression log [B]/[BH⁺] = 0. Each determination was performed at least twice with good precision (generally ±0.01 pH unit).

Kinetic Procedure. Kinetics of amine oxidations were followed by measuring the absorbancy of chlorine dioxide in a Cary Model 14 recording spectrophotometer at a wavelength of 357 mμ (ε 1230).² The nitro-containing amines were followed at 400 mμ (ε 600). A 100-mm cell (capacity slightly greater than 30 ml) was used. Water from a Forma water bath thermostated at 25.0 ± 0.2° was circulated through the spectrophotometer cell compartment to maintain a temperature of 26.95 ± 1.5°. (It was not realized until the end of these experiments that this temperature differential existed, owing to the relative inefficiency of thermostating the closed air space of the cell compartment. Consequently, the *pK* values were not determined at the exact temperature of the kinetics.) The cell was filled with 25 ml of buffer solution containing 2 × 10⁻⁴ *M* chlorine dioxide, and was allowed to equilibrate for 20 min in the cell compartment before 5 ml of the 0.03 *M* amine hydrochloride solution (accurately prepared) was added to start the reaction. The spectrophotometer recorder was started when one-half of the amine solution had been added. A series of buffers (cacodylate, phthalate, phosphate, or borate; cf. ref 2) prepared from commercially available materials were used to cover the pH span 4.5–8.9. Ionic strength was maintained at 0.200 by addition of sodium chloride. Direct measurement of the reaction solution pH was made on a Beckman Model G pH meter.

Plots for absorbancy (corrected for infinity absorbancy after ten half-lives) on semilogarithmic paper vs. time were linear. Inspection of the graph allowed determination of the reaction half-life. The pseudo-first-order rate constant was calculated from

$$k = 0.693/t_{1/2} = \text{pseudo-first-order rate constant}$$

where *t*_{1/2} = half-life of reaction. The second-order coefficients

were calculated by the formula

$$k_2 = k_1([H^+] + K_a)/K_a[B_i] = \text{second-order coefficient}$$

where [H⁺] = hydrogen ion concentration, *K_a* = acid dissociation constant of protonated amine, and [B_{*i*}] = total stoichiometric concentration of amine. Values for the second-order coefficients were consistent for at least two different pH values (cf. ref 2).

Vapor Phase Chromatographic Determinations. In all product determinations, the amine was employed in excess, the limiting reagent being chlorine dioxide. The procedure for the reactions is exemplified by the following.

In 15 ml of 1 *M* phosphate buffer (pH 6.4) was placed 0.1079 g of *N*-*p*-chlorobenzylmethylamine. Then, 15 ml of 0.0397 *M* chlorine dioxide was added with stirring while the color was discharged. After addition of 5 ml of 5 *M* sodium hydroxide, the solution was transferred to a separatory funnel. After three extractions with 5 ml of dibutyl ether, the extracts were treated with 2 g of acetic anhydride followed by 2 g of pyridine. Finally, the solution was diluted volumetrically to 25 ml. For gas chromatographic analysis, 9 ml of the reaction extracts was diluted to 10 ml with 1% methyl stearate in cyclohexane. The *N*-*p*-chlorobenzylmethylacetamide was determined by a dilution analysis as follows. An aliquot of the unknown was added to an aliquot of 0.100 *M* amide in dibutyl ether. After analysis of the undiluted unknown and the diluted unknown, the following formula was applied

$$y = (v_2/v_1)(b/[r_2/r_1 - 1])$$

where *y* = unknown concentration of amide in original solution with standard, *b* = concentration of amide standard = 0.100, *r*₁ = original ratio of peak area of amide to peak area of stearate standard, *r*₂ = ratio of peak area of amide to stearate standard after addition of amide standard aliquot, *v*₁ = volume of unknown sample taken, *v*₂ = volume of standard added to *v*₁. Aromatic aldehyde was determined from the ratio of aldehyde to amide peak areas by application of an independently determined sensitivity factor obtained by comparing equal amounts of the pure substances. Yields were calculated on the basis of available chlorine dioxide and the stoichiometry, 2 moles of chlorine dioxide per mole of oxidized amine. *N*-Acetyl derivatives were prepared by acetylation of the secondary amines, *p*-chloro, bp 126° (1.5 mm), and *p*-methoxy, bp 141° (1.2 mm). Aldehydes were commercial materials, redistilled and stored under nitrogen.

Reaction of *p*-Chlorobenzyl-*N,N*-dimethylamine with Chlorite-Formaldehyde Mixture. Formaldehyde was generated by pyrolysis of paraformaldehyde, and collected in water. The solution was standardized by the sulfite³⁴ method.

To 0.1344 g of the amine hydrochloride in 30 ml of 1 *M* phosphate buffer (pH 6.6) was added 10 ml of stock 0.261 *M* formaldehyde solution and 15 ml of 0.0521 *M* sodium chlorite solution. With stirring, the solution was allowed to react 15 min. After quenching with 10 ml of 5 *M* sodium hydroxide, the solution was extracted and analyzed as in the section on chromatographic determinations.

Reaction of *p*-Chlorobenzyl-*N,N*-dimethylamine with Hypochlorous Acid. A fresh concentrated stock solution of chlorine water was standardized by iodimetry. To 0.2294 g of the amine hydrochloride in 15 ml of 1 *M* phosphate buffer (pH 6.6) was added 10 ml of stock 0.261 *M* formaldehyde solution and 15 ml of 0.0508 *M* aqueous chlorine solution. The solution was stirred for 10 min, treated with 15 ml of 0.100 *M* sodium arsenite solution, and, after further stirring for 5 min, treated with 5 ml of 5 *M* sodium hydroxide. It was then extracted and determined as described in the preceding sections. The absolute yield was not obtained owing to the very low conversion of starting amine to products. However, the ratio of benzyl to alkyl cleavage could be estimated (Table IV).

Kinetics of Reaction of Aldehydes with Chlorite Ion. Commercial formaldehyde (37.2% aqueous, Baker Analyzed Reagent) and acetaldehyde (Eastman) were used without further purification. Solutions were prepared gravimetrically. The evolution of chlorine dioxide was followed at 400 mμ. These kinetics were treated as first order in chlorite and first order in aldehyde. Phosphate buffers were used to control the pH. (A short induction period was observed under the conditions of these experiments, indicating some complexity in this reaction.) The phase of the reaction subsequent

(33) Prepared according to R. L. Shriner, R. C. Fuson, and D. Y. Curtin, "Systematic Identification of Organic Compounds," 4th ed, John Wiley and Sons, Inc., New York, N. Y., 1956, p 219.

(34) J. F. Walker, Ed., "Formaldehyde," 2nd ed, Reinhold Publishing Corp., New York, N. Y., pp 382–384.

Table V. Reaction of Chlorite with Aldehydes at 26.95°, Ionic Strength 0.20

Aldehyde	Aldehyde concn, <i>M</i>	Chlorite concn, <i>M</i>	pH	<i>k</i> ₂ , l./mole min
Formaldehyde	1.239 × 10 ⁻⁴	0.0333	6.60	3.47
	1.239 × 10 ⁻⁴	0.0333	6.60	3.25
Acetaldehyde	6.66 × 10 ⁻⁵	0.1000	6.60	0.396

to the induction period gave straight-line plots when submitted to the pseudo-first-order treatment (chlorite was employed in excess). The results are summarized in Table V.

Estimation of Activation Energy for Chlorine Dioxide Reaction with *p*-Nitrobenzyl-N,N-dimethylamine. The reaction of this amine was studied at 26.95 ± 0.2°, at 14.3 ± 0.2°, and at 40.7 ± 0.2°. Although the Arrhenius plot showed some scatter, the Arrhenius activation energy, *E*_a, was estimated at 12.9 ± 2 kcal/mole, and Δ*F*‡ was estimated to be 13.3 ± 2 kcal/mole.

Oxidations of Amines. III. Duality of Mechanism in the Reaction of Amines with Chlorine Dioxide¹

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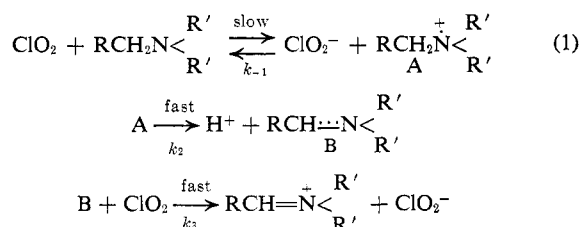
Abstract: Chlorine dioxide reacts with aliphatic amines to give the products of oxidative dealkylation. Reaction of chlorine dioxide with triethylamine, trimethylamine, and diisopropylamine is retarded by addition of chlorite ion. Analyses of these data substantiate a single mechanism in which formation of an aminium cation radical is rate controlling. Reactions of chlorine dioxide with dibenzylamine, benzyl-*t*-butylamine, and benzylamine are also retarded by addition of chlorite, but analyses of the data isolate an additional reaction component unaffected by addition of chlorite ion. A similar, but extremely minor, reaction component is isolated in the reaction with trimethylamine-*d*₉. Deuterium isotope effects were studied with trimethylamine-*d*₉, α,α-*d*₂-benzyl-*t*-butylamine, and α,α-*d*₂-benzylamine. The isotope effects substantiate the belief that the retarded reaction is that involving formation of the aminium radical by electron abstraction, whereas the unretarded component represents α-hydrogen atom abstraction.

Previous studies¹ have elucidated the order, products, stoichiometry, and electronic influences for the reaction of chlorine dioxide with some amines. It was strongly suggested that the principal rate-controlling step in the reaction of tertiary amines was an electron-abstraction process rather than a hydrogen-abstraction process.

Further evidence supporting the previously proposed mechanism for tertiary amines has now been obtained. In this report is presented the discovery that kinetics of amine oxidations by chlorine dioxide are influenced by added chlorite ion, and that analysis of the data for several amines provides evidence for two simultaneous mechanisms, either of which may predominate in a given circumstance, depending upon the structure of the amine.

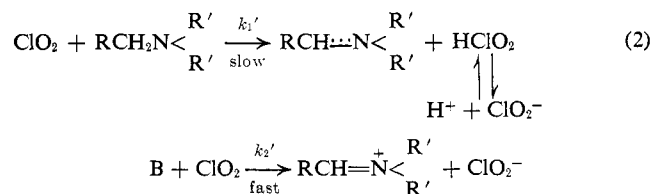
In the mechanism proposed for reaction of chlorine dioxide with amines, at least two steps were considered necessary. This followed from observations of second-order over-all kinetics (first order with respect to each reactant) and a stoichiometric requirement of 2 moles of chlorine dioxide per mole of amine. Reversibility of the first step was not proposed, but this possibility was recognized by analogy of eq 1 with the thoroughly studied S_N1 mechanism (in which reversibility is sometimes detected by addition of a common ion).² Elec-

tronic effects^{1b} and product ratios^{1b} were in agreement with this proposed dominant mechanism (eq 1), in



which the rate-determining step was a reversible one-electron transfer from amine to chlorine dioxide.

An alternative (irreversible) mechanism which would fit the previously observed kinetics (eq 2) was less



satisfactory on the grounds that it was less likely to give the excellent linear free energy correlations observed,^{1b} and was less likely to show the nonselectivity observed in the product-determining step.^{1b} In addition, we now propose that eq 2 would not allow for easy reversibility of the first step, since the chlorous acid produced would be immediately dissociated (and neutralized) at the pH ranges under study. The great difference between this mechanism and mechanism 1 is

(1) Papers I and II of this series: (a) D. H. Rosenblatt, A. J. Hayes, B. L. Harrison, R. A. Sreaty, and K. A. Moore, *J. Org. Chem.*, **28**, 2790 (1963); (b) D. H. Rosenblatt, L. A. Hull, D. C. De Luca, G. T. Davis, R. C. Weglein, and H. K. R. Williams, *J. Am. Chem. Soc.*, **89**, 1158 (1967).

(2) L. C. Bateman, M. G. Church, E. D. Hughes, C. K. Ingold, and N. A. Taher, *J. Chem. Soc.*, 979 (1940).