N ⟶ N′ Intramolecular Acyl Transfer in Acid Media for Alkylenediamine Derivatives

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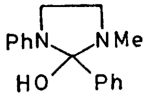
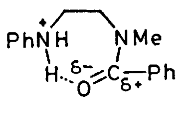
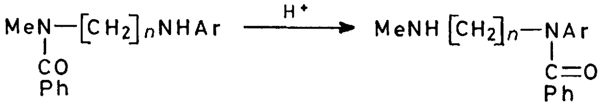
Intramolecular N ⟶ N′ benzoyl migrations in acid media at 25° are reported for *N*′-aryl-*N*-benzoyl-*N*-methylethylene- and trimethylene-diamine derivatives. Kinetic studies were performed on N ⟶ N′ benzoyl transfer for *N*-benzoyl-*N*-methyl-*N*′-phenylethylenediamine (1) in acid solutions over the H_0–pH range −2.28 to 2.30. The existence of a maximum in the pH–rate profile and chromatographic experiments provide evidence for a tetrahedral addition intermediate. Compound (1) undergoes acyl transfer to give *N*-benzoyl-*N*-phenyl-*N*′-methylethylenediamine (4) by a mechanism which involves the formation and rate-determining catalysed decomposition of the addition intermediate over the pH range 0.24—2.30. Below H_0 −0.54 the reaction involves the rate-determining formation of the intermediate and observed rate constants become pH independent. Some factors influencing the rearrangement such as the number of methylene groups, basicity of the attacking nucleophile, and importance of the *N*-methyl group, are analysed. Two reaction schemes are proposed to explain the results.

ALTHOUGH there exist precedents for N ⟶ N′ intramolecular acyl transfer in alkylenediamine derivatives in neutral or alkaline media,[1-3] there have been no reports of these reactions under acid conditions. Several N ⟶ O and N ⟶ S acyl migrations in acid media have been described, but this is the first report on acid catalysed N ⟶ N′ intramolecular acyl migrations observed for *N*′-aryl-*N*-benzoyl-*N*-methylethylenediamines (Scheme 1).


(I)


(II)

Kinetic studies were performed on the reaction of *N*-benzoyl-*N*-methyl-*N*′-phenylethylenediamine (1) in acid media, trying to elucidate the mechanism of the N ⟶ N′ benzoyl migration to give *N*-benzoyl-*N*-phenyl-*N*′-methylethylenediamine (4).* Compound (1) undergoes acid catalysed rearrangement by a mechanism which involves the formation and decomposition of a tetrahedral addition intermediate (I), and it is possible to demonstrate by kinetic methods that this intermediate is present under steady state conditions. In fact, this reaction exhibits a pH rate maximum (Figure 1)



$$\mathrm{MeN(COPh){-}[CH_2]_nNHAr \xrightarrow{H^+} MeNH[CH_2]_n{-}NAr(C{=}O)Ph}$$

	n	Ar		n	Ar
(1)	2	Ph	(4)	2	Ph
(2)	2	p-$NO_2C_6H_4$	(5)	2	p-$NO_2C_6H_4$
(3)	3	Ph	(6)	3	Ph

SCHEME 1

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* The base (4) when liberated from acid solution, appeared to be the same as that obtained by alkaline hydrolysis of 1,2-diphenyl-3-methylimidazolinium iodide.[1]

[1] B. Fernández, I. Perillo, and S. Lamdan, preceding paper.

[2] C. J. M. Stirling, *J. Chem. Soc.*, 1958, 4531.

[3] W. B. Wright, jun., H. J. Brabander, and R. A. Hardy, jun., *J. Org. Chem.*, 1961, **26**, 2120.

which can be explained by postulating a change in the rate-determining step from formation to decomposition of an addition intermediate.

The appearance of (4) was followed spectrophotometrically at 270 nm, and the reaction was found to be irreversible. Over the pH range 0.24—2.30 the reaction follows the rate law $v = k[(1)]a_{\mathrm{H}^+}$ in terms of protonated material and some typical results are shown in Figure 2. It is observed that the appearance of (4) is initially delayed (Figure 2, dashed lines). Then, the reactions become first order throughout and rate constants $[k_{\mathrm{obs}} = k_1k_2/(k_{-1} + k_2)]$ increase upon increasing the hydrogen ion concentration corresponding to an acid catalysed reaction (Table). Chromatographic experiments allowed the presence of an intermediate to be detected and showed that (1) is not completely converted to this intermediate during the initial rapid phase of the reaction (*i.e.* $k_{-1} \neq 0$). Thus, the shape of the curves in Figure 2 indicates that the reaction becomes first order after the equilibrium (1) $\rightleftharpoons$ (intermediate) has been attained.

Rate constants in the Table show that pH >1.15 rates are greater than first order with respect to hydrogen ion concentration and over the pH range 0.24—1.15 the rate is nearly accounted for by a reaction which is first order in $[\mathrm{H}^+]$. These results are interpreted according to the mechanism in Scheme 2 as follows. The intermediate is formed by intramolecular attack of the anilino-group at the protonated carbonyl group of the predominant *O*-protonated form of (1) and accumulates during the initial rapid phase of the reaction. This intermediate then undergoes an acid-catalysed decomposition to give the open product (4) during the subsequent slower phase. Possible intermediates which can account for our results are (I^+) and (I^{2+}). At pH values >1.15 decomposition occurs through both intermediates and then at pH values from 1.15 to 0.24 exclusively through the intermediate (I^{2+}). Thus, at high pH values where the intermediate (I^{2+}) contributes less, rates are greater than first order with respect to $[\mathrm{H}^+]$. As the hydrogen ion activity increases and larger amounts of (I^{2+}) accumulate, the dependence of the observed rate constants on $[\mathrm{H}^+]$ gradually decrease and finally become nearly first order over the pH range 0.24—1.15. In agreement, benzoyl migration was not observed in the uncatalysed reaction of (1) hydrochloride in water and the half-life for benzoyl transfer at pH 2.70 was estimated to be *ca.* 730 days. These results suggest

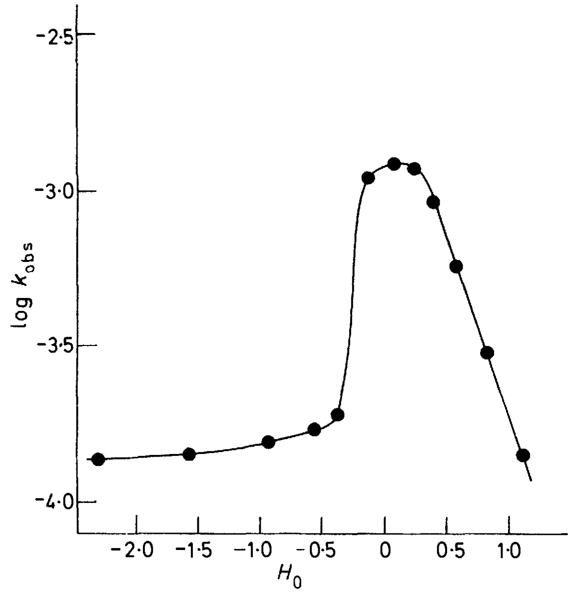


FIGURE 1 Dependence of observed rate constants at 25 °C on pH and H_0 for N $\longrightarrow$ N′ benzoyl migration in *N*-benzoyl-*N*-methyl-*N*′-phenylethylenediamine (1)

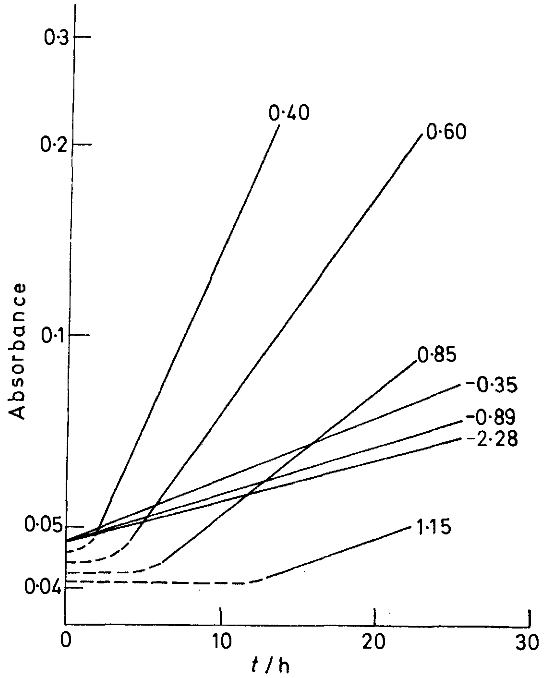


FIGURE 2 Experimental curves for N $\longrightarrow$ N′ benzoyl migration in the *N*-benzoyl-*N*-methyl-*N*′-phenylethylenediamine (1), in acid media from pH 1.15 to H_0 −2.28 at 25 °C

TABLE 1

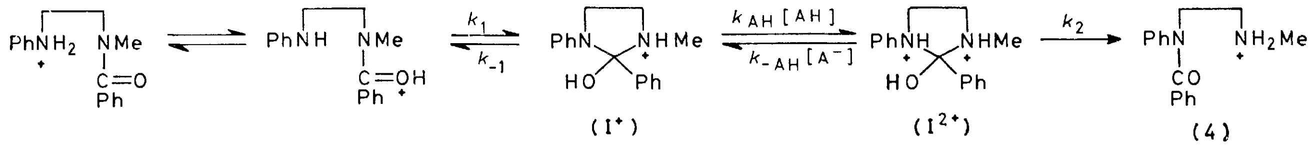
Rate constants and half-lives for benzoyl migration in *N*-benzoyl-*N*-methyl-*N*′-phenylethylenediamine in acid media at 25 °C

$-\log a_{\mathrm{H}^+}$	$k_{\mathrm{obs.}}/\mathrm{min}^{-1}$	$-\log k_{\mathrm{obs.}}$	$t_{1/2}$
2.30	4.4×10^{-6}	5.36	109 days
2.12	9.5×10^{-6}	5.02	50 days
1.60	4.3×10^{-5}	4.37	11.5 days
1.15	1.4×10^{-4}	3.85	82.5 h
0.85	3.09×10^{-4}	3.51	37.3 h
0.60	5.75×10^{-4}	3.24	20.3 h
0.40	9.33×10^{-4}	3.03	12.3 h
0.24	1.20×10^{-3}	2.92	9.6 h
0.08	1.26×10^{-3}	2.90	8.9 h
$-\log h_0$			
−0.16	1.15×10^{-3}	2.94	10.0 h
−0.35	2.04×10^{-4}	3.69	56.6 h
−0.54	1.74×10^{-4}	3.76	66.4 h
−0.89	1.58×10^{-4}	3.80	73.1 h
−1.54	1.41×10^{-4}	3.85	81.9 h
−2.28	1.38×10^{-4}	3.86	83.7 h

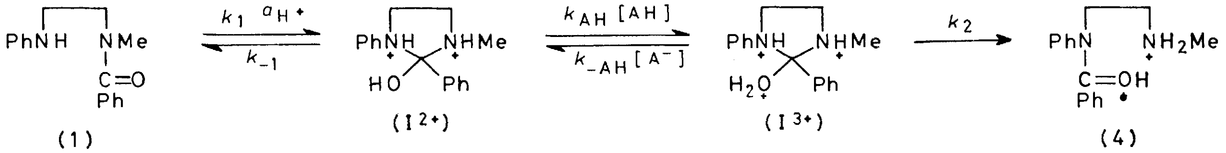
that the breakdown of the intermediate will require complete protonation (I^{2+}) (*i.e.* proton donation by the acid catalyst to the attacking weakly basic amine). So kinetics for benzoyl transfer can be accurately followed at pH values <2.40 according to the expected pK_a value of *ca.* 2 for the weakly basic amine * and proton transfer occurs during decomposition as shown by the presence of acid catalysis over this pH range (Table). Thus, it is concluded that the catalysed *decomposition* of the intermediate is rate determining over the pH range 0.24—2.30.

According to Scheme 2, if catalysed decomposition of the intermediate is rate determining for the N ⟶ N′ benzoyl transfer reaction, there is no reason why there should be a change in rate-determining step on increasing the hydrogen ion concentration as observed below pH 0 (Figure 1). These results demand that a new barrier appear between (I^{2+}) and (4) as the pH is decreased to the H_0 side, *i.e.* that a new step becomes rate determining at this point. Since all steps which involve the making and breaking of bonds to carbon are already included in Scheme 2, this new step must be a simple proton transfer by acid to the intermediate (I^{2+}), which is initially formed in the N ⟶ N′ transfer reaction (k_{AH}, Scheme 3). According to this mechanism the rate-determining step for N ⟶ N′ benzoyl transfer in strongly acid solutions is the *formation* of the tetrahedral addition intermediate, and the breakdown of the intermediate to (4) occurs through an intermediate (I^{3+}). As the pH is decreased, this intermediate decomposes to (4) more rapidly than it is protonated, protonation of the intermediate becomes rate determining (k_{AH}), and the observed rate of N ⟶ N′ benzoyl transfer becomes pH independent.

Furthermore, it can be observed from Figure 2, that the region below H_0 −0.35 becomes unimportant if $k_{obs.}$ is calculated from the initial or a greater part of the reaction. This implies that the achievement of the steady state equilibrium (1) $\rightleftharpoons$ (intermediate) is more rapid upon increasing [H^+]. This is possible only if $k_{-1} \gg k_1$ which implies that $k_1/(k_{-1} + k_2) \ll 1$, specially below H_0 −0.54 where the contribution of the intermediate (I^{2+}) may be considered negligible. According to this, the concentration of the intermediate must decrease on increasing [H^+] and become very low at H_0 values below −0.54. Thus, observed rate constants for the appearance of (4) must decrease on increasing [H^+] over the H_0 range −0.16 to −0.54 and become finally pH independent. This agrees with our results. Observed rate constants decrease and become nearly pH independent on the left hand side of the curve (Figure 1) where the reaction exclusively involves rate-determining *formation* of the tetrahedral addition intermediate ($v = k'[(1)]$).



SCHEME 2



SCHEME 3

The role of acid as catalyst in intramolecular aminolysis has already been studied.[5-7] In this work the importance of the acid in providing complete protonation of the intermediate when decomposition is rate determining was also made evident by a study of the N ⟶ N′ benzoyl migration of compound (2) to give (5) (Scheme 1). It was observed in this case that benzoyl migration does not occur in dilute acid solution as for compound (1). pH Values providing for total protonation of the amino functions of the intermediate are necessary for the occurrence of acyl transfer. Sulphuric acid–water mixtures (30 and 40% w/w) were used in order to achieve the migration in compound (2) (H_0 −1.54, $k_{obs.}$ 5.7×10^{-5} min^{-1}; H_0 −2.28, $k_{obs.}$ 5.91×10^{-4} min^{-1}).

The rearranged product (5) in acid medium cannot be isolated as base because it undergoes instantaneous rearrangement in alkaline media.[1] In this case benzoyl transfer is made evident by the variation in pK_a on passing from the aromatic amine (2) (pK_a *ca.* 1) to the aliphatic amine (5) (pK_a 9.08).

Factors influencing Rearrangement.—(a) *Number of methylene groups.* The rate of rearrangement depends on the number of methylene groups between the nitrogen atoms, as observed by Wright *et al.*[3] We observed that the ethylene derivative (1), in 1N-HCl, rearranges more

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* This pK_a value was estimated according to reported pK_a values for related compounds,[4] and taking into account the decrease in the basicity caused by strain in the five-membered ring.

[4] D. D. Perrin, 'Dissociation Constants of Organic Bases in Aqueous Solution,' Butterworths, London, 1965.

[5] R. Jaunin, *Helv. Chim. Acta*, 1952, **35**, 1414.

[6] R. Jaunin, M. Beretta Piccoli, and T. Charalambous, *Helv. Chim. Acta*, 1954, **37**, 216.

[7] W. P. Jencks, D. G. Oakenfull, and K. Salvesen, *J. Amer. Chem. Soc.*, 1970, **92**, 3201.

rapidly ($t_{\frac{1}{2}}$ 82.5 h) than the trimethylene derivative (3) ($t_{\frac{1}{2}}$ *ca.* 5 months). These results agree with data reported by Wieland and Hornig[8] and by Martin and Parcell[9] for S $\longrightarrow$ N migrations and are related to the facility of formation of the intermediate.[9] In fact, it seems plausible that the formation of an intramolecular hydrogen bond as in (II) explains the rate differences. Such a hydrogen bond would increase the positive charge of the carbonyl) carbon atom, facilitating attack by the nucleophile ($\mathrm{Ph}\ddot{\mathrm{N}}$). On the other hand, this intramolecular hydrogen bond catalysis is expected to be of little importance in the trimethylene derivative because it implies the formation of an eight-membered ring.[1]

(b) *Basicity of the attacking amine.* pH Values providing for protonation of the starting open products (1)—(3) are sufficient to enable the formation of the respective addition intermediates. But the appearance of the rearranged products (4)—(6) is only observed if pH is lowered sufficiently to provide total protonation of the intermediate (both amine functions).

These experimental observations support our proposed mechanism (Scheme 2) according to which catalysis acts upon the weakly basic amine of the intermediate when decomposition is rate determining. Thus, the less basic the nucleophile, the more concentrated the acid solution required to perform acyl transfer.

(c) *Importance of the* N-*methyl group.* The presence of an *N*-methyl group in the molecule appears to be a very important factor in acyl transfer. Attempts to rearrange *N*-acyl-*N'*-arylethylene- and trimethylenediamine derivatives without an *N*-methyl group failed and no explanation could be found for this fact. The following compounds were assayed: *N*-benzoyl-*N'*-phenylethylenediamine, *N*-benzoyl-*N'*-(*p*-methoxyphenyl)ethylenediamine, *N*-benzoyl-*N'*-phenyltrimethylenediamine, and *N*-(*p*-nitrobenzoyl)-*N'*-phenylethylenediamine. Negative results were obtained in every case which indicates that the enhanced susceptibility of the *N*-(*p*-nitrobenzoyl) derivatives to nucleophilic attack is not enough to promote rearrangement.

EXPERIMENTAL

Analytical samples of *N*-acylalkylenediamines were used to perform the kinetic studies. Compounds (1),[1] (2),[10] and (3)[1] were obtained by alkaline hydrolysis of the corresponding cyclic amidinium salts. *N*-Benzoyl-*N'*-phenylethylenediamine,[11] *N*-benzoyl-*N'*-(*p*-methoxyphenyl)ethylenediamine,[11] *N*-(*p*-nitrobenzoyl)-*N'*-phenylethylenediamine[12] and *N*-benzoyl-*N'*-phenyltrimethylenediamine[13] were obtained by reaction of the corresponding aromatic amines with *N*-bromoalkylbenzamides.

Kinetic Measurements.—Reactions (1) $\longrightarrow$ (4) and (2) $\longrightarrow$ (5) were performed at 25 °C using HCl–KCl solutions over the pH range 0.4—2.30. Ionic strength was maintained at 1.0M with added potassium chloride. Sulphuric acid–water mixtures were used for reactions below pH 0.16. The pH of each buffer solution above 0.40 was measured at 25 °C in a Beckman Zeromatic II pH meter using a standardized glass electrode. Values of H_0 were taken from Hine.[14] Reactions performed with initial concentrations of 2×10^{-3}—1×10^{-2}M-(1) and -(2) showed first-order dependence on the substrate at every hydrogen ion concentration at which migration occurred.

All rate constants were obtained from 2×10^{-3}M initial concentrations of the substrates.

The appearance of (4) and (5) was followed spectrophotometrically in a Beckman DB-G grating spectrophotometer at 270 nm where (1) and (2) have low absorptions (ε 560 and 620 respectively). The extinction coefficients of (4) and (5) at 270 nm were obtained from transfer reactions (1) $\xrightarrow{H^+}$ (4) and (2) $\xrightarrow{H^+}$ (5) at infinite time. Complete transformation was controlled by potentiometry.

Pseudo-first-order rate constants were calculated from plots of ln $(A - A_0)$ against time on semilogarithmic graph paper and the relationship $k_{\mathrm{obs.}} = 0.696/t_{\frac{1}{2}}$.

General Kinetic Procedure.—Solutions (2×10^{-3}M) of compounds (1) and (2) in the acid buffers were prepared and thermostatted at 25 ± 0.1°. At known intervals samples (2 ml) were taken and diluted with distilled water to give final solutions 8×10^{-5}M. The pH of the final solutions was above 2.5 in order to stop the reaction, and the absorbance at time zero was estimated by extrapolation.

Rearrangement (3) $\longrightarrow$ (6) in 1N-HCl was followed by potentiometric titration of the aromatic amine (3) ($\mathrm{p}K_a'$ 4.76). Reaction was followed until 70% disappearance of (3) was achieved and the $t_{\frac{1}{2}}$ reported is an approximate value due to the slowness of the reaction.

Chromatographic Experiments.—Simultaneously with the u.v. kinetic procedures performed at pH values 2.30 and 1.60, these two reactions were followed by t.l.c. using 20 × 20 cm non-activated silica gel $\mathrm{HF}_{254+366}$ plates (0.2 mm). 1M-Acetic acid–water and 1M-monochloroacetic acid–water solutions providing the same pH values as those for kinetic runs were used as developing solvents.

Reaction at pH 2.30 was observed to undergo, during the first 15 days, a partial transformation of (1) (R_F *ca.* 0.40) into a second product (R_F *ca.* 0.31). After 16—17 days the spot corresponding to (3) appeared clearly (R_F *ca.* 0.52). At both pH values (2.30 and 1.60), the intervals during which (3) was not detected were verified as the same as those occurring in curves of Figure 2 (dashed lines).

Reactions were followed until 60—70% appearance of (3); however, the spots corresponding to (1) and the intermediate (R_F *ca.* 0.31) could still be observed (*i.e.* $k_{-1} \neq 0$). At infinite time, only (3) was detected.

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