Studies of the Mechanism of Chlorination of Indoles. Detection of *N*-Chloroindole and 3-Chloro-3*H*-indole as Intermediates[1]

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N-Chloroindole was stable at low concentration and temperature in nonprotic solvents. It rearranged in alkaline alcoholic media to give 3-chloroindole. Iodometry was used to follow the rearrangement of *N*-chloroindole to 3-chloroindole. An induction period was observed prior to a pseudo-first-order process. The length of the induction period depended on the alcohol used and its proportion relative to *n*-hexane, the presence or absence of base, and traces of water. Addition of water during the rearrangement caused an increase in the apparent concentration of *N*-chloroindole. This indicated the formation of another intermediate capable of reacting with water to either regenerate *N*-chloroindole or form another species which can oxidize iodide ion. The anion of 3-chloroindole is proposed as the intermediate. In the absence of base the formation of a new intermediate which absorbed at 252 nm was observed. During its formation no change in the apparent concentration of *N*-chloroindole could be detected by iodometry. 3-Chloro-3*H*-indole is proposed as this new intermediate. Addition of base caused the rapid disappearance of this band. A mechanism is proposed in which the induction period is seen as the establishment of an equilibrium between *N*-chloroindole, 3-chloro-3*H*-indole, and the conjugate base of 3-chloroindole.

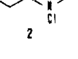
The chlorination of indole and its derivatives has been extensively studied.[3] Early workers used sulfuryl chloride to obtain 3-chloroindole and 2,3-dichloroindole.[4] Since then, besides this reagent,[5-7] others such as chlorine,[5,8-10] *N*,*N*-dichlorocarbamates,[11-14] *N*-chloroamines,[15] *N*-chlorobenzotriazole,[16] *N*-chlorosuccinimide,[5] phosphorus pentachloride,[5-7,17] *tert*-butyl hypochlorite,[16,18] and aqueous sodium hypochlorite[19,20] have been used to chlorinate indole and its derivatives. These procedures have yielded not only monochloroindoles,[5,7,9,10,15,17,20] but also polychloroindoles,[6,7,17] polychlorinated oxidized products,[5,8,11,15] and 3-chloroindolenines.[16,18,19] The chemistry of the latter group of compounds has been extensively studied.[16,18,19,21] Mono and polychlorinated indoles have also been prepared by indirect routes.[3a,6]

In 1972 the intermediacy of an *N*-chloroindole was suggested as a possibility in the chlorination of 2,3-dimethylindole with aqueous sodium hypochlorite.[19] This suggestion was analogous to the known intermediacy of *N*-chloroanilines in the chlorination of aniline derivatives.[22-24] Recently in a preliminary communication we presented the first evidence for the existence of an *N*-chloroindole as an intermediate in the chlorination of indole with aqueous sodium hypochlorite.[20] In this work the experimental details on the formation and stability of *N*-chloroindole are presented. A mechanism is proposed, based on kinetic and spectral data for the rearrangement of *N*-chloroindole to 3-chloroindole and also that under certain experimental conditions it is possible to detect the formation of 3-chloro-3*H*-indole. This appears to be the first instance in which this type of intermediate has been detected. The mechanism proposed is similar to the mechanisms previously proposed by others for the base-catalyzed hydrogen exchange of indoles and diazo coupling to indoles.[25,26]

Formation and Stability of *N*-Chloroindole

Stirring a solution of indole (1) in *n*-hexane, chloroform, or carbon tetrachloride with a freshly prepared solution of aqueous sodium hypochloride resulted in the formation of a light yellow solution containing an intermediate which oxidized iodide ion to iodine. The structure of the titrimetrically observed species could be that of either *N*-chloroindole (**2**) or 3-chloro-3*H*-indole (**3**).

N-Chloroamines[22] and 3-chloroindolenines[19] analogous to the above structures are known to oxidize iodide ion. Spectroscopic evidence previously presented conclusively demonstrated that the initially formed intermediate was **2**.[20] In another section of this work evidence will be presented for the subsequent formation of **3** from **2**.



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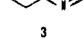

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The yields of **2** obtained varied between <80 and 92%. The highest yields were obtained using concentrations of starting indole (**1**) of 0.01 M and with the aqueous sodium hypochlorite prepared from fresh calcium hypochlorite. It was found that as the calcium hypochlorite aged, the yields of **2** progressively diminished. Solutions of **2** can be prepared in the range of 0.01 to ca. 0.06 M. Solutions of *N*-chloroindole (**2**) 0.01 M in *n*-hexane can be stored for more than 14 days at 0 °C with only a slight change in the amount of tritratable chlorine. This can be contrasted with solutions of **2** ca. 0.06 M in *n*-hexane in which no titratable chlorine was observed after 3 days.[27] Unidentified colored material and HCl vapors were produced when **2** decomposed. Concentrated solutions of this species were found to be light sensitive and solid material began to form on exposure to direct sunlight. In general dilute solutions of **2** were stable in aprotic solvents, but upon mixing with alkaline alcohol solutions rearrangement took place.

N-Chloroindole (**2**) rearranged in refluxing alkaline *n*-butyl alcohol to give a 75% yield of 3-chloroindole (**5**). It was more convenient to carry out the kinetic and spectral studies described below in methanol and *n*-propyl alcohol.

Kinetics

Iodometric titrations were used to follow the disappearance of **2** with time. The results of treating the reaction as a pseudo-first-order process are illustrated in Figure 1. As can be seen in this figure, regular kinetics were not observed throughout the whole course of the reaction. An induction period was observed prior to a pseudo-first-order process. During the induction period the apparent concentration of **2** was observed to increase ca. 5% after an initial rapid decrease.

The expression ln (*N*-chloroindole) is used to indicate the total concentration of all species containing titratable chlorine, since the titrimetic method employed in this study cannot differentiate between the *N*-chloroindole (**2**) originally present and any other intermediate formed during the reaction which can also oxidize iodide ion. The induction period was sensitive to the following factors: alcohol used and its proportion relative to that of *n*-hexane, presence or absence of an added base (potassium carbonate in this study), and traces of water. The

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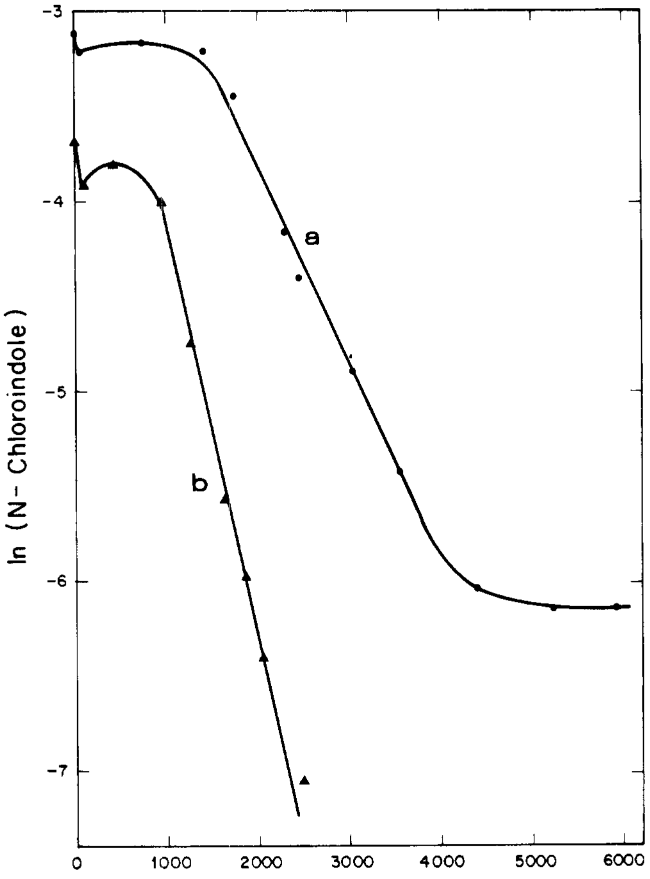


Figure 1. The rearrangement of *N*-chloroindole in *n*-hexane–*n*-propyl alcohol (6:1 v/v): (a) without base; (b) with 2 g of anhydrous potassium carbonate.

Table I. Effect on Solvent, Base, and Water on the Induction Period

Solvent mixture (v/v)	Base (K_2CO_3)	Water, mL	Induction period, s
n-Hexane–*n*-propyl alcohol (6:1)			1500
n-Hexane–*n*-propyl alcohol (6:1)	2 g		900
n-Hexane–*n*-propyl alcohol (6:1)		0.2[a,b]	8000
n-Hexane–methanol (1:6)			*c*
n-Hexane–methanol (1:6)	Sat.[d]		*e*
n-Hexane–methanol (50:1)			6000
n-Hexane–methanol (50:1)	Sat.[d]		*e*

[a] Water added to alcohol prior to start of the reaction. [b] This volume of water was soluble in the solvent mixture used. [c] Reaction took 104 h for the rate to level off. [d] Methanol saturated with anhydrous potassium carbonate prior to use. [e] Reaction too fast to measure (50 s).

changes in the induction period associated with variations in these factors are summarized in Table I.

The effect of adding water to a rearrangement run in *n*-hexane–*n*-propyl alcohol (6:1 v/v) with added base, after the pseudo-first-order process began, can be seen in Figure 2. The added water led to an apparent increase in the concentration of *N*-chloroindole.[29] This implied that another intermediate was formed during the reaction which can react with water to give either **2** or another species which also oxidized iodide ion. This was followed by a decrease in the rate of disappearance of **2**.

Another effect of added base can be noted in Figure 1. Only in the presence of added base does the reaction go to completion. Without added base the reaction went only to the extent of 4 half-lives and titratable chlorine was detected with little or no change for at least an additional 4 half-lives.

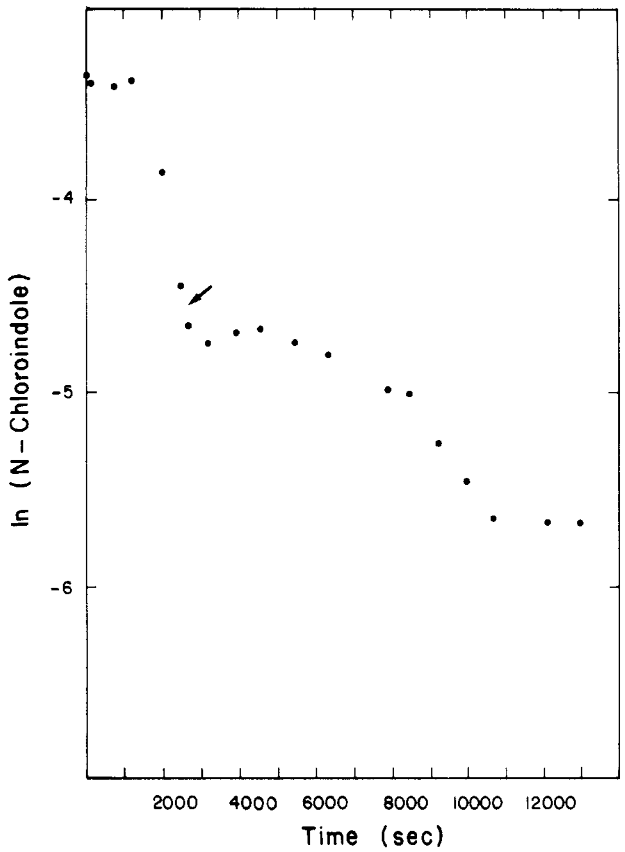


Figure 2. The rearrangement of *N*-chloroindole in *n*-hexane–*n*-propyl alcohol (saturated with potassium carbonate) (6:1 v/v), addition of 0.2 mL of water →.

It is clear from the kinetic data that the rearrangement of *N*-chloroindole was not a simple pseudo-first-order process. The data in Table I indicated that the induction period changes with both the nature and the proportion of alcohol used. Comparison of these results with those noted in Figure 2 for water indicated that the alcohol was also a reactant. The nature of the species which can react with water or alcohols will be discussed in a later section.

Spectral Studies

The conversion of *N*-chloroindole with a λ_{max} of 265 nm to 3-chloroindole which had a characteristic λ_{max} of 283 nm was observed in the UV when the reaction was run in *n*-hexane–*n*-propyl alcohol (6:1 v/v) with added base (Figure 3). For reactions run in other solvent mixtures and particularly in the absence of base this transformation was not as clearly defined. In these instances there appeared to be formed another species which could be detected as an unresolved broadening in the UV absorbance at lower wavelengths. When the rearrangement was run in *n*-hexane–*n*-propyl alcohol (1:6 v/v) in the absence of base, it was possible to detect the formation of a shoulder at 252 nm. This is illustrated in Figure 4. The shoulder was not detectable when base was present. Ultraviolet spectrum, Figure 4b, was obtained 300 min after the initiation of the reaction and did not change appreciably for at least an additional 60 min. Addition of potassium carbonate 360 min after the initiation of the reaction caused the complete disappearance of this shoulder and a shift in the observed λ_{max} to that of product. This can be seen in Figure 4.

The ultraviolet spectra indicated a pre-equilibrium prior to the formation of product. This was clearly demonstrated by the absence of a change in the spectra for an appreciable

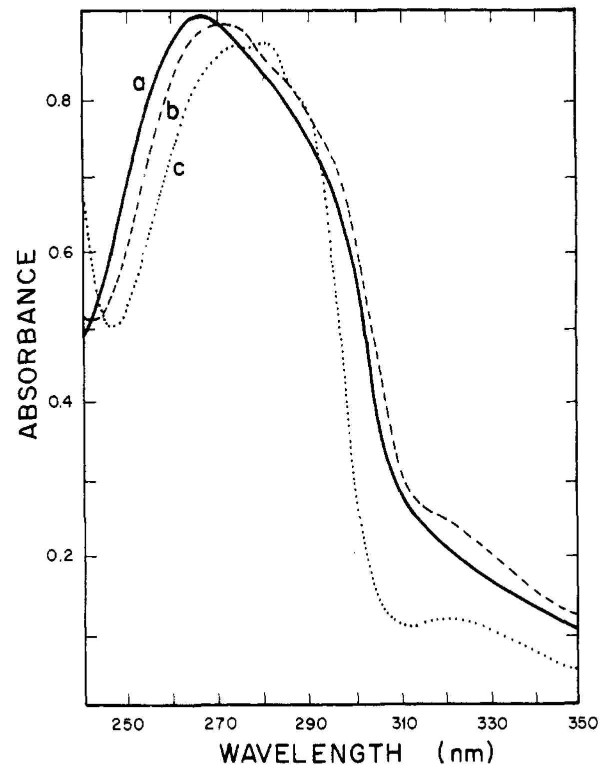


Figure 3. The rearrangement of *N*-chloroindole in *n*-hexane–*n*-propyl alcohol (6:1 v/v) with added base: (a) 3 min; (b) 5 min; (c) 60 min.

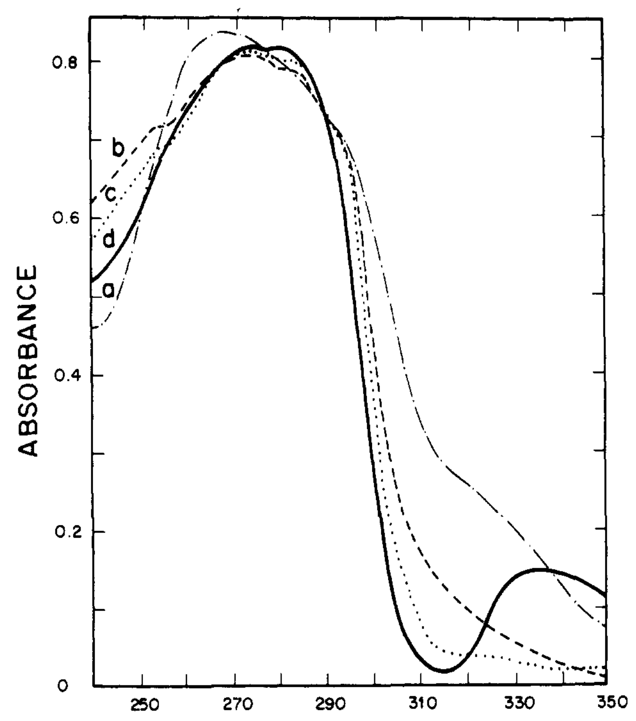


Figure 4. The rearrangement of *N*-chloroindole in *n*-hexane–*n*-propyl alcohol (1:6 v/v): (a) 15 min; (b) 300–360 min (potassium carbonate added at 360 min); (c) 370 min; (d) 390 min.

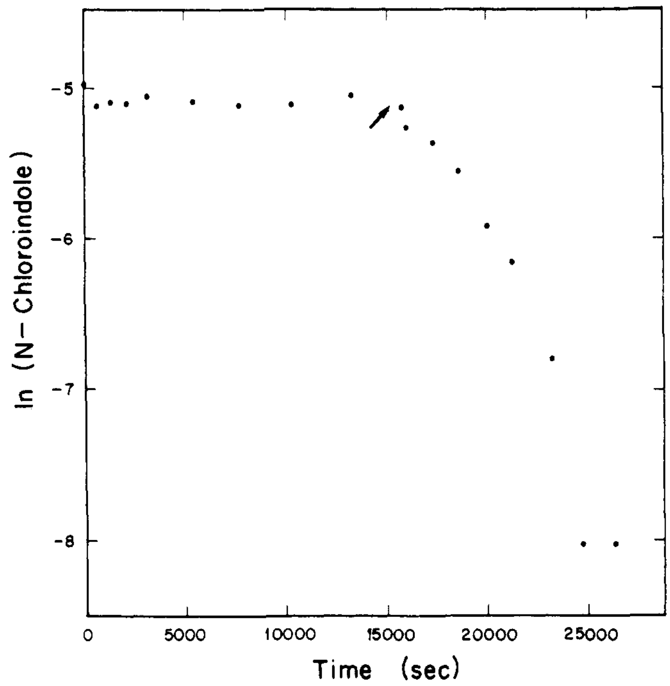


Figure 5. The rearrangement of *N*-chloroindole in *n*-hexane–*n*-propyl alcohol (1:6 v/v); addition of potassium carbonate →.

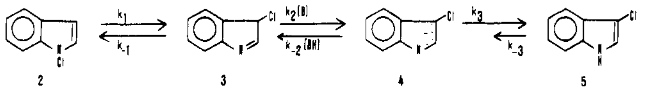
period of time. It can be seen by comparing the spectra in Figure 4 with the kinetic data in Figure 5 that the induction period, where little change was observed in the apparent concentration of *N*-chloroindole, corresponded spectrally to the formation of the shoulder at 252 nm and the equilibrium previously noted. The new species formed must also be capable of oxidizing iodide ion since during its formation, as observed by ultraviolet spectroscopy, no change was noted titrimetrically in the apparent concentration of **2**. The disappearance of the shoulder, observed by UV spectroscopy, corresponded to a drop in the apparent concentration of **2**. The spectral data indicated that **2** and the species absorbing at 252 nm must be interconvertible since no continuous conversion of **2** to this new species was noted.

Formation of yet another species can be observed by UV spectroscopy as a weak absorbance at 320–335 nm. This band can be observed in Figure 4a. In Figure 4b it can be noted that this absorbance has disappeared and the shoulder at 252 nm has formed. The conjugate bases of indoles have been reported to have weak absorbance in the region of 300–350 nm in the UV.[30] Indole (**1**) and 3-chloroindole (**5**) in *n*-hexane–*n*-propyl alcohol (1:6 v/v) in the presence of potassium carbonate formed detectable amounts of their conjugate bases and small peaks were observed at 332 and 327 nm, respectively. It is likely that the band detected at 320–335 nm was due at least in part to the anion of 3-chloroindole. The formation and disappearance of this band during the rearrangement would indicate that the anion of 3-chloroindole is an intermediate in the reaction.

Discussion

The kinetic and spectral data indicated the establishment of a pre-equilibrium which could involve at least three different species: N-chloroindole, the species absorbing at 252 nm, and an intermediate able to react with alcohol or water. It has been reported that in the chlorination of 2,3-dimethylindole with aqueous sodium hypochlorite 3-chloro-2,3-dimethylindolenine was formed.[19] This 3-chloroindolenine derivative was reported to oxidize iodide ion and had a λ_{max} of 266 nm (CH_2Cl_2) as opposed to a λ_{max} of 280 nm for 2,3-dimethylindole. Recently it was reported that the bromination of 2-ethanosulfonyl-3-methylindole with *N*-bromosuccinimide gave the *N*-bromo derivative which absorbed in the UV (EtOH) at 238 and 312 nm.[31] This compound can be converted to the corresponding 3-bromoindolenine which absorbed at 230 and 290 nm in the same solvent. Both compounds were reported to oxidize iodide ion. In general indolenines have

Scheme I



been reported to absorb lower than the comparably substituted indole.[32] The spectral data previously presented strongly indicated that the intermediate absorbing in the UV at 252 nm was 3-chloro-3*H*-indole. This intermediate, by analogy to the other haloindolenines previously noted, would be expected to oxidize iodide ion and its λ_{max} of 252 nm can be contrasted with a λ_{max} of 282 nm for 3-chloroindole (**5**) in the same solvent mixture and of 265 nm for *N*-chloroindole (**2**) in hexane. This is the first instance in which a 3-chloro-3*H*-indole, without further substitution at C-3, has been observed. Kinetic evidence previously presented indicated that a species was formed during the rearrangement reaction that can react with either the alcohol present or water. This species was most likely the conjugate base of 3-chloroindole (**5**). The conjugate base of **5** could react with an alcohol or water to give either 3-chloro-3*H*-indole (**3**) or 3-chloroindole (**5**). A proposed mechanism for the rearrangement of *N*-chloroindole (**2**) to 3-chloroindole (**5**) is summarized in Scheme I.

The induction period may be seen as involving an equilibrium between *N*-chloroindole, 3-chloro-3*H*-indole, and the conjugate base of 3-chloroindole.

This mechanism can be used to explain the observed changes in the induction period as summarized in Table I. The rise noted in the value of ln (*N*-chloroindole) during the induction period can be attributed to the reaction of **4** with the alcohol used to give **3** which was in equilibrium with **2**. Formation of 3-chloro-3*H*-indole (**3**) instead of the more stable **5** would then seem to be the kinetically favored process. The presence of base appeared to shift the equilibrium toward product due to the reduction in the hydrogen ion activity of the medium or because of base involvement in the rate-determining step; however, a combination of both effects is also probable. To obtain a rate expression, for the reaction in *n*-hexane–*n*-propyl alcohol (6:1 v/v) with added base, the steady state approximation was applied to **3**. This was reasonable based on the observation that the formation of this species was not observed by UV spectroscopy when the reaction was run under these conditions (Figure 3). When 3-chloroindole was dissolved in *n*-hexane–*n*-propyl alcohol (6:1 v/v) with added base, **4** could be detected by UV spectroscopy, but the formation of **3** could not be detected by either UV or iodometric analysis. This indicated that k_{-2} could be disregarded. The following rate expression was then obtained:

$$v = k_r[N\text{-chloroindole}]$$

$$k_r = \frac{k_1}{1 + \{(k_{-1})/k_2[\mathrm{B}]\}}$$

Least-squares treatment of the linear portion of Figure 1b gave a value of k_r of $1.8 \times 10^{-3}\ \mathrm{s}^{-1} \pm 0.2 \times 10^{-3}\ \mathrm{s}^{-1}$. The rate-determining step could be either the cleavage of the N–Cl bond, resulting in the formation of **3**, or the reaction of **3** with base to give **4**. The effect of added base on the reaction would seem to indicate that the latter was the rate-determining step. However, the effect of base on the hydrogen ion activity could also be a factor in the rate change observed. The heterolytic cleavage of the N–Cl bond, leading to the formation of **3**, could occur by two different processes: formation of an indoyl anion and chloro cation or formation of a nitrenium ion and chloride ion. Recent work indicated that 3-bromoindolenines could dissociate to give either a bromo cation or a bromide anion.[31] At present there is not enough evidence to determine which was the preferred mode of cleavage. Kinetic studies on the base-catalyzed hydrogen exchange reactions of [3-^{2}H$_1$]- and [3-^{3}H$_1$]indoles[25] and the base-catalyzed diazo coupling to indoles[26] have appeared. An A-S$_E$2 mechanism has been proposed in these reactions. The reaction scheme proposed in this work is similar to those put forward in the above instances both with respect to the intermediates proposed and the kinectic expression for k_r.

Further studies are in progress on the influence of base on the rearrangement and the direction of heterolysis of the N–Cl bond.

Experimental Section

Infrared spectra were taken on a Perkin-Elmer 567 spectrophotometer and ultraviolet spectra with a Cary 15 spectrophotometer or with a Beckman DB-G with an external recorder. A Varian T-60 instrument was used for recording ^{1}H NMR spectra. Kinetic studies were conducted in a Masterline 2160 constant temperature bath at 30 ± 0.1 °C. Melting points were taken on a Fisher-Johns hot stage and are uncorrected. Indole (Aldrich Gold Label 99%) was used as is. The methanol and *n*-propyl alcohol used in the kinetic and spectral studies were dried prior to use by distilling from magnesium turnings under a static blanket of dry nitrogen.

Aqueous Sodium Hypochlorite Solutions. In a 250-mL flask there was combined 100 mL of water and 1.5 g of calcium hypochlorite (70%, HTH) with stirring until all the solid was dissolved or suspended; to this there was added 4 g of anhydrous sodium carbonate, with stirring for 10 min, and the solution was filtered under suction to remove the calcium carbonate precipitate. This solution was prepared fresh prior to use and gave maximum yields of **2** when 0.01 M of **1** was used. A solution of sodium hypochlorite prepared as above but utilizing 10 g of calcium hypochlorite and 20 g of sodium carbonate in 100 mL of water was used to prepare more concentrated solutions of **2**.

***N*-Chloroindole (2).** To a vigorously stirred solution containing 0.117 g (1.0 mmol) of indole in 100 mL of *n*-hexane there was added 25 mL of freshly prepared sodium hypochlorite solution and 25 mL of water. This mixture was stirred for 3 h at 0 °C and then the organic layer was separated, dried over anhydrous potassium carbonate, and analyzed iodometrically. Solutions were thus obtained which contained 90–92% of *N*-chloroindole (**2**): IR (*n*-hexane) no NH or C=N, 1210, 945, and 730 cm^{-1} (broad); NMR (*n*-pentane) δ 6.49 (1 H, d, C(3)H, J = 3 Hz), and 6.81–7.68 (m, 5 H, C(2)H and aromatic H); λ_{max} (*n*-hexane) 265 nm (log ϵ 3.72). This procedure gave the optimum yields of **2**. *N*-Chloroindole can be prepared in concentrations of ca. 0.06 M using 100 mL of a more concentrated sodium hypochlorite solution but the yields were lower (<80–83%).

3-Chloroindole (5). To a flask containing 250 mL of *n*-butyl alcohol and 5 g of anhydrous potassium carbonate there was added 4.7 mmol of *N*-chloroindole in 250 mL of *n*-pentane. The solution was heated to distill off the *n*-pentane and then refluxed for 60 min. At the end of this time no active chlorine was detectable. The alcohol was removed under reduced pressure and water and chloroform were added to the residue. The layers were separated and the aqueous phase was extracted with chloroform. The combined fractions were dried with potassium carbonate, filtered, and reduced in volume; the residue was deposited on 2 g of silica gel 60 (70–230 mesh). This was placed on top of a previously prepared column containing 100 g of silica gel 60 and eluted with chloroform; the first 200 mL of eluent contained the product. The residue was recrystalized from petroleum ether (40–60 °C) to give a 75% yield of 3-chloroindole: mp 90–92 °C dec (lit.[4] mp 91.5 °C); IR (KBr) 3415, 1460, 750, 745 cm^{-1}; NMR (CDCl$_3$) δ 7.03–7.73 (m, 5 H, C(2)H and aromatic H).

Kinetics. The kinetics of the rearrangement were followed under anhydrous conditions. Dry nitrogen was obtained by passing nitrogen gas through two columns in series: the first contained silica gel (with an indicator) and the second molecular sieve (Linde 4 Å). Solutions of **2** in *n*-hexane were dried by passing them through a column of anhydrous potassium carbonate (dried for 24 h at 120 °C) into a two-necked flask fitted with a rubber septum. This was carried out in a glove bag in an atmosphere of dry nitrogen. Solutions of **2** in *n*-hexane and the alcohol to be used were thermostated to a temperature of 30 ± 0.1 °C and introduced into a flame-dried three-necked flask, through which nitrogen was passing, with oven dried syringes. Aliquots were removed with calibrated 5.0-mL (±2%) syringes and added to 20 mL of ethanol–acetic acid (1:1 v/v) containing 2 g of potassium iodide. The liberated iodine was titrated with a standardized solution of sodium thiosulfate and the end point was determined visually.

Spectral Studies. The solution of 2 in *n*-hexane was mixed with the appropriate alcohol under dry conditions and then quickly diluted with the same solvent mixture. Spectra were run at room temperature.

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References and Notes

(1) Accepted for presentation in part at the 174th National Meeting of the American Chemical Society, Chicago, Ill., August 1977.

(2) From the Tesis Especial de Grado of J. L. Triana Alonso submitted in partial fulfilment of the degree requirements for the Licenciatura degree, Universidad Simón Bolivar, 1976.

(3) For recent reviews on the chlorination of indole and its derivatives see: (a) J. C. Powers in "Indoles", Part II, W. J. Houlihan, Ed., Wiley-Interscience, New York, N.Y., 1972, pp 137–39 and 155–59; (b) R. J. Sundberg, "The Chemistry of Indoles", Academic Press, New York, N.Y., 1970, pp 14–17.

(4) G. Mazzara and A. Borgo, *Gazz. Chim. Ital.*, **35**, 320, 563 (1905).

(5) J. C. Powers, *J. Org. Chem.*, **31**, 2627 (1966).

(6) G. M. Brooke, R. D. Chambers, W. K. R. Musgrave, R. A. Storey, and J. Yeadon, *J. Chem. Soc., Perkin Trans. 1*, 162 (1976).

(7) M. Kunori, *Nippon Kagaku Zasshi*, **81**, 1431 (1960); *Chem. Abstr.*, **56**, 3441 (1962).

(8) J. Bergman, *Acta Chem. Scand.*, **25**, 2865 (1971).

(9) G. Pappalardo and T. Vitali, *Gazz. Chim. Ital.*, **88**, 1147 (1958).

(10) R. Weissgerber, *Chem. Ber.*, **46**, 651 (1913).

(11) R. J. Bass, *Tetrahedron*, **27**, 3263 (1971).

(12) J. M. Muchowski, *Can. J. Chem.*, **48**, 422 (1970).

(13) T. A. Foglia and D. Swern, *J. Org. Chem.*, **33**, 440 (1968).

(14) P. Chabrier, *Ann. Chim. (Paris)*, **17**, 353 (1942).

(15) V. Snieckus and M. S. Lin, *J. Org. Chem.*, **35**, 3994 (1970).

(16) R. J. Owellen, *J. Org. Chem.*, **39**, 69 (1974).

(17) S. Gabriel, W. Gerhard, and R. Wolter, *Chem. Ber.*, **56B**, 1024 (1923).

(18) (a) R. J. Owellen and C. A. Hartke, *J. Org. Chem.*, **41**, 102 (1976), and references cited therein; (b) A. Walser, J. F. Blount, and R. I. Fryer, *J. Org. Chem.*, **38**, 3077 (1973).

(19) P. G. Gassman, G. A. Campbell, and G. Mehta, *Tetrahedron*, **28**, 2749 (1972).

(20) M. De Rosa, *J. Chem. Soc., Chem. Commun.*, 482 (1975).

(21) For a recent example in the area of indole alkaloids see E. Wenkert, J. S. Bindra, C. J. Chang, D. W. Cochran, and D. E. Rearick, *J. Org. Chem.*, **39**, 1662 (1974). See also ref 16 for other leading references.

(22) D. F. Paul and P. Haberfield, *J. Org. Chem.*, **41**, 3170 (1976).

(23) P. G. Gassman and G. A. Campbell, *J. Am. Chem. Soc.*, **94**, 3891 (1972).

(24) P. G. Gassman and G. A. Campbell, *J. Am. Chem. Soc.*, **93**, 2567 (1971).

(25) B. C. Challis and E. M. Millar, *J. Chem. Soc., Perkin Trans. 2*, 1111 (1972).

(26) B. C. Challis and H. S. Rzepa, *J. Chem. Soc., Perkin Trans. 2*, 1209 (1975).

(27) A similar relation between concentration and stability has been observed for certain *N*-chloroanilines.[28]

(28) D. F. Paul, Ph.D. Thesis, The City University of New York, New York, N.Y., 1968.

(29) Occasionally increases in the apparent concentration of 2 larger than illustrated in Figure 2 were observed.

(30) G. Yagil, *Tetrahedron*, **23**, 2855 (1967).

(31) T. Hino, M. Endo, M. Tonozuka, and M. Nakagawa, *Heterocycles*, **2**, 565 (1974).

(32) W. A. Remers, ref 3a, Part II, p 23.

Generation and Reactions of Halodifluoromethide Ions[1]

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Methyl chlorodifluoroacetate undergoes facile thermal decarbomethoxylation induced by the 1:1 lithium chloride/hexamethylphosphoric triamide complex (LiCl/HMPA). This ester decomposition generates either the chlorodifluoromethide ion or the chlorodifluoromethyllithium/hexamethylphosphoric triamide complex. The nucleophilic intermediate from this ester decomposition may be trapped upon decomposition of the ester in the presence of appropriate electrophilic reagents.

The increasing interest in organofluorine chemistry has resulted in the rapid development of methods for the introduction of fluorinated groups into organic molecules. One area which has received considerable attention in recent years is the generation and reactions of polyfluorinated carbanions.[2,3] Although a wide variety of fluorinated carbanions are known, halodifluoromethide ions have been considered to have no finite existence. The major contributors to this hypothesis are the investigations by Hine and co-workers[4-6] which indicate that the formation of difluorocarbene by either the action of a base upon halodifluoromethanes or the thermally induced decarboxylation of halodifluoroacetate ions is a concerted process not involving the intermediacy of halodifluoromethide ions. In addition, none of the numerous reports in the literature involving difluorocarbene generation via decarboxylation of alkali metal chlorodifluoroacetates present any concrete evidence to indicate the existence of halodifluoromethide ions as reaction intermediates.

In spite of the lack of evidence for the existence of halodifluoromethide ions in the literature, substituted difluoromethide ions which possess substituents that are good carbanion stabilizing groups have been demonstrated to exist as reaction intermediates. Treatment of difluoromethyl phenyl sulfone with sodium methoxide in methanol in the presence of thiophenoxide results in the formation of difluoromethyl phenyl sulfide via trapping of difluorocarbene by the thiophenoxide.[7] In this case, however, the formation of difluorocarbene is a two-step process involving an intermediate difluoromethide ion 1. The intermediacy of 1 in the

$$PhSO_2CF_2H \xrightarrow[MeOH]{NaOMe} PhSO_2CF_2^- \rightarrow PhSO_2^- + :CF_2$$

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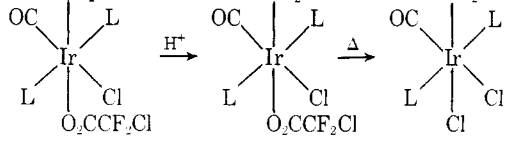
formation of carbene is indicated by the observation that the sulfone undergoes deuterium exchange much more rapidly than it consumes thiophenoxide. Evidence for a metal-stabilized difluoromethide ion has been reported in the literature recently.[8] Refluxing sodium chlorodifluoroacetate and $IrCl(CO)(PPh_3)_2$ in diglyme resulted in the isolation of either of two difluoromethyl complexes. The formation of these complexes was taken as evidence for the intermediacy of the metallocarbanion 2.



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