

A NEW MECHANISM (S_{Ei}) FOR ELECTROPHILIC SUBSTITUTION IN INDOLES.
 CHLORINATION OF INDOLES WITH SODIUM HYPOCHLORITE BY COMPETITIVE
 S_{E2} AND S_{Ei} MECHANISMS

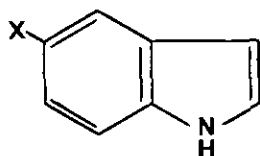
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Abstract — The chlorination of 5-substituted indoles (OCH_3 , CH_3 , Br, CN, NO_2) with NaOCl was studied. Mixtures of N-chloro- and N-chloro-3-chloro-indoles were formed. Indoles reacted with OCl^- in a S_{Ei} process to give N-chloroindoles. This reaction was favored by substituents which increased the acidity of the indolic N-H. Indoles or their conjugate bases also reacted with HOCl in a S_{E2} reaction to give 3-chloroindoles which were then converted to their N-chloro derivatives with excess NaOCl.

N-Chloroindole was the initial product formed in the chlorination of indole (1) with NaOCl.² This study reports on the mechanism of chlorination of indoles with NaOCl.

The chlorination of 5-substituted indoles (2-6) with excess NaOCl was studied in a number of solvents and the results summarized in Table 1.



- 1, X=H
- 2, X=OCH₃
- 3, X=CH₃
- 4, X=Br
- 5, X=CN
- 6, X=NO₂

In each case, solutions were obtained which contained species which oxidized iodide ion. When electron-withdrawing substituents (indoles 4-6) were present, the IR spectra (no N-H or C=N groups) and ¹H NMR spectra (C3H/C4H ratio less than one) of the product (pH 9.4) indicated the formation of a mixture of N-chloroindole and N-chloro-3-chloroindole. In contrast, when electron-donating groups were present, the IR spectra of the chlorination products at pH 9.4 showed the presence of a strong carbonyl band at 1770 cm⁻¹ for 5-methoxyindole (2) and at 1735 cm⁻¹ for 5-methylindole (3). In both systems the ¹H NMR indicated the disappearance of C2H and C3H. The signals attributed to the OCH₃ group in 2 and the CH₃ group in 3 were broad. A mixture of carbonyl containing

Table 1
Chlorination of 5-Substituted Indoles with NaOCl

<u>5-X</u>	<u>Solvent</u>	<u>pH</u>	<u>Time (h)</u>	<u>% Total Yield</u>	<u>% N-Cl^a</u>	<u>% N-Cl-3-Cl^a</u>
OCH ₃	CCl ₄	9.4	24	95	b	b
OCH ₃	CCl ₄	11.8	2	66	38-54	62-46
CH ₃	CCl ₄	9.4	24	68	b	b
CH ₃	CCl ₄	11.8	2	81	40-26	60-74
Br	CCl ₄	9.4	24	81	40	60
Br	CHCl ₃	9.4	24	85	e	e
Br	CDCl ₃	9.4	24	d	40	60
Br	CH ₂ Cl ₂	9.4	24	88	e	e
CN	CCl ₄ ^f	9.4	4	55	70	30
CN	CHCl ₃	9.4	2	87	e	e
CN	CDCl ₃ ^c	9.4	2	d	68	32
CN	CH ₂ Cl ₂	9.4	4	70	e	e
NO ₂	CCl ₄ ^g	9.4	2	80	78	22
NO ₂	CHCl ₃	9.4	2	90	e	e
NO ₂	CDCl ₃ ^c	9.4	2	77	80	20
NO ₂	CH ₂ Cl ₂	9.4	2.5	84	e	e
NO ₂	CCl ₄	11.8	2	64	83	17

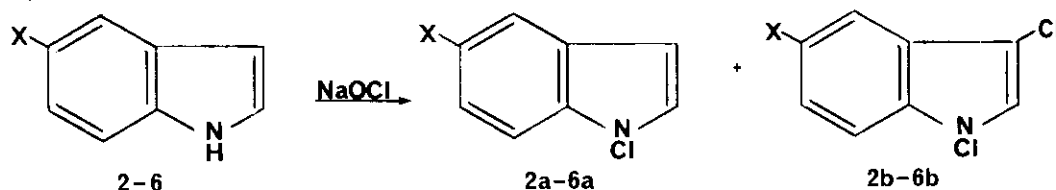
^a Determined by ¹H NMR. ^b Carbonyl containing compounds formed.

^c NaOCl prepared in D₂O. ^d Run in 1.0 ml of CDCl₃ and not titrated.

^e Solvent interference in ¹H NMR. ^f Solution was opaque.

^g Reaction over when insoluble indole no longer evident.

products were apparently formed at pH 9.4. When the chlorination of 2 and 3 was carried out at pH 11.8, the IR and ^1H NMR spectra (see below) indicated the formation of a mixture of N-chloroindole and N-chloro-3-chloroindole. Product mixtures obtained from indoles 2 and 3 were not stable and decomposed in a random fashion. Total yields were also more variable than for 4-6. The chlorination of 5-nitroindole was carried out at pH 11.8 and no substantial change was observed. Indoles 4-6 gave the same ratio of products at higher pH but the total yield was lower than at pH 9.4.



^1H NMR data of N-chloroindoles formed: 2a: δ (CCl_4) 3.87 (OCH_3 , s), 6.50 (H_3 , d, $J_{32}=3.5$ Hz), 6.90-7.47 (arom 3H and H_2 , m); 2b: δ (CCl_4) 3.92 (OCH_3 , s), 6.90-7.47 (arom 3H and H_2 , m); 3a: δ (CCl_4), 2.45 (CH_3 , s), 6.50 (H_3 , d, $J_{32}=3.5$ Hz), 6.97-7.45 (arom 3H and H_2 , m); 3b: δ (CCl_4) 2.50 (CH_3 , s), 6.97-7.45 (arom 3H and H_2 , m); 4a: δ (CCl_4) 6.47 (H_3 , d, $J_{32}=3.5$ Hz), 6.98 (H_2 , d, $J_{23}=3.5$ Hz), 7.05-7.48 (arom 2H, m), 7.63 (H_4 , d, $J_{46}=1$ Hz); 4b: δ (CCl_4) 6.98 (H_2 , s), 7.05-7.48 (arom 2H, m), 7.70 (H_4 , d, $J_{46}=2$ Hz); 5a: δ (CCl_4) 6.63 (H_3 , d, $J_{32}=4$ Hz), 7.12 (H_2 , d, $J_{23}=4$ Hz), 7.47 (arom 2H, br), 8.53 (H_4 , d, $J_{46}=3$ Hz); 5b: δ (CCl_4) 7.18 (H_2 , s), 7.47 (arom 2H, br), 7.73 (H_4 , d, $J_{46}=3$ Hz); 6a: δ (CCl_4) 6.75 (H_3 , d, $J_{32}=3.5$ Hz), 7.18 (H_2 , d, $J_{23}=3.5$ Hz), 7.41 (H_7 , d, $J_{76}=9.5$ Hz), 8.08-8.37 (H_6 , m), 8.53 (H_4 , d, $J_{46}=2$ Hz); 6b: δ (CCl_4) 7.18 (H_2 , s), 7.41 (H_7 , d, $J_{76}=9.5$ Hz), 8.08-8.37 (H_6 , m), 8.53 (H_4 , d, $J_{46}=2$ Hz).

In the following discussions 5-methoxyindole (2) and 5-nitroindole (6) were used as models for indoles containing electron-donating and electron-withdrawing substituents, respectively. Chlorination of 6, with a three fold excess of NaOCl, was complete after 2 h. No change was noted by ^1H NMR in the C3H/C4H ratio when the product mixture was kept in contact with fresh NaOCl for an additional 48 h. During this period the iodometrically determined total yield changed by 2-4%. Clearly N-chloro- and N-chloro-3-chloro-5-nitroindole were formed independently.

One possibility for the separate formation was that the indoyl anion was attacked at both nitrogen and C-3.³ Small equilibrium ($\text{pK}_a=14.75$) concentrations of the anion of 5-nitroindole⁴ (6) would be expected to be present at the alkaline pH used for the chlorination studies. 5-Nitroindole deuterated at C-3 was prepared.⁵ No D/H exchange at C-3 was observed by ^1H NMR either during chlorination at pH 9.4 or in a control (no NaOCl) at the same pH. These results would seem to indicate that no detectable concentration of anion was present during the chlorination process at pH=9.4. It should be noted that the results obtained by Challis and coworkers⁶ indicated that exchange should be slow at the pH used above. Therefore the possibility that chlorination

at C-3 of the indoyl anion was much faster than protodeuteration can not be eliminated.

Previous studies on the mechanism of N-chlorination with aqueous NaOCl were based on pH-rate profiles. Soper^{7,8} reported that anilides reacted with OCl⁻ in what is now considered a concerted four-center process⁹ to give N-chloroanilides. It was also observed that the rates of N-chlorination of N-methylacetamide and acetylglycine varied with the concentrations of OCl⁻ and HOCl.⁸

In 1949, both Weil¹⁰ and Soper¹¹ published studies on the N-chlorination of aliphatic amines with NaOCl/HOCl. Similar pH-rate profiles were found. It was proposed by Weil¹⁰ that the amine reacted with HOCl. Soper,¹¹ by analogy to the anilide work,⁸ indicated that the reaction of the ammonium ion with OCl⁻ was the likely mechanism. The reaction of anilides^{7,8} with OCl⁻ is of the type termed S_Ei by Hughes and Ingold.¹² Reactivity in a S_Ei reaction depends in part on the acidity of the proton lost.¹³

N-Chloroindoles² were not stable in protic solvents and it was not possible to study chlorination rates under homogenous conditions. The qualitative dependence of rate on changes in substituent and pH were determined under heterogeneous conditions. Results obtained should be considered to be illustrative of reactivity trends. We have previously shown that when aqueous NaOCl reacted with a 10-fold excess of 2-methylindole only mono-chlorination took place.² A qualitative order of reactivity of indoles (1-6), 3-chloro-5-methoxyindole¹⁴ (7) and 3-chloro-5-nitroindole¹⁵ (8) in CH₂Cl₂ towards aqueous NaOCl was obtained by reacting NaOCl with a 10-fold excess of indole for 60 sec. Results are summarized in Table 2.

Table 2

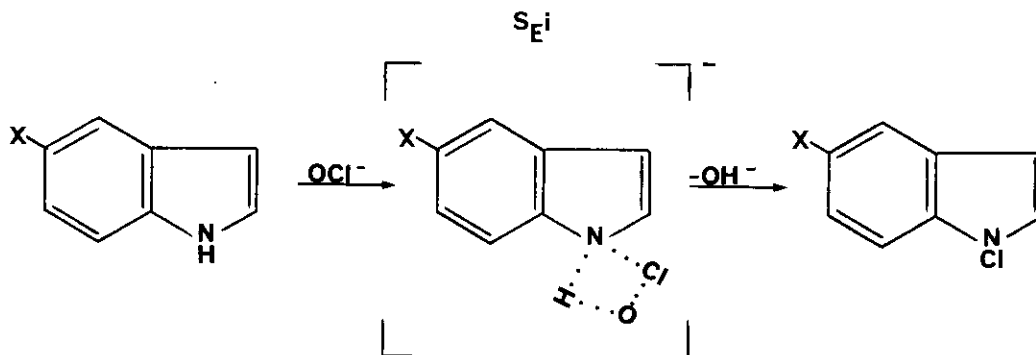
Reactivity of Indoles Towards NaOCl^a

Substituent		% NaOCl Consumed
<u>5-X</u>	<u>3-X</u>	
OCH ₃	H	100
OCH ₃	Cl	29
CH ₃	H	100
H	H	82
Br	H	28
CN	H	42
NO ₂	H	57
NO ₂	Cl	94

^apH 9.4 ± 0.2.

These results were only compatible with either a change in mechanism or rate determining step as the substituent was changed from electron-withdrawing to electron-donating. This was most clearly seen in the change in reactivity upon the introduction of a 3-chloro substituent in 5-methoxy- and 5-nitroindole, respectively. In the former, reactivity decreases; whereas, in the latter, it increases. To further clarify the above, the qualitative dependence of the rate of mono-chlorination with pH was determined for 5-methoxyindole and 5-nitroindole at pH 10.2 and 12.1. In this pH range HOCl (pKa=7.53) was almost completely (>99%) converted to OCl⁻. A solution of the indole (0.065 M) in CH₂Cl₂ was shaken at 25.0 ± 0.1° C with an equal volume of NaOCl (0.0065 M) at pH 10.2 and repeated at 12.1. Chlorination of 5-nitroindole for 60 sec at pH 10.2 consumed 34 ± 6% of the NaOCl and 30 ± 2% at pH 12.1. This clearly indicated that the rate was pH independent. In contrast, after 30 sec at pH 10.2, 5-methoxyindole had reacted with 38 ± 3% of the NaOCl and with 7 ± 1% at pH 12.1. A five-fold change in rate was observed. Indoles with electron-withdrawing groups respond to changes in pH differently than indoles which contain donating groups. These results confirm the conclusions drawn from Table 2.

It appeared likely to us that the changes in the effective chlorinating agent noted in previous studies^{7,8,10,11} reflected the acidity of the proton lost during N-chlorination with NaOCl. The reactivity trends noted in this study would then be, in part, a function of the acidity of the indolic N-H group. To test this possibility, chlorinations were carried out in the presence of an HOCl trap (phenol). Phenol (as phenoxide) has been shown to react rapidly with the HOCl in equilibrium with OCl⁻ in alkaline solutions.¹⁷ 5-Nitroindole (0.5 mmole) in CH₂Cl₂ and phenol (6 mmole) in H₂O were combined and this mixture was stirred with aqueous NaOCl (15 mmole) at pH 10.7-11.0 and after 10 min there was formed a 75% yield of a species whose ¹H NMR spectrum showed it was essentially pure (≥ 95%) N-chloro-5-nitroindole (6a). Therefore N-chloro-5-nitroindole (6a) is the product of the S_Ei reaction of OCl⁻ with 6.



The concentrations of OCl⁻ (pKa=7.53) and 5-nitroindole (pKa=14.75) were essentially constant (>99% in the form indicated) in the pH range of 10.2-12.1. 5-Nitroindole was the most acidic

5-substituted indole used in this study and the above would also apply to indoles (1-5). Therefore the S_Ei reaction of an indole with OCl^- was pH independent between pH 10.2 and 12.1.

N-Chloro-5-nitroindole (6a) and N-chloro-3-chloro-5-nitroindole (6b) were formed independently. If they were the products of the reaction of HOCl at N or C-3 of 5-nitroindole (6) or its conjugate base, then the addition of an HOCl trap would influence the total yield of 6a and 6b but not their relative proportions. Such a change would only be observed if they were formed by the reaction of 6 with different chlorinating agents. The essentially complete disappearance of 6b when the reaction was carried out in the presence of phenoxide demonstrated that N-chloro-5-nitroindole (6a) was the product of a S_Ei reaction of OCl^- with 6. Indole 6b was then derived from the reaction of 6 or its conjugate base with HOCl. Our results do not unambiguously rule out either possibility.

The chlorination of 5-methoxyindole was also carried out in the presence of phenol. Definite conclusions could not be drawn because the products were unstable and the results could not be reproduced. These factors also complicated mechanistic study of 2 and 3 at different pH values. The data in Table 2 indicate that at low pH 2 and 3 reacted with HOCl in a S_E2 process. This process was slower at high pH and when electron-withdrawing substituents were introduced.

We propose that indoles can react, in a pH independent process, with OCl^- to give N-chloroindoles. This reaction was favored by electron-withdrawing substituents and high pH (low equilibrium concentrations of HOCl). Competing with this process was a S_E2 reaction between indole or its conjugate base and HOCl which produced 3-chloroindole. In the presence of excess NaOCl, the 3-chloroindole was converted to its N-chloro derivative. Formation of N-chloroindole via this process can not be ruled out. The S_E2 reaction was favored by electron-donating substituents and low pH (high equilibrium concentrations of HOCl). The products observed were a function of substituent, pH and stability of the initially formed products or intermediates.

This is the first study which has indicated that indoles can undergo N-substitution by a S_Ei process.

ACKNOWLEDGEMENT

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EXPERIMENTAL

Infrared spectra were taken on a Perkin-Elmer 567. A Varian T-60 and a Varian XL-100 were used for recording ^1H NMR spectra. Elemental analyses were carried out by Dr. F. Pascher, Mikroanalytisches Laboratorium, Bonn, W. Germany. Melting points were taken on a Fisher-John hot stage and are uncorrected. Solutions of NaOCl were prepared by passing Cl_2 through a solution of NaOH and the solutions were ca. 1.2 M and pH 13. Prior to use, 10% HCl was added to the NaOCl solution to adjust the pH to the appropriate value. Indole (1), 5-methoxyindole (2), 5-methylindole (3), 5-bromoindole (4), and 5-cyanoindole (5) were obtained from Aldrich Chemical Co. and used without further purification. 5-Nitroindole (6) was used as is in the chlorination studies but samples used to prepare 3-chloro-5-nitroindole (8) were dissolved in ether, filtered to remove a small amount of insoluble material and the solvent removed under reduced pressure.

Chlorination of Indoles: Indole to NaOCl Ratio of 1:3

To 10 ml of a 0.08 M solution of indole, there was added 2.0 ml of 1.2 M NaOCl at pH 9.4 and the mixture was stirred in the dark at 25° C. Yields were determined iodometrically. The Dead-Stop method was used to determine yields for indoles (3-6). Solvents used, reaction times and yields are summarized in Table 1.

Chlorination of Indoles: Indole to NaOCl Ratio of 10:1

A solution containing 0.76 mmol of indole in 10.0 ml of CH_2Cl_2 was combined with 10.0 ml of H_2O containing 0.076 mmol of NaOCl at pH 9.4 ± 0.2 . This mixture was shaken for 60 sec in a separatory funnel, a 3.0 ml aliquot of the aqueous layer was removed and under nitrogen, was titrated by the Dead-Stop method with a 0.01 N $\text{Na}_2\text{S}_2\text{O}_3$ solution. Using this technique and a microburet, volumes of $\text{Na}_2\text{S}_2\text{O}_3$ used in duplicate titrations varied ± 0.05 ml and yields varied $\pm 3\%$ (Table 2).

Chlorination of Indoles: Chlorination in the Presence of Phenol

To 81.6 mg (0.50 mmol) of 5-nitroindole (6) in 5.0 ml of CH_2Cl_2 , there was added 5.0 ml of H_2O and 0.53 ml (6.0 mmol) of phenol. This stirred mixture was cooled in an ice-bath. The ice-bath was removed and 16 ml (15.0 mmol) of NaOCl added and stirred for 60 sec. The organic layer was separated, diluted to 10.0 ml in a volumetric flask with CH_2Cl_2 , dried over K_2CO_3 and a 1.0 ml aliquot was titrated by the Dead-Stop method. Indole 6 reacted to the extent of 15% and under the same conditions indole 2 reacted only 2%. When 6 was reacted for 10 min under the above conditions, there was obtained a 75% yield of a species whose ^1H NMR spectrum indicated it was essentially pure (C3H/C4H ratio equal to 1) N-chloro-5-nitroindole (6a). The ^1H NMR spectrum was obtained after adding 0.5 ml of hexachlorobutadiene to the CH_2Cl_2 solution containing 6a and the CH_2Cl_2 removed under reduced pressure.

REFERENCES AND NOTES

1. Taken in part from the Tesis Especial de Grado of M. R. Fernandez.
2. M. De Rosa and J. L. Triana Alonso, J. Org. Chem., 1978, 43, 2639 and M. De Rosa, L. Carboognani and A. Febres, J. Org. Chem., 1981, 46, 2054.
3. R. J. Sundberg, "The Chemistry of Indoles", Academic Press, New York, 1970, pp 19-31 and pp 33-39.
4. G. Yagil, Tetrahedron, 1967, 23, 2855.
5. 5-Nitroindole-1,3-d₂ prepared with 95% deuterium incorporation at C-3 (¹H NMR) by procedure previously used for tritiation.^{6a}
6. (a) B. C. Challis and E. M. Millar, J. Chem. Soc., Perkin Trans. 2, 1972, 1111; (b) B. C. Challis and E. M. Millar, J. Chem. Soc., Perkin Trans. 2, 1972, 1625.
7. D. R. Pryde and F. G. Soper, J. Chem. Soc., 1931, 1510.
8. R. P. Mauger and F. G. Soper, J. Chem. Soc., 1946, 71.
9. P. B. D. de la Mare, "Electrophilic Halogenation", Cambridge Press, Cambridge, 1976, p 37.
10. I. Weil and J. C. Morris, J. Am. Chem. Soc., 1949, 71, 1664.
11. C. R. Edmund and F. G. Soper, J. Chem. Soc., 1949, 2942.
12. H. B. Charman, E. D. Hughes and C. Ingold, J. Chem. Soc., 1959, 2523 and J. March, "Advanced Organic Chemistry Reactions, Mechanisms and Structures", Third Ed., Wiley-Interscience, New York, 1985, p 513.
13. R. E. Dessy and F. Paulik, J. Chem. Educ., 1963, 40, 185 and references therein.
14. Treatment of 2 with SO₂Cl₂¹⁶ gave a 59% yield of 7, mp (dec) 80-85° C (pet. ether 30-60° C), ¹H NMR (CDCl₃) δ 3.85 (3H, s), 6.8-8.0 (4H, m). This product was extremely light sensitive and it was not possible to get an accurate elemental analysis.
15. Treatment of 6 with SO₂Cl₂¹⁶ gave a 48% yield of 8, mp 217-219° C, ¹H NMR (100 MHz, (CD₃)₂SO) δ 7.62 (H₇, d, J₆₇=9.1 Hz), 7.76 (H₂, d, J₁₂=3.0 Hz), 8.07 (H₆, dd, J₄₆=2.1 Hz, J₆₇=9.1 Hz), 8.38 (H₄, d, J₄₆=2.1 Hz), 12.18 (NH, br). It had the correct elemental analysis.
16. G. Mazzara and A. Borgo, Gazz. Chim. Ital., 1905, 35, 320, 563.
17. F. G. Soper and G. F. Smith, J. Chem. Soc., 1926, 1582.

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