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The use of an electrophile carrier to determine the number of intermediates in the chlorination of 1-methylpyrrole

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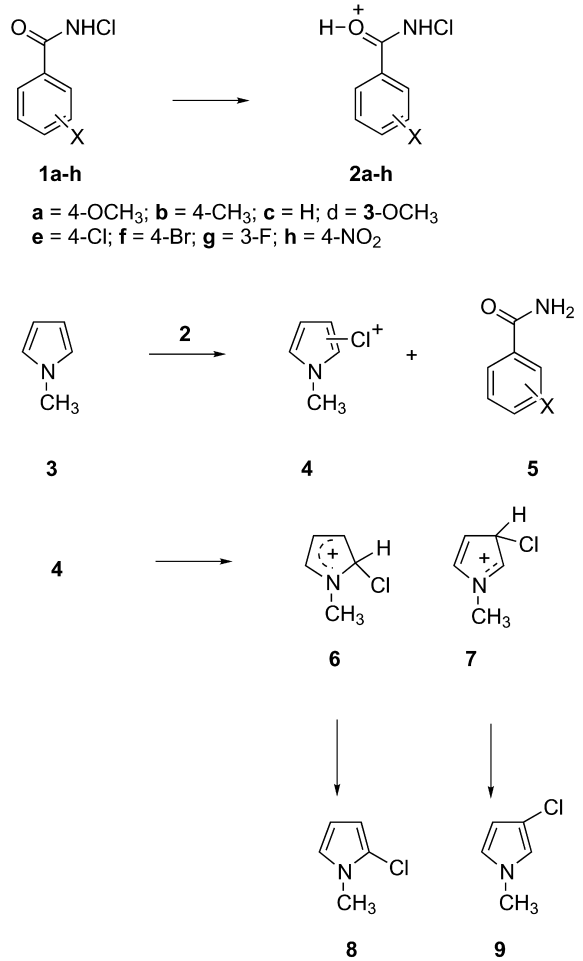
Abstract—A kinetic and product study of the dichloroacetic acid catalyzed chlorination of 1-methylpyrrole with 3- and 4-substituted *N*-chlorobenzamides was carried out. Protonated *N*-chlorobenzamides served as carriers of CI^+. A Hammett correlation was obtained with $\rho=-0.68$ ($r=0.98$, $n=8$). General acid catalysis was observed with $\alpha=0.48$ ($r=0.99$ and $n=7$). The yields of 2-chlorination ($84\pm0.7\%$) and 3-chlorination ($2.6\pm0.4\%$) were essentially constant (constant intramolecular selectivity) as the substituent on the *N*-chlorobenzamide was varied. Observation of constant intramolecular selectivity indicated that two intermediates were formed during the acid catalyzed chlorination of 1-methylpyrrole with *N*-chlorobenzamides. The carrier method is applicable to all types of aromatic systems and limited only by the availability of suitable carrier molecules.

Electrophilic aromatic substitution is one of the most studied reactions in organic chemistry.[1] In spite of this there still exist controversies over the number and/or the nature of the intermediates formed in this reaction. The generally accepted mechanism is an AES_E2 process in which the rate determining step is usually the attack of the electrophile to give a σ-complex which upon deprotonation gives the product.[2] It has also been suggested that the transition state is variable and early transitions states are 'π-complex like' and late transitions states are 'σ-complex like'.[2,3] Early transition states resemble starting materials' and have been described as oriented π-complexes.[4] Solution studies have appeared presenting evidence for[5] and against[6] the initial formation of a π-complex. Other workers have proposed that the initially formed intermediate is an encounter pair[7] or that electron transfer occurs and an ion radical pair is formed.[8]

In previous solution studies the electrophilicity of the attacking reagent has been varied either by changing the solvent or the structure of the electrophile.[9] An alternative approach is a system in which the electrophile is completely transferred to the ring from an electrophile carrier molecule.[10] Changes in the structure of the carrier would be reflected in the rate of formation of the π-complex (or initial intermediate) but not in the subsequent step (σ-complex formation) where the carrier would no longer be part of the activated complex. Experimentally, what



Scheme 1.

Keywords: pyrroles; electrophilic aromatic substitution; chlorination; mechanism.

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would be expected is that as the substituent is varied, the rate of reaction would change but not the isomer ratio (intramolecular selectivity) since the same π-complex (or initial intermediate) would be formed irrespective of the nature of the substituent present on the carrier molecule. This point is illustrated in Scheme 1 for the acid catalyzed chlorination of 1-methylpyrrole with a series of 3- and 4-substituted *N*-chlorobenzamides.

To our best knowledge the only comparable studies are those by Pearson and Olah on the transfer nitration of benzene and toluene with substituted *N*-nitropyridinium and quinilinium ions.[11] Essentially constant intramolecular selectivity was observed for toluene, but only a limited number of different substituents were used in the study. Scott studied the acid catalyzed chlorination of anisole with three *N*-chloroacetanilide derivatives.[12] Constant intramolecular selectivity (*ortho*/*para* ratio) was found. The authors suggested that this was observed because the ρ values for formation of the *ortho* and *para* isomers were identical or equal to zero. In light of the discussion above the results of this study can be reinterpreted as one in which the conjugate acids of *N*-chloroacetanilides were acting as carriers of 'CI^+' and this was the reason why constant intramolecular selectivity (*ortho*/*para* ratio) was observed.

In a preliminary study the chlorination of 1-methylpyrrole (**3**) with *N*-chlorobenzamide (**1c**) was found to be catalyzed by dichloroacetic acid (DCA).[13] Protonated *N*-chlorobenzamide served as a carrier of 'CI^+'. A kinetic isotope effect of 5.19±0.19 was observed and from this it was concluded that deprotonation of the σ-complex was the rate determining step. This was the first reported example of a rate determining proton transfer during electrophilic aromatic substitution in pyrroles. In the present study the chlorination with a series of 3-and 4-substituted *N*-chlorobenzamides has been carried out. Evidence is presented in this paper for the formation of two intermediates during the chlorination of 1-methylpyrrole with *N*-chlorobenzamides. It is proposed that a carrier reaction can be used to determine the number of intermediates formed during electrophilic aromatic substitution.

1. Results and discussion

The DCA catalyzed chlorination of 1-methylpyrrole (**3**) with a series of 3-and 4-substituted *N*-chlorobenzamides[14] was carried out at 40°C. Reactions were carried out under a nitrogen atmosphere. In the presence of air neither the kinetics nor the product yields were reproducible. No reaction was noted after 48 h under nitrogen when DCA was not present. The kinetics of the reaction were studied, in most cases, by following the disappearance of the *N*-chlorobenzamide (NCB) by standard iodometric methods. *N*-Chlorobenzamides **1e** and **1h** were not very soluble and it was difficult to determine the end-point visually. An ion-selective electrode based analytical method was developed by us and used to follow their disappearance.[15] The order of reaction was determined by the method of initial rates and reactions were first order with respect to **3**, *N*-chlorobenzamide **1c** and dichloroacetic acid.[13] Similarly, in this study, the order with respect to *N*-chlorobenzamides **1a**, **e** and **h** was also found to be one. The rate expression is then:

$$\text{rate} = k_3[\text{NCB}][\mathbf{3}][\text{DCA}].$$

where k_3 is the third order rate constant. Kinetic studies were typically run under pseudo-first-order conditions with **3** and DCA in excess with respect to the NCB used and

$$k_{obs} = k_3[\mathbf{3}][\text{DCA}].$$

Linear plots were obtained for 98% disappearance of *N*-chlorobenzamide ($r \geq 0.995$). Results for the various kinetic runs are summarized in Table 1.

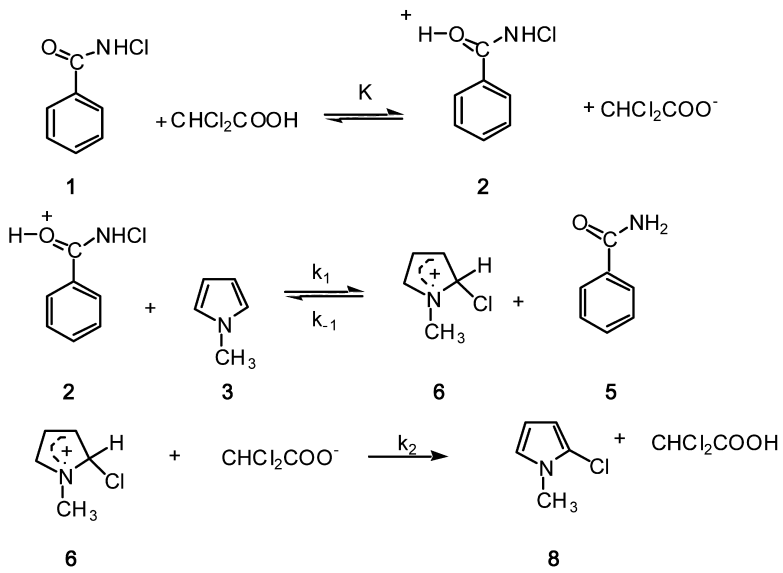
Table 1. Carboxylic acid catalyzed chlorination of 1-methylpyrrole with 3- and 4-substituted-*N*-chlorobenzamides

Product yields (%)[a]						
Substituent	log k_3	1MP[b]	2-Cl[c]	2,5-diCl[d]	3-Cl[e]	2+2,5
4-OCH_3	−1.543	14.5	72	11	2.5	83
4-CH_3	−1.856	14	73	12.5	2.5	85.5
H	−2.000	14	71	13	2	84
3-OCH_3	−2.088	13	70	14	3	84
4-Cl	−2.158	14	74	10	2	84
4-Br	−2.320	13	70	14	3	84
3-F	−2.260	13	72	12	3	84
4-NO_2	−2.612	13.5	73	11	2.5	84
Acid[f]	TCA[g]	MCA[h]	αCA[i]	PAA[j]	AA[k]	IBA[l]
log k_3	−1.886	−2.689	−3.430	−3.578	−3.529	−3.909

[a] Product studies carried out with a Pyrrole/NCB ratio of 1:1. Yields determined by percentage (%) area ratio and are ±0.5%.
[b] 1-Methylpyrrole
[c] 2-Chloro-1-methylpyrrole
[d] 2,5-Dichloro-1-methylpyrrole
[e] 3-Chloro-1-methylpyrrole
[f] Reaction of 1-methylpyrrole and *N*-chlorobenzamide.
[g] Trichloroacetic acid
[h] Monochloroacetic acid
[i] α-Chloropropionic acid
[j] Phenylacetic acid
[k] Acetic acid
[l] Isobutyric acid

The DCA catalyzed chlorination of **3** with *N*-chlorobenzamide **1c** gave a mixture of 2-chloro-1-methylpyrrole, 3-chloro-1-methylpyrrole and 2,5-dichloro-1-methylpyrrole. These products had been isolated and identified in a previous study and a similar analytical method was used in the present study.[13] Benzamide was recovered in 96% yield.

It is sometimes observed in multi-step reactions that changes in substituents can lead to either a change in the rate determining step or in the mechanism.[16] In these cases observation of a non-linear Hammett plot can be diagnostic.[16] A Hammett correlation was carried out by plotting log k_3 (third order rate constant) vs. σ (σ^+ was used for 4-OCH_3 and 4-CH_3). A straight line (r=0.98, n=8) was obtained with ρ=−0.68. No curvature was detected and therefore no change in the rate determining step or mechanism occurred as the substituent on the *N*-chlorobenzamide was varied. The observed value of ρ is the sum of the ρ's for the first two steps (where the benzamide ring is present in the activated complex) in the mechanism in Scheme 2. Interestingly the basicities of ring-substituted *N*-(2,2,2-trifluoroethyl)benzamides correlate best with σ^+.[17] Transfer of 'CI^+' would be expected to have a positive ρ as



Scheme 2.

does the deprotonation of anilinium ions.[16] This implies that the ρ for the first step has a larger absolute value than that for the second step and is therefore more sensitive to changes in the ring substituent.

Similar kinetics were obtained when the carboxylic acid catalyzing the reaction between 1-methylpyrrole and *N*-chlorobenzamide was varied (see Table 1). General acid catalysis was observed with α=0.48 (r=0.99 and n=7). Kinetically general acid catalysis can be the result of a combination of specific acid–general base catalysis[18] where a rapid protonation (pre-equilibrium) is followed by rate determining deprotonation. From Scheme 2 it can be seen that protonation of the NCB corresponds to the rapid pre-equilibrium and step 3 is the rate determining deprotonation which is expected to be base catalyzed. Base catalysis has been reported in several examples of electrophilic aromatic substitution in which a deuterium isotope effect was found.[19] Observation of general acid catalysis is consistent with rate determining deprotonation of the σ-complex in the chlorination reaction under study.[13] As indicated in Scheme 2 the most likely base is the carboxylate anion. The concentration of other species present that could act as potential catalytic bases (benzamide or pyrrole) varies as the reaction progresses. Linear kinetics would not be expected if either were acting as a base.

Chlorination at C-2 of the pyrrole ring leads to the formation 2-chloro-1-methylpyrrole and subsequently 2,5-dichloro-1-methylpyrrole. The total yield of attack at C-2 is therefore the sum of the yields of 2-chloro-1-methylpyrrole and 2,5-dichloro-1-methylpyrrole. From the results in Table 1 it can be seen that the yields (±standard deviation, n=8) of 2-chlorination (84±0.7%) and 3-chlorination (2.6±0.4%) were essentially constant. Constant intramolecular selectivity was observed in the DCA catalyzed chlorination of 1-methylpyrrole with substituted *N*-chlorobenzamides.

Isomerization, in acid, of 2-bromopyrroles to the thermodynamically more stable 3-bromopyrroles has been reported.[20] An analogous rearrangement of 2-chloropyrroles has not been reported. Results of calculations by Radom and co-workers would predict that a 2-chloropyrrole is less stable than a 3-chloropyrrole.[21] Therefore the possibility that the yields of 2- and 3-chloropyrroles were determined by thermodynamic factors was considered. Authentic 2-chloro-1-methylpyrrole was obtained by the chlorination of 1-methylpyrrole with SO_2Cl_2.[22] No rearrangement and/or decomposition was/were observed when a mixture of 2-chloro-1-methylpyrrole and DCA in chloroform was kept at 50°C for 2 h under a nitrogen atmosphere. Clearly the yields of chloropyrroles reported in Table 1 are kinetically determined.

Constant intramolecular selectivity could be the result of several other factors. One possibility was that acetyl hypochlorite was formed during the reaction and it was the chlorinating agent in all the reactions. Analogous proposals have been made to explain some of the carboxylic acid catalyzed reactions of *N*-haloacetanilides where acetyl hypohalites (formed in situ) have been proposed as the halogenating agents.[23,24] Acetyl hypochlorite decomposes to give CO_2 and other products.[25] The nitrogen gas used as the inert atmosphere was, after exiting the reaction vessel, passed through a solution of $Ba(OH)_2$ and no precipitation of $BaCO_3$ was detected. In contrast turbidity was detected in the $Ba(OH)_2$ solution when 1-methylpyrrole was reacted with an authentic sample of acetyl hypochlorite[26] under the same conditions as with *N*-chlorobenzamide. The gas chromatogram of the reaction of 1-methylpyrrole with acetyl hypochlorite showed a number of products that were not present when an *N*-chlorobenzamide was used as the chlorinating agent. These results eliminated the possibility that acetyl hypochlorite was formed during the reaction and confirmed that protonated *N*-chlorobenzamides were the chlorinating agents. Another possibility is that the ρ values for formation of the 2-chloro and 3-chloro isomers are identical or equal to zero.[12] It seems unlikely that this would be observed both in this study with pyrroles and by Scott[12] working with anisole.

Observation of constant intramolecular selectivity indicated

that two intermediates were formed during the acid catalyzed chlorination of 1-methylpyrrole with *N*-chlorobenzamides. If a single intermediate had been formed both the reaction rate and the product yields would have been expected to vary as the substituent on the *N*-chlorobenzamide was varied. The data obtained in this study showed only that two intermediates were present but did not indicate what was the nature of the initially formed intermediate. In the case of 1-methylpyrrole a π-complex is the most likely initially formed intermediate.

The carrier method used in this study makes no suppositions as to the velocity of the reaction or the nature of the initial intermediate. In two-step reactions, constant intramolecular selectivity would be expected regardless of the nature of the intermediate preceding the formation of the σ-complex. Therefore this is a general method applicable to all types of aromatic systems and limited only by the availability of suitable carrier molecules.

2. Experimental section

Infrared spectra were taken on a Perkin–Elmer 735-B instrument. A Varian T-60 and an XL-100 FT were used to record ^{1}H NMR spectra. Gas chromatography was carried out using a Hewlett-Packard HP-5830A or a HP-5840A using either a 6′×1/4″ 10% DEGS on Chromosorb Q 100/120 mesh or a 40 m×0.2 mm OV 101 on fused quartz. Melting points were taken on a Fisher-John hot stage and are uncorrected. Chloroform was washed with water, dried with $CaCl_2$ and stored over molecular sieve 5A under a nitrogen atmosphere. 1-Methylpyrrole was commercially available and distilled from zinc dust and stored over pellets of KOH. *N*-Chlorobenzamides[14] and acetyl hypochlorite[26] were prepared by literature procedures.

2.1. General kinetic method

Reactions were carried out at 40.0±0.1°C under an atmosphere of nitrogen which had been dried by successively passing it through concentrated sulfuric acid, KOH and $CaCl_2$ and then passed through dry chloroform. 1-Methylpyrrole and the *N*-chlorobenzamide were combined with chloroform and the reaction started by the addition of a previously thermostated solution of dichloroacetic acid in chloroform. The reaction was followed by titrating 1.00 mL aliquots of the reaction mixture by standard iodometric methods. In the case of *N*-chlorobenzamides **1e** and **1h** the solutions were too dilute to follow by this method and an ion-selective electrode method was used.[15]

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