Kinetics and Mechanism of the Oxidation of Substituted Benzylamines by *N*-Chlorosuccinimide

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The oxidation of *ortho*-, *meta*-, and *para*-substituted benzylamines by *N*-chlorosuccinimide (NCS), to the corresponding benzaldehydes, is first-order with respect to NCS and the amine. The pH dependence of the reaction rate suggests that the unprotonated benzylamine is the reductant. There is no effect of added succinimide. NCS itself has been postulated as the reactive oxidising species. The oxidation of [α,α-$^2H_2$]benzylamine exhibited a substantial primary kinetic isotope effect (k_H/k_D = 6.20). The rates of oxidation of the *meta*- and *para*-substituted benzylamines were separately correlated in Taft and Swain's dual substituent parameter equations. For the *para*-substituted compounds, the best correlation is obtained with σ_I and σ_R^+ values; *meta*-substituted compounds correlate with σ_I and σ_R^0 values. The reaction constants have negative values. The oxidation rates of the *ortho*-substituted compounds yield an excellent correlation in a triparametric equation involving Taft's σ_I and σ_R^+ values and Charton's steric parameter, *V*. A mechanism involving transfer of a hydride ion from the amine to the oxidant in the rate-determining step is proposed.

The kinetics and mechanism of oxidations by *N*-chlorosuccinimide (NCS) have not been studied extensively. Reported investigations indicate that mechanistically this reagent behaves differently from *N*-bromosuccinimide.[1,2] The oxidation of benzylamine is known to yield a large number of products including those resulting from condensation of intermediates with the parent amine.[3] In addition benzamide, benzaldehyde, and benzoic acid are formed.[3] Wei and Stewart have studied the oxidation of some substituted benzylamines with permanganate ion.[4] We have been interested in oxidations by *N*-halogenoamides [5] and now report the oxidation of a series of *ortho*-, *meta*-, and *para*-monosubstituted benzylamines by NCS in buffered alkaline solutions. Attempts have been made to correlate structure and reactivity in this reaction.

Table 1. Rate constants for the oxidation of benzylamine by NCS at 298 K and pH 10.6

[$PhCH_2NH_2$]/M	10^3[NCS]/M	$10^4k_1/s^{-1}$
0.05	5.0	2.60
0.10	5.0	5.28
0.20	5.0	10.7
0.30	5.0	15.8
0.40	5.0	21.0
0.50	5.0	26.5
0.20	2.0	11.0
0.20	3.5	10.7
0.20	7.5	10.4
0.20	10.0	10.8
0.20	15.0	10.4

Experimental

Materials.—[α,α-$^2H_2$]Benzylamine was prepared by reduction of phenyl cyanide with lithium aluminium deuteride.[6] The isotopic purity, determined by ^1H n.m.r., was 94 ± 4%. *m*-Amino- and *o*-nitro-benzylamine were prepared by reported methods.[7,8] The other amines were commercially available and were purified by distillation. Borate buffers were used to keep the pH constant.

The aqueous solutions of the amines were prepared from freshly distilled amines and doubly distilled water. The concentrations of the amines were determined by titration with standard hydrochloric acid, with Methyl Red as indicator.

Product Analysis.—Ammonia was produced in 91% yield by the oxidation of benzylamine at pH 10.6 as shown by partial distillation of the aqueous reaction mixture and titration of the distillate with standard acid. Benzaldehyde was isolated as the 2,4-dinitrophenylhydrazone (DNP).

Freshly distilled benzylamine (5.35 g, 0.05 mol) and NCS (1.34 g, 0.01 mol) were made up to 100 ml in water at pH 10.6. The mixture was set aside for *ca.* 6 h to ensure completion of the reaction. It was then treated with an excess (250 ml) of a saturated solution of 2,4-dinitrophenylhydrazine in 2M-HCl and kept overnight in a refrigerator. The precipitated DNP was filtered off, dried, weighed, recrystallised, and weighed again. The DNP was identical (m.p. and mixed m.p.) with an authentic sample of benzaldehyde DNP. The yields of the DNP before and after recrystallisation were 2.75 g (96%) and 2.55 g (89%), respectively. In similar experiments with the other amines, the yields of DNP, after recrystallisation, were 86—93%.

Kinetic Measurements.—The reactions were studied under pseudo-first-order conditions by keeping a large excess of the amine over NCS. Preliminary experiments showed that the reaction is not sensitive to ionic strength (0.05—1.5M); hence no attempt was made to keep the ionic strength constant. The reactions were followed at pH 10.6, where the amines are almost completely unprotonated. Corrections were applied to the rate constant for partial ionisation of the amines. The reactions were followed iodometrically for up to 70% of the extent of reaction. The pseudo-first-order rate constant, k_1, was determined from linear plots of log[NCS] *vs.* time. The second-order rate constant, k_2, was obtained from the relation $k_2 = k_1$/[benzylamine]. Duplicate kinetic runs showed that the rates were reproducible to within ±3%. The average error limits in the values of ΔH^*, ΔS^*, and ΔG^* (at 298 K) are ±2 kJ mol^{-1}, ±3 J mol^{-1} K^{-1}, and 2.5 kJ mol^{-1}, respectively.

Results and Discussion

Rate laws and other data were obtained for all the compounds investigated. Since the results were similar, only representative data are reproduced here.

Oxidation of the amines by NCS gives the corresponding benzaldehydes and ammonia [reaction (1)]. The reactions are

Table 2. Kinetic isotope effect in the oxidation of benzylamine by NCS ([NCS] 0.005M; pH 10.6, *T* 298 K)

[amine]/M	Labelling	$10^5k_1/s^{-1}$	
0.05	None	26.0	$10^4k_H = 52.8 \pm 0.5\ l\ mol^{-1}\ s^{-1}$
0.10	None	52.8	
0.20	None	107	
0.05	[$^2H_2$]	4.23	$10^4k_D = 8.52 \pm 0.04\ l\ mol^{-1}\ s^{-1}$
0.10	[$^2H_2$]	8.60	
0.20	[$^2H_2$]	17.0	

$k_H/k_D = 6.20 \pm 0.06$
k_H and $k_D = k_1/[\text{amine}]$

Table 3. Effect of succinimide on the oxidation of benzylamine by NCS ([NCS] 0.005M; [amine] 0.10M; pH 10.6; *T* 298 K)

10^2 [succinimide]/M	0	2.5	4.0	5.0	7.5	10.0
$10^4k_1/s^{-1}$	5.28	5.10	5.25	5.42	5.31	5.15

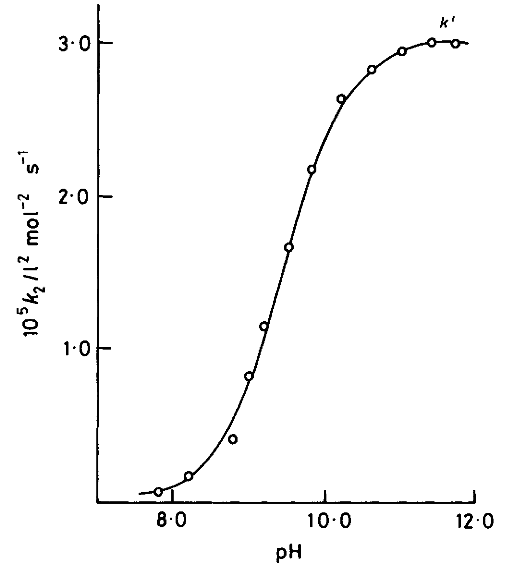


Figure 1. Dependence of the rate of the oxidation of benzylamine on pH (*T* 288 K)

$$PhCH_2NH_2 + Cl\text{-}N\!< + H_2O \longrightarrow PhCHO + NH_3 + HCl + HN\!< \quad (1)$$

found to be first-order with respect to NCS and the amine (Table 1).

The rate of oxidation of benzylamine increases with increasing pH but the dependence is not linear. A plot of rate constant *vs.* pH produces a typical ionisation curve (Figure 1). This indicates that neutral benzylamine is the reactive reducing species. In such a case, it has been shown[4] that a plot of log $[k_2/(k' - k_2)]$ *vs.* pH, where k' is the rate maximum, should be linear with unit slope, and the intercept is the pK_{BH^+} value of the benzylammonium ion. Figure 2 presents this plot: the measured pK_{BH^+} value of benzylamine is 9.40, close to the literature value of 9.34.[9]

Kinetic Isotope Effect.—To ascertain the importance of the cleavage of the C(α)–H bond in the rate-determining step, the oxidation of $PhCD_2NH_2$ was studied. The results showed the presence of a substantial primary kinetic isotope effect (Table 2).

Effect of Succinimide.—The rate of the reaction is not affected by the addition of succinimide (Table 3).

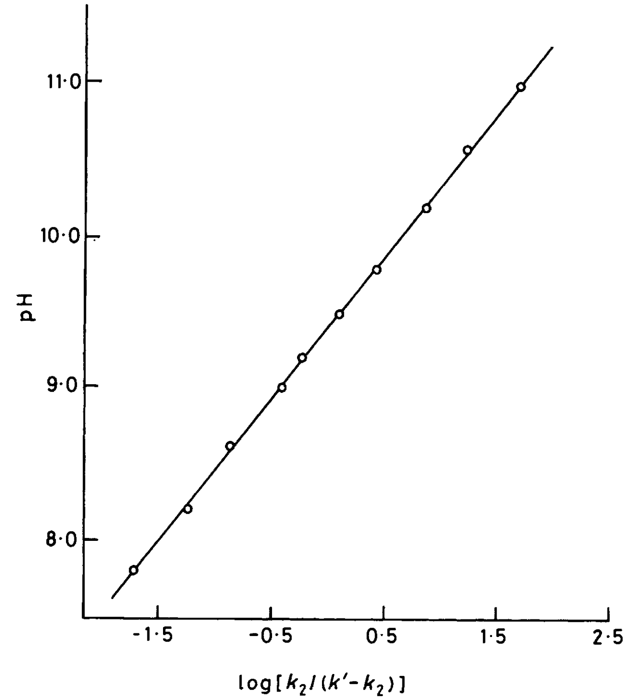


Figure 2. Plot of pH against the function log $[k_2/(k' - k_2)]$ for the oxidation of benzylamine by NCS

Effect of Substituents.—The rates of oxidation of benzylamine and nine *para*-substituted, nine *meta*-substituted, and nine *ortho*-substituted benzylamines were determined at various temperatures and the activation parameters were evaluated (Table 4).

N-Halogeno-amides are known to undergo hydrolysis and/or disproportionation in aqueous solution to give hypohalous acids.[2,5] Hypohalous acids have been proposed as the reactive species in many reactions[2,5,10] of *N*-halogeno-amides. However, the lack of any effect of the parent amide on the reaction rate rules out the involvement of such pre-equilibria in the present oxidation process; NCS itself seems to the oxidising species in the oxidation of benzylamines.

Correlation Analysis of Reactivity.—(i) para- *and* meta-*Substituted benzylamines.* Since the rates of oxidation of the mono-substituted benzylamines failed to show satisfactory correlation with any single substituent parameter, the rates of the *meta*- and *para*-substituted benzylamines were separately subjected to analysis by Taft and Swain's dual substituent parameter (DSP) equations (Table 5).[11,12] The rates of the *para*-substituted amines show excellent correlation with σ_I and σ_R^+ values. We have used the standard deviation (SD), the coefficient of multiple correlation (r), and the parameter f as measures of the goodness of fit; f has been defined[11] as

Table 4. Rate constants and activation parameters for oxidation of substituted benzylamines by NCS

	10^5k_2/l mol^{-1} s^{-1}						
Subst.	288 K	293 K	298 K	303 K	308 K	ΔH^* kJ mol^{-1}	ΔS^* J mol^{-1} K^{-1}
H	283	402	528	628	890	37.7	−161
p-Me	1 200	7 710	2 180	2 960	4 000	40.9	−138
p-OMe	11 700	17 400	24 000	34 300	50 400	50.3	−76
p-F	415	682	1 130	2 000	3 140	72.7	−37
p-Cl	150	258	402	680	1 050	68.9	−58
p-Br	176	270	401	635	900	58.0	−95
p-NO_2	6.80	12.0	20.1	35.3	56.5	75.5	−61
p-CF_3	23.6	40.2	63.5	100	158	69.2	−81
p-CO_2Me	43.0	63.5	89.2	138	200	54.0	−121
p-NHCOMe	6 600	9 340	13 000	17 100	23 800	44.0	−114
m-Me	503	680	876	1 200	1 580	21.8	−150
m-OMe	278	373	500	623	765	34.8	−172
m-F	40.0	65.5	108	160	224	61.3	−95
m-Cl	44.8	66.5	91.8	142	200	52.6	−125
m-I	50.5	76.0	113	157	215	50.7	−130
m-NO_2	3.99	6.76	9.83	18.6	31.8	73.2	−74
m-CF_3	16.7	24.4	38.0	59.2	80.6	56.8	−119
m-CO_2Me	29.8	50.3	74.5	110	167	59.6	−104
m-NH_2	472	682	890	1 320	1 770	46.0	−128
o-Me	6 430	8 350	10 200	13 200	16 500	31.9	−156
o-OMe	10 000	12 400	14 700	18 700	22 500	27.3	−168
o-F	393	470	615	805	1 000	32.8	−176
o-Cl	500	675	868	1 180	1 440	36.8	−160
o-Br	703	960	1 180	1 520	2 000	35.0	−164
o-NO_2	330	482	685	971	1 370	49.6	−119
o-CF_3	368	475	560	728	901	30.1	−186
o-CO_2Me	370	503	735	1 070	1 370	47.0	−108
o-NHCOMe	27 000	38 200	52 200	69 000	88 600	41.1	−113

Table 5. Correlation of the rates of oxidation of substituted benzylamines by NCS with dual substituent parameters at 298 K[a]

	para-Substituted					*meta*-Substituted				
Subst. constants	ρ_I	ρ_R	*r*	S.D.	*f*	ρ_I	ρ_R	*r*	S.D.	*f*
σ_I, σ_R^0	−2.32	−4.70	0.9359	0.56	0.18	−2.29	−1.25	0.9910	0.05	0.02
σ_I, σ_R^{BA}	−2.17	−3.40	0.9876	0.25	0.08	−2.89	−0.84	0.9884	0.11	0.05
σ_I, σ_R^-	−2.07	−2.96	0.8659	0.79	0.25	−2.18	−0.89	0.9862	0.06	0.03
σ_I, σ_R^+	−1.80	−2.16	0.9991	0.07	0.02	−2.24	−0.46	0.9752	0.16	0.07
Swain *et al.*[b]	−0.48	−1.22	0.9895	0.23	0.07	−1.33	−0.34	0.9897	0.10	0.04

[a] S.D. = standard deviation; *r* = coefficient of multiple correlation, *f* = S.D./(root mean square of log k/k_0); σ_I and σ_R values are from ref. 13. [b] Field and resonance substituent constants are from ref. 12.

S.D./R.M.S., where R.M.S. is the root mean square of the data points (here log k/k_0). Comparison shows that *f* is smaller for the $\sigma_R{}^+$ scale than for other scales by factors of *ca.* 3 to *ca.* 11. Thus it is apparent that the rates of the oxidation of *para*-substituted benzylamines by NCS correlate best with σ_I and $\sigma_R{}^+$.

The rates for the *meta*-substituted benzylamines show excellent correlation with σ_I and $\sigma_R{}^0$, though the discriminating factor for precision of fit with the other σ_R scales or with Swain's equation is not as sharp as in the case of the *para*-substituted compounds. In fact the correlation with $\sigma_R{}^-$ meets the requirement[13] for a satisfactory fit ($f < 0.1$). Even the correlation with σ_R^{BA} and Swain's equation is not poor. This agrees with the observation of Ehrenson, Brownlee, and Taft[13] that the correlation of *meta*-substituted compounds is generally best with the $\sigma_R{}^0$ scale; *meta*-substituted compounds are less discriminating.

The reaction constants and the statistical data at various temperature are given in Table 6. The values of λ^p(1.05—1.45) showed that the oxidation of *para*-substituted benzylamines is more susceptible to the resonance effect than to the field effect. In the oxidation of the *meta*-substituted compounds, however, the value of λ^m is *ca.* 0.54, indicating the greater importance of the field effect.

(ii) ortho-*Substituted benzylamines.* The rates of oxidation of *ortho*-substituted benzylamines failed to yield any significant correlation with Taft's polar or steric substituent constant.[14] The rates were, therefore, analysed by Charton's method.[15] The rates were correlated by using equations (2) and (3), where σ_I, σ_R, and *V* are field, resonance, and steric substituent constants; the values used were those compiled by Aslam *et al.*[16]

The results of correlation analysis in the terms of equation (2) are given in equation (4), where *n* is the number of data points.

$$\log k_{ortho} = \alpha\sigma_I + \beta\sigma_R + h \qquad (2)$$

$$\log k_{ortho} = \alpha\sigma_I + \beta\sigma_R + \varphi V + h \qquad (3)$$

$$\log k = -1.63\ \sigma_I - 1.97\ \sigma_R - 1.39 \qquad (4)$$

$$r = 0.7502;\ \text{S.D.} = 0.76;\ n = 10.$$

In the multiple linear regression using equation (2), the correlation coefficient is poor and the standard deviation is high.

Table 6. Temperature dependence of the reaction constants

T/K	ρ_I	$\rho_R{}^a$	λ^b	r	S.D.	f
			para-Substituted			
288	−2.12	−2.23	1.05	0.9982	0.10	0.03
293	−1.97	−2.19	1.11	0.9987	0.08	0.03
298	−1.80	−2.16	1.20	0.9991	0.07	0.02
303	−1.56	−2.14	1.37	0.9993	0.06	0.02
308	−1.45	−2.10	1.45	0.9995	0.05	0.01
			meta-Substituted			
288	−2.46	−1.29	0.52	0.9965	0.07	0.03
293	−2.38	−1.27	0.53	0.9984	0.04	0.02
298	−2.29	−1.25	0.55	0.9980	0.05	0.02
303	−2.10	−1.19	0.57	0.9994	0.02	0.01
308	−2.03	−1.10	0.54	0.9984	0.03	0.01

[a] ρ_R is ρ_R^+ or ρ_R^0 for the *para*- or *meta*-substituted compounds, respectively. [b] $\lambda = \sigma_R/\rho_I$.

Table 7. Temperature dependence of the reaction constants for the oxidation of *ortho*-substituted benzylamines by NCS

T/K	ρ_I	ρ_R^+	φ	r	S.D.	P_R	P_S
288	−2.63	−1.85	1.47	0.9972	0.10	41.3	24.7
293	−2.64	−1.82	1.48	0.9968	0.10	40.8	24.9
298	−2.65	−1.81	1.51	0.9969	0.10	90.6	25.3
303	−2.63	−1.81	1.55	0.9969	0.10	40.8	25.9
308	−2.64	−1.78	1.55	0.9959	0.11	40.3	26.0

Correlation in terms of equation (3) was performed assuming both orthogonal and planar conformations for NO_2 and CO_2Me groups. The correlation was better with a planar conformation of both groups. The results [equation (5)] showed that the correlation with equation (3) is satisfactory but not very good.

$$\log k = -3.41\,\sigma_I - 3.58\,\sigma_R + 1.94\,V - 2.41 \quad (5)$$
$$r = 0.9784;\ \text{S.D.} = 0.26;\ n = 10$$

Since the rates of oxidation of *para*- and *meta*-substituted benzylamines showed excellent correlation in Taft's[11] DSP equation with $\sigma_R{}^+$ and $\sigma_R{}^0$ constants, respectively, the rates of the oxidation of the *ortho*-substituted benzylamines were correlated in triparametric equations using Taft's σ_I and $\sigma_R{}^+/\sigma_R{}^0$, and Charton's steric parameters. Excellent correlations were obtained with Taft's σ_I and $\sigma_R{}^+$ and Charton's V values. The reaction constants and the statistical data are recorded in Table 7. The behaviour of *ortho*-NO_2 and *ortho*-CO_2Me is consistent with their planar conformation.

To test the significance of the three substituent constants, multiple linear regression analyses were carried out with Taft's σ_I and $\sigma_R{}^+$, Taft's σ_I and V, and $\sigma_R{}^+$ and V. The absence of significant correlations [equations (6)—(8)] showed that all three substituent constants (σ_I, $\sigma_R{}^+$, and V) are significant.

$$\log k = -1.37\,\sigma_I - 1.26\,\sigma_R{}^+ - 1.53$$
$$r = 0.8350;\ \text{S.D.} = 0.64;\ n = 10 \quad (6)$$

$$\log k = -2.63\,\sigma_I + 0.38V - 0.91$$
$$r = 0.5188;\ \text{S.D.} = 0.99;\ n = 10 \quad (7)$$

$$\log k = -1.81\,\sigma_R{}^+ + 0.88V - 2.34$$
$$r = 0.8573;\ \text{S.D.} = 0.60;\ n = 10 \quad (8)$$

There is no significant collinearity between Taft's σ_I and V, $\sigma_R{}^+$ and V, and Taft's σ_I and $\sigma_R{}^+$ (r = 0.5100, 0.5329, and 0.2690) for the ten substituents.

The regression coefficients of σ_I and $\sigma_R{}^+$ are negative, indicating that electron-releasing groups accelerate the reaction. The positive regression coefficient for the steric term indicates that the reaction is subject to steric acceleration by the *ortho*-substituents. The contribution of the resonance effect[15] to the total polar effect of the *ortho*-substituents was calculated by using equation (9).

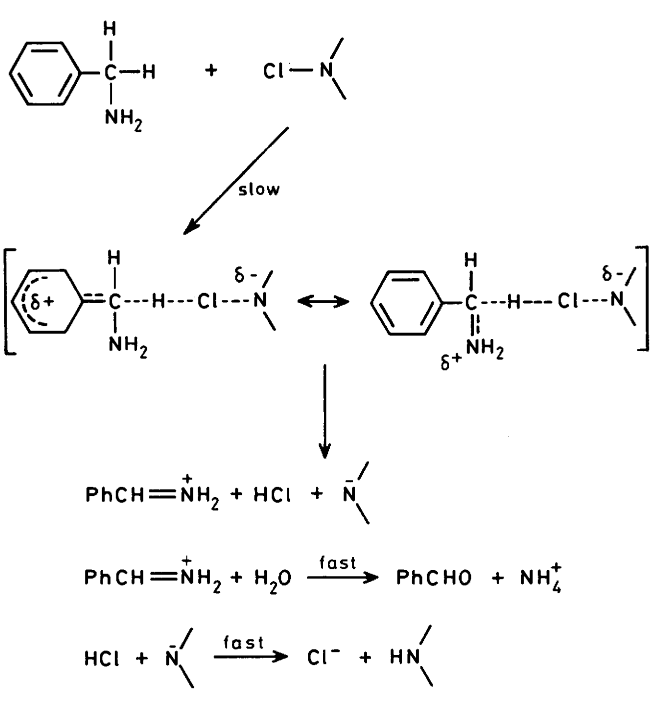
$$P_R = \frac{100\,|\rho_R^+|}{|\rho_I| + |\rho_R^+|} \quad (9)$$

The contribution of the steric parameters[15] to the total effect of the substituents, P_S, was determined by using equation (10).

$$P_S = \frac{100\,|\varphi|}{|\rho_I| + |\rho_R^+| + |\varphi|} \quad (10)$$

The values of P_R and P_S are also listed in Table 7; P_R is *ca.* 41%. The value of P_R for the *para*-substituted compounds ranges from 51 to 59%. This shows that the balance of field and resonance effects is different for *ortho*- and *para*-positions, resonance effects being less pronounced in the former case. This may be due to the twisting away of the methylamino group from the plane of the benzene ring. The value of P_S shows that there is a considerable steric effect in this reaction.

Mechanism.—The kinetics are consistent with a mechanism in which one molecule of the neutral amine and one of NCS participate in the rate-determining step. The observed kinetic isotope effect confirms that the rupture of the C(α)–H bond occurs in the rate-determining step. The large negative polar



Scheme.

reaction constants and the correlation of the rates of *para*- and *ortho*-substituted benzylamines with σ_R^+ point to a transition state in which there is a strong resonance interaction between the substituent and a developing positive charge. This suggests the transfer of a hydride ion from the methylene group to the oxidant. There is no doubt that the amino group strongly activates the adjacent methylene group and this supports the idea of hydride transfer. Thus the mechanism shown in the Scheme is suggested.

The steric acceleration of the reaction may be explained on the basis of high ground-state energy of the sterically crowded amines. Since the crowding is relieved in the product aldehyde as well as in the transition state leading to it, the transition state energies of the crowded and uncrowded amines will not differ much, and steric acceleration therefore results.

Acknowledgements

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