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# REACTIONS OF ARYLCARBAMOYL CHLORIDES–II

## REACTION WITH AROMATIC AMINES

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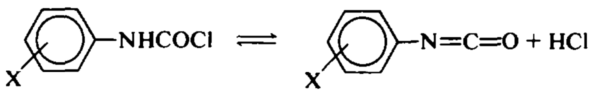
**Abstract**—The reaction of N-arylcarbamoyl chlorides with anilines in acetonitrile initially gives isocyanates, which can react with primary or secondary amines to give N,N-diaryl ureas. The rate of HCl elimination fits the Bronsted catalysis law with $\beta \approx 1$, suggesting that there is extensive proton transfer in the transition state. Plots of log k against $\sigma$ have $\rho \approx 0$ when the aryl substituent has a negative $\sigma$ and $\rho \approx 1$ when it has a positive $\sigma$ value. These observations and the kinetic deuterium isotope effect suggest that with electron attracting substituents, an initial proton transfer gives an ion pair which then loses chloride ion, but with electron releasing substituents, these steps become more concerted.

In an earlier paper we discussed the spontaneous elimination of HCl from N-aryl carbamoyl chlorides (1).[1] This paper discusses the mechanism of the reaction catalyzed by aromatic amines in acetonitrile. Carbamoyl chlorides could give products of either 1,2-elimination or substitution, but we find that the initial reaction is HCl elimination to give an isocyanate which can slowly give a diaryl urea by addition of a primary or secondary amine.



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### EXPERIMENTAL

The preparation and purification of the carbamoyl chlorides and some of the reagents has been described[1]. Most of the amines were commercial samples which were distilled before use, but some of the N,N-dimethyl anilines were prepared by methylating the aniline with $Me_2SO_4$, followed by treatment with $Ac_2O$ to remove primary and secondary amines.[2] N-Methyl-N-phenylcarbamoyl chloride was a commercial sample, m.p. 88–89° (Eastman-Kodak). The chemical purity of the carbamoyl chlorides was tested by quantitative hydrolysis in the presence of standard NaOH.

The reaction was followed spectrophotometrically by measuring the decreasing absorbance of the catalyzing aromatic amine as it is protonated by HCl eliminated from 1. A Gilford spectrophotometer with a water jacketed cell compartment was used.

Carbamoyl chlorides spontaneously eliminate HCl, and the reactions were followed by adding a known amount of the mixture of carbamoyl chloride and the accompanying HCl and the isocyanate in MeCN to the amine in MeCN, and following the absorbance with time. The absorbance extrapolated back to zero time allowed us to calculate the amount of HCl initially present and hence the initial concentration of carbamoyl chloride.

The second order rate constants were calculated using the integrated form of the rate Eq (1):

$$k = \frac{2{\cdot}3}{t(b-a)}\log\left\{\frac{a(b-x)}{b(a-x)}\right\} \qquad (1)$$

where a and b are the initial concentrations of carbamoyl chloride and amine, and x is calculated from the absorbance at various times. We verified that the absorbances followed the Beer–Lambert law. Despite the complexity of the calculations, this method gave good data; for example for the reaction of N-4-methoxyphenylcarbamoyl chloride ($1{\cdot}85 \times 10^{-4}$ M) and N,N-dimethyl-3-chloroaniline ($6{\cdot}15 \times 10^{-4}$ M) at 25·0° the second order rate constant $k = 26{\cdot}9 \pm 0{\cdot}1$ l. mole$^{-1}$ sec$^{-1}$ calculated using 12 data points obtained for up to 96% reaction. In a second test using the same reagents, the second order rate constants were calculated for 10 reactions in which the concentration of the carbamoyl chloride was varied from 0·88 to $1{\cdot}48 \times 10^{-1}$ M, and that of the amine from 5·07 to $7{\cdot}34 \times 10^{-4}$ M, and the mean of these 10 averaged values of $k = 27{\cdot}0 \pm 0{\cdot}3$ l. mole$^{-1}$ sec$^{-1}$.

All the rate constants are mean values obtained from 7–10 independent runs.

The kinetic deuterium isotope effect was calculated using the relation:

$$k_D = (k - C_H k_H)/C_D$$

(where $C_D$ and $C_H$ are the molar concentrations of the deutero and protio carbamoyl chlorides.) The isotopic purity of the carbamoyl chloride was determined by IR

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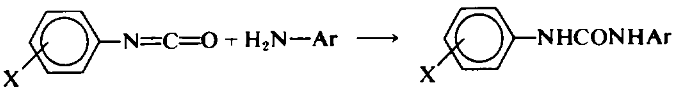
spectrophotometry using the N-H stretching frequency (3270 cm$^{-1}$) and the isocyanate asymmetric stretching frequency (2240 cm$^{-1}$). The second order rate constants for these reactions at 25·0° are given in Tables 1-3.

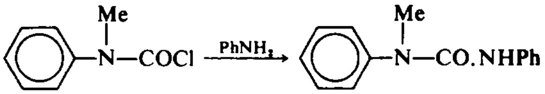
The product composition was determined using IR spectrophotometry for all the compounds. Except for one reaction, the initial products were the isocyanates even when primary or secondary amines were used, but in the presence of primary or secondary amines the initially formed isocyanates are converted slowly into the diaryl ureas.



Initial formation of an isocyanate was observed in the reactions of N-phenyl-N-4-methoxyphenyl- and N-4-chlorophenyl-carbamoyl chlorides with aniline, and 3-chloro-, N,N-dimethyl-, and N-methylaniline, and N-methyl toluidine.

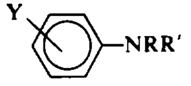
For the reaction of N-3-chlorophenylcarbamoyl chloride with N-methylaniline or N-methyltoluidine, the reaction of amine with isocyanate was too fast for our IR spectroscopic technique to detect formation of the isocyanate in the reaction of carbamoyl chloride and amine, although it is reasonable to assume that it was the initial product.

N-Methyl-N-phenylcarbamoyl chloride (**2**) was allowed to react with aniline in MeCN, and the IR spectra were examined on mixing and after 2 hr and 50 hr at room temp. There was no change in the spectra after 2 hr, but after



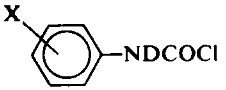
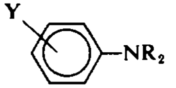
**2** **3**

Table 1. Second order rate constants for reaction of (I, X = 4-OMe; 3-Cl) with aromatic amines[a]

| | | | | | k, l. mole$^{-1}$ sec$^{-1}$ | |
|---|---|---|---|---|---|---|
| |  | | | $pK_a^b$ | | |
| Run | X | R | R' | | (I, X = 4-OMe) | (I, X = 3-Cl) |
| 1 | 4-OMe | Me | Me | 5·85 | 8890 | |
| 2 | 4-Me | Me | Me | 5·63 | 4310 | |
| 3 | 3-Me | Me | Me | 5·22 | 1880 | 5110 |
| 4 | H | Me | Me | 5·07 | 948 | 3390 |
| 5 | 4-Br | Me | Me | 4·23 | 76·6 | 218 |
| 6 | 3-Cl | Me | Me | 3·82 | 27·0 | 90·8 |
| 7 | H | Et | Et | 6·52 | 5920 | |
| 8 | H | nBu | nBu | 6·21 | 2850 | 8010 |
| 9 | H | H | Me | 4·89 | 452 | 1750 |
| 10 | H | H | H | 4·65 | 338 | 1290 |
| 11 | 3-Cl | H | H | 3·32 | 18·8 | 63·4 |
| 12 | 2,6-Me$_2$ | Me | Me | 5·30 | 497 | 1600 |

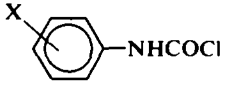
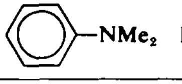
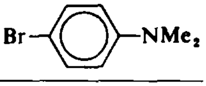
[a] At 25·0° in MeCN; [b] from Ref 3.

Table 2. Deuterium kinetic isotope effect[a]

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| |  | |  | | | k$_D$, l. mole$^{-1}$ sec$^{-1}$ | |
| Run | X | %D$^b$ | Y | R | $pK_a$ | | k$_H$/k$_D$ |
| 1 | 3-Cl | 79 | 4-Br | Me | 4·23 | 182 | 1·25 |
| 2 | 3-Cl | 74 | 3-Cl | Me | 3·82 | 73·4 | 1·34 |
| 3 | 3-Cl | 74 | 3-Cl | H | 3·32 | 45·7 | 1·61 |
| 4 | 4-OMe | 84 | 4-Br | Me | 4·23 | 60·0 | 1·35 |
| | | 88 | | | | 59·8 | 1·33 |
| 5 | 4-OMe | 80 | 3-Cl | H | 3·32 | 7·5 | 4·06 |
| | | 71 | | | | 8·5 | 4·39 |

[a] At 25·0° in MeCN; [b] from IR spectra.

Table 3. Structural effects upon the second order rate constants for reactions with tertiary amines[a]

|  |  | k, l. mole$^{-1}$ sec$^{-1}$ |  |
|---|---|---|---|
| X | $\sigma$ |  |  |
| 4-PhCH$_2$O | −0·41 |  | 83·1 |
| 4-MeO | −0·27 | 948 | 76·6 |
| 4-EtO | −0·24 | 894 |  |
| 4-Me | −0·17 | 1093 | 86·6 |
| 3-Me | −0·069 | 968 | 78·2 |
| H | 0·00 | 1035 |  |
| 3-MeO | +0·115 | 1221 | 101 |
| 4-Cl | +0·227 | 2347 | 166 |
| 3-Cl | +0·373 | 3386 | 218 |
| 3-NO$_2$ | +0·710 |  | 481 |
| 4-NO$_2$ | +0·778 |  | 451 |
| 2,6-Et$_2$ |  |  | 183 |

[a] At 25·0° in MeCN.

50 hr, the bands characteristic of the reactants; NH$_2$ stretch, 3450 and 3370 cm$^{-1}$; CO stretch of 2, 1750 cm$^{-1}$; NH$_2$ bend, 1640 cm$^{-1}$, had decreased, and new bonds due to N-methyl-N,N'-diphenylurea (3) had appeared at 3510 and 3600 cm$^{-1}$ (NH) and 1690 cm$^{-1}$ (CO). These observations indicate that amine attack upon the carbamoyl group is much slower than the elimination of HCl from N-arylcarbamoyl chlorides by aromatic amines.

## RESULTS AND DISCUSSION

*Nature of the reaction.* The initial reaction between a carbamoyl chloride and an amine is an elimination of HCl; and a diarylurea can be formed by subsequent reaction of a primary or secondary amine with the isocyanate.

*Substituent effects and amine reactivity.* The rate constants for N-4-methoxyphenyl- and N-3-chlorophenyl-carbamoyl chloride with amines fit the Bronsted catalysis relation between log k and $pK_a$ of the amine (Fig 1):

$$(\mathrm{I, 4\text{-}OMe}) \quad \log k = 1{\cdot}26\, pK_a - 3{\cdot}43 \qquad (2)$$

$$(\mathrm{I, 3\text{-}Cl}) \quad \log k = 1{\cdot}28\, pK_a - 3{\cdot}00 \qquad (3)$$

where the $pK_a$ values are for the amines in water at 25°.[3] There is a serious problem in calculating $\beta$ values using reaction rates in an aprotic solvent and amine dissociation constants in water. However there is a reasonably good linear relation between $pK$ values in MeCN and water for a large number of aliphatic, aromatic and heterocyclic amines.[4]

$$pK_a^{A} = 5{\cdot}33 + 1{\cdot}23 pK_a^{W}$$

(where $pK_a^{A}$ and $pK_a^{W}$ are values in MeCN and water respectively).

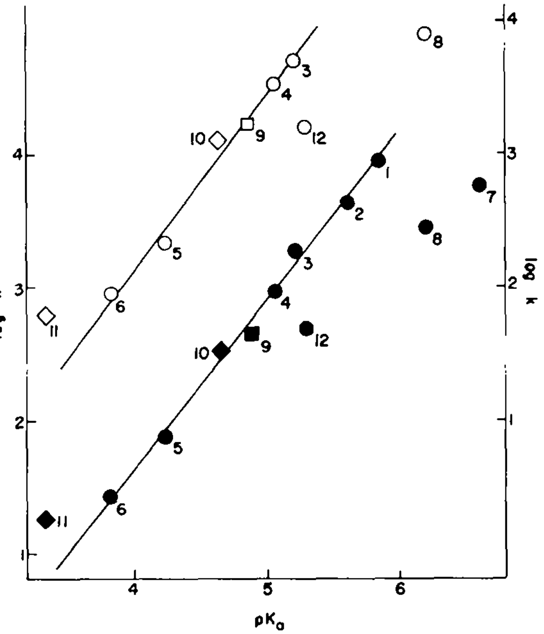
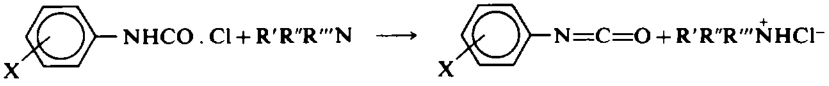


Fig. 1 Reaction of N-4-methoxyphenylcarbamoyl chloride (solid points) and N-3-chlorophenylcarbamoyl chloride (open points) with aromatic amines in MeCN 25·0°. ◊ ◆ primary; □ ■ secondary; ○ ● tertiary amines. The numbers refer to Table 1.

Therefore for both substrates, $\beta \approx 1$ if we use $pK_a$ in MeCN corrected for the solvent effect, suggesting that there is considerable proton transfer in the transition state. However sterically hindered amines are less effective catalysts than predicted by the linear free energy relations (2) and (3), suggesting that the amines are involved in the

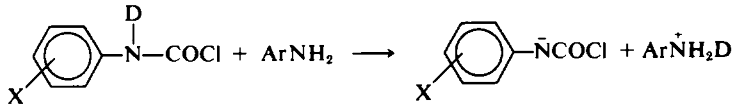


transition state rather than in an initial pre-equilibrium proton transfer giving free ions.

The Bronsted catalysis law is generally applied to reactions in aqueous solvents, and we do not place much reliance on the exact value of $\beta$.* In addition we note that nucleophilicity towards carbonyl carbon also often correlates well with basicity.[7]

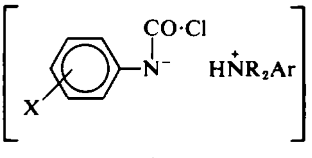
*Deuterium kinetic isotope effects.* The kinetic results suggest that there is no pre-equilibrium proton transfer between the amine and the carbamoyl chloride giving free ions. Had there been a rapid and reversible proton transfer between the amine and the carbamoyl chloride most of the deuterium in the latter should have been rapidly washed out because there was always greater than 5-fold excess of protium in the amine over deuterium in the carbamoyl chloride.

The values of $k_H/k_D$ range from *ca* 1·3 to *ca* 4·2 (Table 2), and are largest for reaction of the least acidic carbamoyl chloride (the 4-methoxy derivative) with the least basic amine (3-chloroaniline, $pK_a = 3{\cdot}32$). The lower values of $k_H/k_D$ are however lower than the value of $k_H/k_D = 1{\cdot}82$ which is the calculated secondary isotope effect for proton transfer, based on changes in stretching and bending vibrations.[8]



This calculated value uses the following frequencies experimentally determined (for PhNHCOCl and $PhNH_2^+HCl$) in MeCN: carbamoyl chloride; NH stretching 3270 cm$^{-1}$; NH bending, 1340 cm$^{-1}$, and for the anilinium ion, $\overset{+}{N}H$ stretching, 2170 cm$^{-1}$; and bending, 1470 cm$^{-1}$. These frequencies were measured using N-phenylcarbamoyl chloride, aniline and aniline hydrochloride in MeCN. Substituents should not markedly affect these values. The calculated value is based upon the frequencies of aniline hydrochloride, rather than those of an ion pair which would probably be formed by proton transfer, and H-bonding decreases hydrogen stretching frequencies, *cf* Ref 9.

There is no large primary isotope effect in reactions 1–4, (Table 2), and for these reactions it seems probable that an intimate ion pair (4) is a reaction intermediate, but that its formation does not give complete scrambling of the deuterium label although our results are consistent with partial scrambling, which could make the experimental values too low.



**4**

The situation is different for reaction 5, which shows an appreciable primary kinetic isotope effect. This observation is understandable because the acidity of the carbamoyl chloride and the basicity of the amine are low; so that the rate of proton loss should be reduced, but the rate of loss of chloride ion should be increased so that the two processes could become concerted and the proton loss be incomplete in the transition state, in other words we could be observing a classical E2 reaction without deuterium scrambling. This reaction of N-4-methoxy phenylcarbamoyl chloride with 3-chloro aniline is faster than predicted by the Bronsted relation (point 11 in Fig 1).

*Effect of structural changes in the carbamoyl chloride.* The striking rate retardation by N-methylation has already been noted. The effects of aryl substituents upon reactions of **1** with N,N-dimethylaniline and 4-bromo N,N-dimethylaniline are shown in Fig 2. For substituents having positive $\sigma$ values there is a good linear relationship between log k and $\sigma$, with:

$$\log k = 0{\cdot}86\sigma + 2{\cdot}03$$

but there is a sharp break at $\sigma \approx 0$, and for substituents having negative $\sigma$ values

$$\log k = 0{\cdot}84\sigma + 1{\cdot}92$$

for the reaction with 4-bromo-N,N-dimethylaniline. The $\rho$ values for reaction with N,N-dimethylaniline are very similar to those cited (Fig 2).

Sharp breaks of this type in Hammett plots are generally associated with changes of mechanism,[10] provided that the appropriate substituent constants are used (*cf* Ref 11*a*,*b*). We could therefore suppose that when the carbamoyl chloride contains an electron withdrawing substituent ($\rho \approx 0{\cdot}9$)

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*For discussions of the significance of this parameter in acid-base catalyzed reactions see Refs 5, 6.

the rate limiting step is loss of a proton, to give an intermediate (**4**) which rapidly breaks down to products. When the carbamoyl chloride contains electron attracting groups, and $\rho \approx 0$, an alternative mechanism could be followed in which proton and chloride loss are concerted, i.e., the mechanism is analogous to the classical E2 mechanism. (We have of course no evidence regarding the configuration of the transition state for this mechanism.)

In this mechanism, electron releasing substituents should assist loss of chloride ion, but hinder that of the hydrogen ion, and the large deuterium isotope effect in the reaction of N-4-methoxyphenylcarbamoyl chloride with 3-chloroaniline (Table 2) is consistent with a concerted mechanism.

The timing of bond making and breaking steps in $\beta$-eliminations has been discussed by many workers.[12,13]

We note that the situation for the reaction with amines is completely different from that for the spontaneous elimination of HCl where the equilibrium constants can be related to $\sigma^-$ (preceding paper).

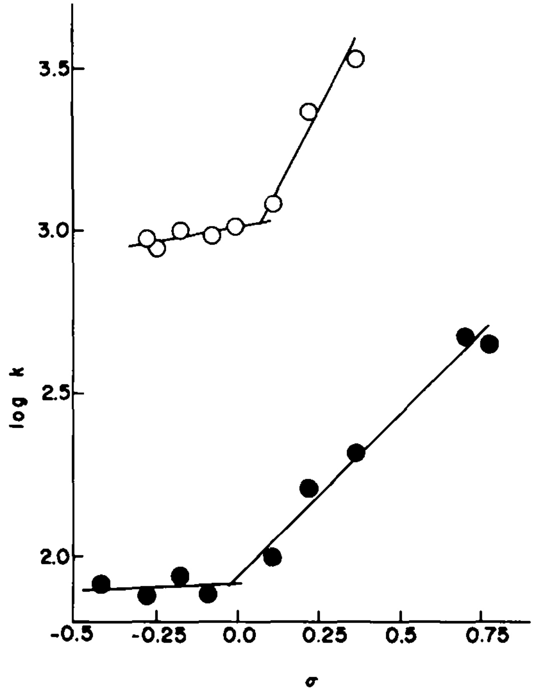
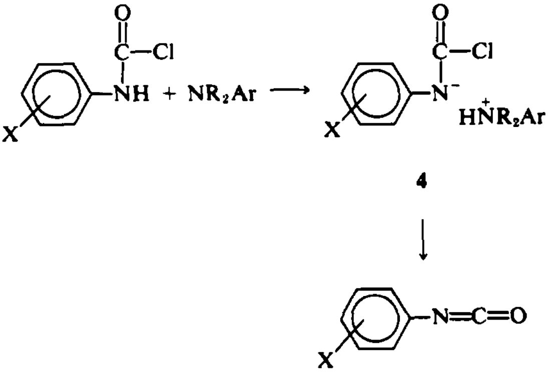


Fig 2. Reactions of N-arylcarbamoyl chlorides with N,N-dimethylaniline (open points) and N,N-dimethyl-$p$-bromoaniline (solid points).



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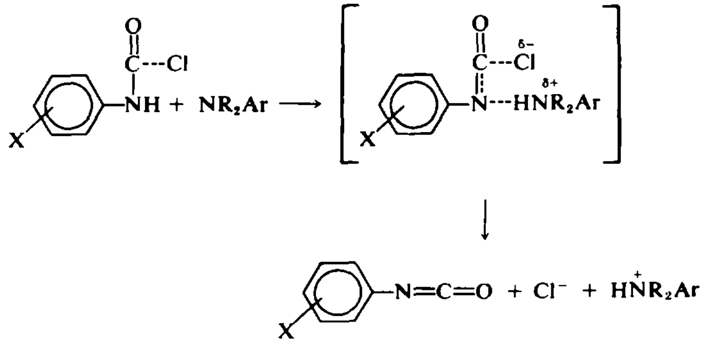

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