Amidines. Part 39.[1] Formation of N^1,N^1-dialkylamidines in the reaction between amide acetals and substituted anilines in pyridine. Reaction mechanisms

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The reaction rates of six *N*,*N*-dialkylformamide acetals $(R^1)_2N–CH(OR^2)_2$ with a series of anilines substituted on the phenyl ring have been measured in pyridine. The reaction is found to be irreversible and obeys second-order kinetics. Reaction rates are correlated with Hammett σ constants. Based on the plots and a comparison of reaction rate constants it is shown that the reaction proceeds *via* two mechanisms which differ from that for the reaction in neutral solvents. It is shown that for compounds with weakly basic NH_2 groups the reaction rates in pyridine are markedly higher than in neutral solvents.

Amidines have been known for years to be biologically active compounds particularly as antibacterial, antiprotozoal and antitumour drugs.[2–4] It has also been found that the introduction of an amidine group into the molecule of an antibiotic, such as penicillin, may enhance its antibacterial activity,[5–7] and an antibiotic such as anthracycline may show enhanced anticancer activity and decreased toxicity.[8] For this reason methods of introducing an amidino group are still the subject of interest.

Dialkyl acetals of *N*,*N*-disubstituted amides of carboxylic acids are very convenient reagents for this purpose because they readily react with unsubstituted amino groups giving an amidino group (Scheme 1).

Scheme 1

This reaction occurs with various compounds containing an NH_2 group, such as primary amines,[9–13] carboxamides,[10,14,15] sulfonamides[16] and many others.[10,16–18] For this reason it is used for derivatization of such compounds prior to gas chromatography analysis.[19–22]

It seemed obvious that the rate of this reaction would depend on the structure of both reagents as well as on the reaction conditions. Thus the question arose as to how far it might also depend on the structure of the compound possessing the amino group, on the substituents in the amide acetal and on the solvent, because studies of such factors could provide information relevant to the possibility of selective derivatization of polyfunctional compounds.

In our previous paper[23] the kinetics of the reaction of *N*,*N*-dialkylformamide acetals $(R^1)_2N–CH(OR^2)_2$ with anilines substituted on the phenyl ring were studied in neutral solvents, such as methanol and benzene, commonly used for derivatization with amide acetals. It was found that the reaction is second order and that the reaction rate depends on the solvent, on substitution at the nitrogen and oxygen atoms of the amide acetal molecule as well as on substitution in the amine molecule. All the reactions studied obeyed a Hammett linear equation and the reaction parameters ρ obtained indicated that in these reactions aniline acts as a nucleophilic reagent.

Derivatization reactions of the NH_2 group with amide acetals is often carried out in pyridine as a solvent, because most compounds containing an NH_2 group are very soluble in it, and some companies offer amide acetals for derivatization as solutions in pyridine. Therefore, in the present paper we have studied reaction rates in pyridine. For comparative purposes in this study the same set of amide acetals and primary amines was selected as in our previous work.[23]

Experimental

Materials

Amide acetals were prepared by Bredereck's procedure[24] from the corresponding *N*,*N*-dialkylformamides. The substituted anilines were all commercial samples of analytical grade. Their purity, as judged by GLC, was >99%. Substituted anilines, pyridine and triethylamine were dried over barium oxide and redistilled in a dry argon atmosphere before use.

Kinetics

Reactions of amide acetals with unsubstituted aniline were followed kinetically by GLC. Typical concentrations were: aniline 0.05 M, amide acetal 1.0 M, standard 0.05 M; reaction volume 5 ml. Reactions were carried out at 25 ± 0.1 °C under a small pressure of dry argon (passed through 4 Å molecular sieves) to avoid decomposition of amide acetal by traces of humidity during sample withdrawals. In each experiment, ten samples (each 0.2 ml) were taken at precise intervals (30 or 60 min, depending on reaction rate, so that the reaction was followed to at least 70% conversion). After addition of water (*ca*. 0.05 ml; fifteen-fold excess) to decompose the acetal, and ethanol (0.5 ml) for homogenization if necessary, the concentration of the N^1,N^1-dialkylformamidine formed was determined.

Competitive reaction of an amide acetal with aniline and substituted aniline were followed kinetically, also by GLC. Concentrations of the substrates were: aniline and substituted aniline 0.5 M each, amide acetal 0.05 M; total volume 2 ml. Reactions were carried out at 25 ± 0.1 °C. After 4 h water (0.1 ml) was added to the reaction mixture to hydrolyse unchanged amide acetal; the ratio of the concentrations of amidines formed was determined.

Quantitative determinations

The concentrations of amidines formed were determined by the internal standard method (with *n*-dodecane or *n*-hexadecane as standard). Relative molar responses[25] were determined for each compound separately using authentic samples. Other experimental details (apparatus and settings) were the same as in our previous paper.[23]

Results and discussion

Measurement conditions

To ensure reliability and reproducibility of results the following precautions were taken. Before analysis each sample taken from the reaction was treated with an excess of water in order to stop the reaction. Under these conditions amide acetals hydrolyse almost instantaneously[25] while hydrolysis of amidines is undetectable. Each rate constant was determined from two experiments using a different ratio of substrate concentrations. In each experiment at least nine samples at various time intervals were taken and the concentration of amidine in each sample was determined as a mean from at least three GLC analyses.

Relative rate constants were determined from two parallel experiments, and the ratios of product concentrations were calculated as a mean from at least five GLC analyses of each sample.

Reaction rates

In this study the same set of amide acetals and primary amines as in our previous work[23] were selected so as to obtain results comparable with those for reactions in neutral solvents (benzene or methanol).

We found that, as in neutral solvents, for all compounds studied the reaction in pyridine is irreversible and the sole products, as indicated by GLC analysis, are the corresponding N^1,N^1-dialkyl-N^2-phenylformamidine and alcohol R^2OH. The reaction obeys second order kinetics, first order with respect to aniline and to amide acetal. The calculated rate constants were independent of the ratio of concentrations of the substrates. The rate constants for the reactions studied carried out in pyridine, calculated with confidence intervals at a significance level of 0.05, are given in Table 1.

The rate of the reaction could depend on the substituents on the nitrogen and oxygen atoms of amide acetals and on the substituent on the NH_2 group of amine. It was found that in neutral solvents, such as methanol, benzene, THF or chloroform, the reaction rate depends on the structure of the alkoxy groups.[23] In pyridine, however, a dependence of this kind was not observed. This indicates that in pyridine cleavage of the C–O bond is not involved in the rate-determining step. The influence of the structure of the $N(R^1)_2$ amino moiety in the amide acetal molecule on the reaction rate is also insignificant. Only for the morpholino moiety is a considerable increase in reaction rate observed.

Table 1 Rate constants ($dm^3\ mol^{-1}\ s^{-1}$) for the reaction of dialkylacetals of *N*,*N*-dialkylformamide $(R^1)_2N–CH(OR^2)_2$ with aniline in pyridine at 25 °C compared with those in benzene

		$10^5\ k$	
$(R^1)_2N$	OR^2	Pyridine	Benzene[a]
Dimethylamino	OMe	2.20 ± 0.13	2.07 ± 0.22
Dimethylamino	OCH_2Ph	2.20 ± 0.27	2.73 ± 0.48
Dimethylamino	OEt	2.57 ± 0.27	17.50 ± 3.50
Dimethylamino	OPr^i	1.85 ± 0.18	17.83 ± 2.67
Piperidino	OMe	1.50 ± 0.25	3.40 ± 0.63
Hexamethyleneimino	OMe	1.17 ± 0.08	4.02 ± 0.55
Morpholino	OMe	6.35 ± 0.62	18.00 ± 2.00

[a] Ref. 23.

Hammett-type relations are very convenient tools for investigating reaction mechanisms. Therefore, we have determined the rate constants (k_i) for reactions of substituted anilines relative to unsubstituted aniline ($k°$) by competitive reactions. The logarithms of the relative rate constants for anilines studied with amide acetals studied are summarized in Table 2 and the plots of $\log(k_i/k°)$ *vs.* σ values[26] for substituents on the phenyl ring in the anilines are shown in Figs. 1 and 2.

From Figs. 1 and 2 it is seen that only for formylmorpholine acetal [Fig. 2(*c*)] does the reaction obey the Hammett equation $\log(k_i/k°) = \rho\sigma$, and the following parameters were found: $\rho = (-2.43 \pm 0.52)$, $r = 0.986$. For other acetals the relations show a minimum at *ca.* $\sigma = 0.5$. Note that non-linearity concerns nitroanilines and is observed only for reactions in pyridine. For reactions in neutral solvents a good linear relation for all anilines and acetals studied was obtained, and relative rate constants decreased with a decrease in the electron-donating character of the substituent on the phenyl ring in the aniline molecule.[23] In pyridine, however, relative rate constants for nitroanilines differ markedly from those expected on the basis of the Hammett type relations obtained for other anilines. For *p*-nitroaniline relative rates are higher than those for *p*-chloroaniline. Without nitroanilines the linear relations between $\log(k_i/k°)$ and σ values are of good quality (Table 3). The identity (within experimental error) of the parameters ρ obtained for strongly and moderately basic anilines indicate that in this case the structure of the alkoxy group in the amide acetal has no significant influence on the reaction rate.

The differences between the experimental values of relative rate constants $\log(k_i/k°)$ obtained for nitroanilines could be caused either by a systematic error in their determination, by specific interactions between the NH_2 and NO_2 groups, or by the basicity of pyridine.

It is known that in the method of competitive reactions the following conditions must be fulfilled:[27] both reactions should be of the same kinetic order, any additional reactions or interactions in the reaction mixture cannot occur, and conversion of both substrates must not exceed 10%, when the ratio of product concentrations is measured. If even one of these conditions is not fulfilled, the reaction rate constants measured directly and calculated from the competitive reactions will differ.

For reactions of *m*- and *p*-nitroanilines with DMF–DMA the following results are obtained from direct measurements: for aniline $k° = 2.20 \times 10^{-5}\ dm^3\ mol^{-1}\ s^{-1}$ (Table 1), for *m*-nitroaniline $k_i = 0.33 \times 10^{-5}\ dm^3\ mol^{-1}\ s^{-1}$, thus $\log(k_i/k°) =$

Table 2 Values of $\log(k/k°)$ for the reaction of dialkylacetals of *N*,*N*-dialkylformamides $(R^1)_2N–CH(OR^2)_2$ with substituted anilines $XC_6H_4NH_2$ in pyridine at 25 °C

$R^1{}_2N$ OR^2 X_i	NMe_2 OMe	NMe_2 OEt	NMe_2 OPr^i	piperidino OMe	hexamethyleneimino OMe	morpholino OMe
p-OMe	0.92 ± 0.01	1.02 ± 0.04	1.08 ± 0.12	1.07 ± 0.03	0.85 ± 0.07	0.77 ± 0.04
p-Me	0.44 ± 0.03	0.46 ± 0.03	0.46 ± 0.03	0.44 ± 0.02	0.43 ± 0.05	0.33 ± 0.05
m-Me	0.20 ± 0.05	0.05 ± 0.02	0.06 ± 0.02	0.03 ± 0.01	0.10 ± 0.04	0.13 ± 0.06
m-OMe	−0.23 ± 0.04	−0.12 ± 0.07	−0.13 ± 0.07	−0.14 ± 0.03	−0.20 ± 0.07	−0.02 ± 0.04
p-Cl	−0.44 ± 0.06	−0.44 ± 0.04	−0.50 ± 0.02	−0.39 ± 0.03	−0.41 ± 0.06	−0.40 ± 0.06
p-Br				−0.46 ± 0.04	−0.53 ± 0.06	−0.71 ± 0.07
m-Cl	−0.76 ± 0.01	−0.87 ± 0.06	−0.90 ± 0.02	−0.48 ± 0.04	−0.73 ± 0.07	−0.78 ± 0.10
m-Br				−0.95 ± 0.03	−0.89 ± 0.10	−1.04 ± 0.13
m-NO_2	−0.80 ± 0.07	−0.98 ± 0.12	−0.82 ± 0.04	−1.21 ± 0.10	−0.91 ± 0.05	⩽−1.8
p-NO_2	−0.28 ± 0.03	−0.04 ± 0.01	−0.62 ± 0.04	−0.30 ± 0.19	−0.34 ± 0.10	⩽−1.8

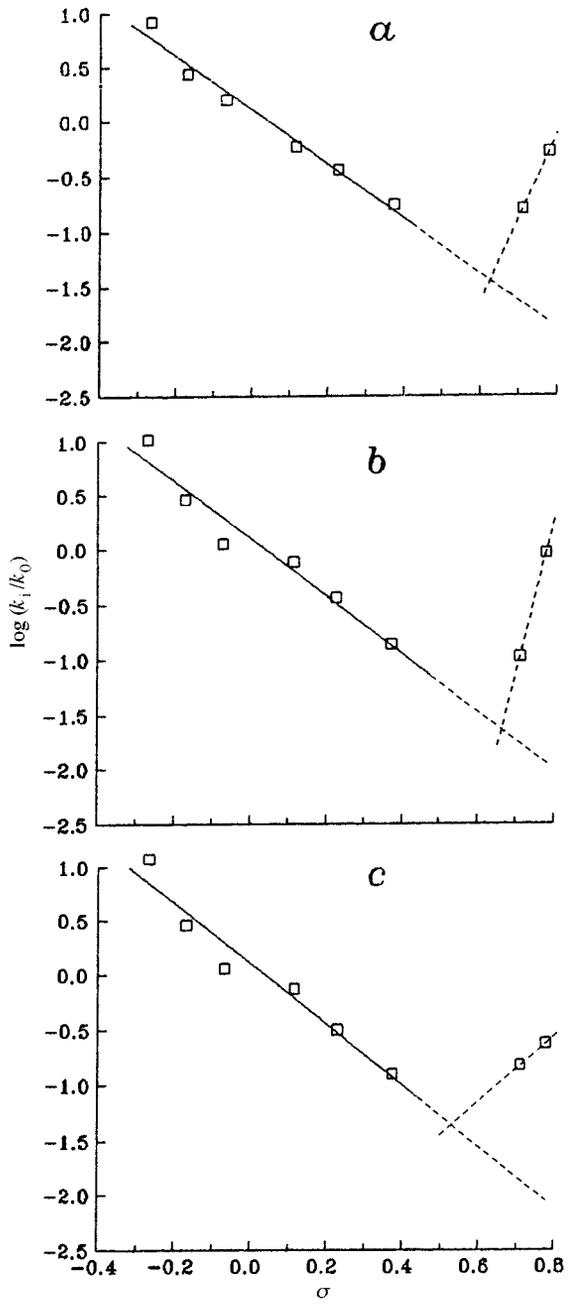


Fig. 1 Correlation of relative rate constants with Hammett σ constants for the reaction of dialkylacetals of *N*,*N*-dimethylformamide $Me_2N–CH(OR)_2$ with substituted anilines: (*a*) dimethylacetal; (*b*) diethylacetal; (*c*) diisopropylacetal

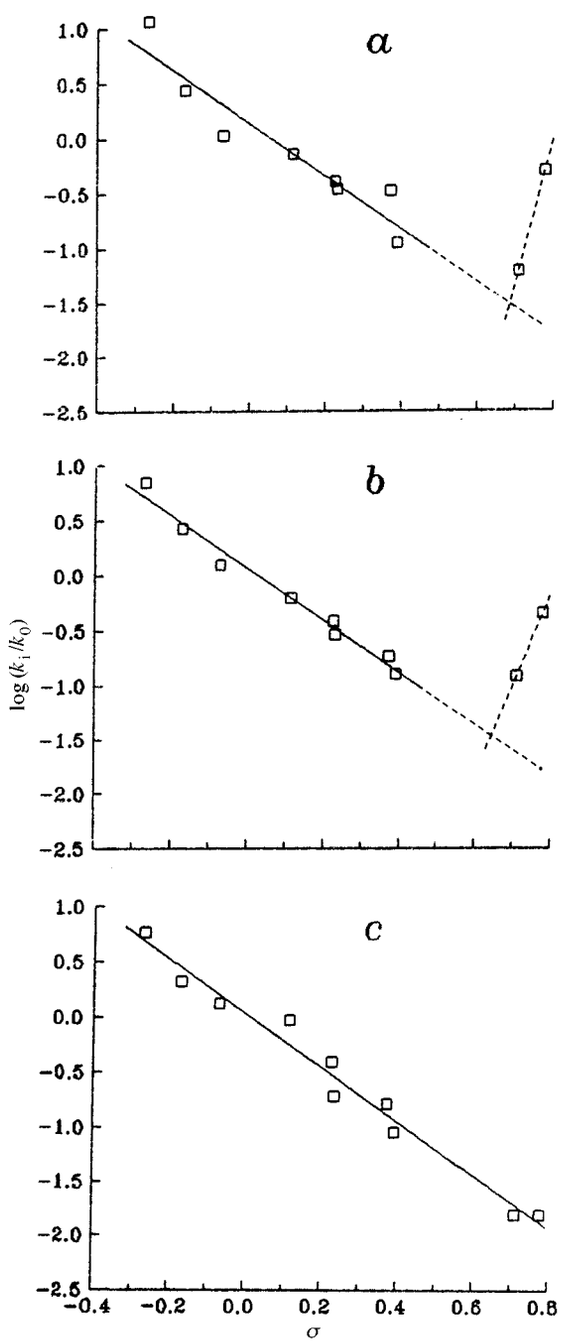


Fig. 2 Correlation of relative rate constants with Hammett σ constants for the reaction in pyridine of substituted anilines with dimethylacetals of: (*a*) *N*-formylpiperidine; (*b*) *N*-formylhexamethyleneimine; (*c*) *N*-formylmorpholine

-0.82; and for *p*-nitroaniline $k_i = 3.92 \times 10^{-5}$ dm^3 mol^{-1} s^{-1}, thus $\log(k_i/k^\circ) = 0.25$. The values obtained, identical within experimental error to those listed in Table 2, from competitive reactions provide evidence that the difference in reaction rates for nitroanilines cannot be attributed to experimental errors.

If the values for the reactions of nitroanilines resulted from complex formation between NO_2 and NH_2 groups, the reaction rate constant for aniline in the presence of nitrobenzene would be increased. We have therefore measured the reaction rate constant of DMF–DMA with aniline in pyridine in the presence of an equimolar quantity of nitrobenzene. The value obtained, $k = (2.35 \pm 0.21) \times 10^{-5}$ dm^3 mol^{-1} s^{-1}, identical within experimental error to that obtained without addition of nitrobenzene (Table 1), proves that any interactions between NO_2 and NH_2 groups have no significant influence on the reaction rates for nitroanilines.

To determine whether solvent basicity may have an influence on the reaction we have measured relative reaction rates for nitroanilines with DMF–DMA in methanol in the presence of various amounts of triethylamine (Table 4). The results obtained clearly indicate that the basicity is the real cause of increased reactivity of nitroanilines.

Table 3 Regression parameters obtained for logarithms of rate constants in pyridine with σ values

$(R^1)_2N$	OR^2	ρ	r
Dimethylamino[a]	OCH_3	-2.47 ± 0.48	0.986
Dimethylamino[a]	OC_2H_5	-2.63 ± 0.74	0.971
Dimethylamino[a]	$OCH(CH_3)_2$	-2.76 ± 0.79	0.971
Piperidino[a]	OCH_3	-2.61 ± 0.56	0.972
Hexamethyleneimino[a]	OCH_3	-2.38 ± 0.33	0.958
Morpholino[b]	OCH_3	-2.43 ± 0.52	0.973

[a] Without nitro derivatives. [b] For all experimental points.

Table 4 Values of $\log(k/k^\circ)$ for the reaction of dimethylformamide dimethylacetal with *p*-nitroaniline in methanol with addition of triethylamine (TEA) at 25.0 °C

TEA (% mol)	$\log(k/k^\circ)$
0	−1.84
33	−1.48
90	−0.64
100	−0.30

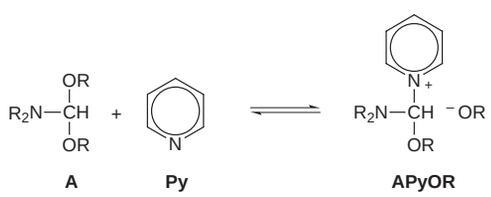
Two experimental points for nitroanilines do not allow us to calculate reliable ρ values, but discernible differences between the slopes of the correlation lines for these amines may serve as an indication of the influence of the structure of the alkoxy group.

Non-linearity of Hammett plots is usually ascribed to a change in the rate determining step, or to competition between two mechanisms with opposing electronic demands.[28] A minimum or maximum is an indication that the reaction occurs by two mechanisms, and that their relative proportion changes with a change in the σ value. In the case studied it changes with changes in the basicity of the amine. The results obtained indicate that in the rate determining step strongly and moderately basic anilines are nucleophilic reagents (negative ρ values), but nitroanilines (very weakly basic ones) behave as electrophilic reagents (positive ρ values).

Possible mechanisms

As indicated by the Hammett plots the reaction occurs by two mechanisms.

In the first step, common to both mechanisms, amide acetal reacts with pyridine and as a result of a reversible reaction a transition compound (the salt of an aminal ester, APyOR) is formed as shown in Scheme 2.



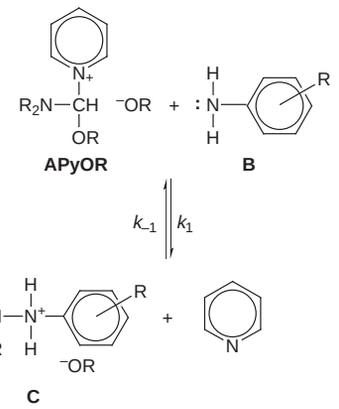
Scheme 2

The two mechanisms differ in the second and third steps of the reaction. The salt of the aminal ester APyOR does not contain hydrogen at the nitrogen atom, thus it cannot be directly transformed into the aminal ester **D**, but it may react in the second step with an aniline molecule.

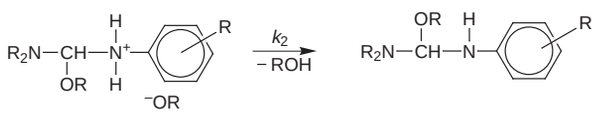
Depending on the nucleophilicity of the primary amine the salt APyOR may react according to one of two mechanisms.

According to the first mechanism (a), which predominates in the case of strongly and moderately basic amines, an electron pair on the nitrogen atom of the aniline attacks the aminal carbon atom (Scheme 3) and the salt of another aminal ester (**C**) is formed. In this step aniline is a nucleophilic reagent and therefore a negative ρ value is observed. This salt is transformed in the third step (Scheme 4) into free aminal ester **D** by elimination of an alcohol molecule.

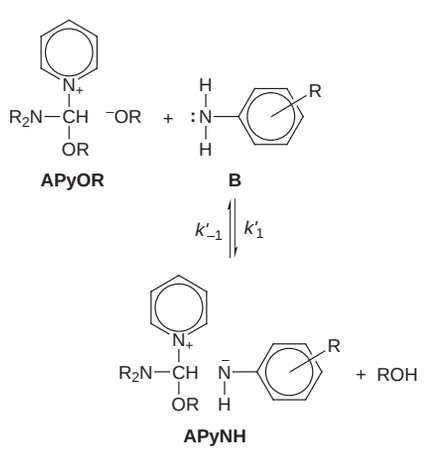
In the case of weakly basic amines a second mechanism (b) takes place. Nitroanilines (specifically, the hydrogen atoms of the NH_2 group) become an electrophilic reagent, and therefore a positive value of the ρ parameter is obtained. With the increase in σ constant the basicity of the substituted aniline decreases, so the nucleophilicity of the amino nitrogen also decreases and weakens the hydrogen–nitrogen bonds in the aniline molecule. The amino hydrogen atoms become electrophilic reagents. Thus, the hydrogen atom of the aniline NH_2 group can be removed in the second step by the alkoxyl anion and as a result a phenylamide anion $RC_6H_4NH^-$ is formed



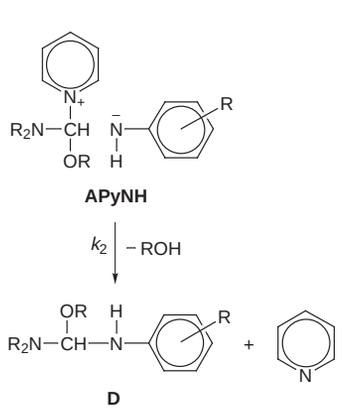
Scheme 3



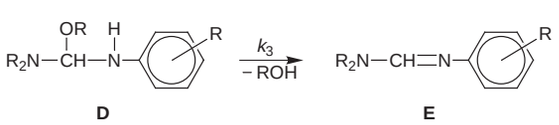
Scheme 4



Scheme 5



Scheme 6



Scheme 7

(Scheme 5), which in the third step is converted into aminal ester **D** by elimination of a pyridine molecule (Scheme 6).

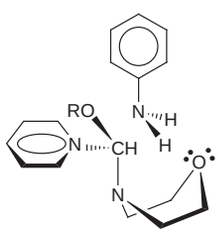
In the fourth step, common to both mechanisms, aminal ester **D** is converted into amidine molecule **E** (Scheme 7) by elimination of alcohol ROH.

It can be assumed that the reaction of formation of a salt of ester aminal APyOR, common to both mechanisms, is not a rate determining step, because the concentration of pyridine is relatively high and the reaction of formation of the salt (APyOR), common to both mechanisms, is a fast one.

The values of the rate constants, as well as the shapes of the plots of reactions of $\log(k_i/k^\circ)$ *vs.* σ, indicate that the reaction of *N*-formylmorpholine acetal with amines in pyridine substantially differs from that for other acetals. Over the whole range of σ values the relation is linear and the parameter ρ is -2.43, which indicates that the reaction proceeds according to the mechanism (a).

The different behaviour of *N*-formylmorpholine acetal calls for a separate explanation. The structure of the morpholine ring is similar to that of piperidine and the oxygen atom in the morpholine moiety is four bonds away from the reaction centre, therefore an explanation can neither be based on steric effects nor on the inductive effect of the oxygen atom.

The high rate constant for the amide acetal containing a morpholine moiety may be explained according to the proposed mechanism by formation of a hydrogen bond between the oxygen atom of the morpholine ring in the aminal salt and the amino hydrogen of aniline (Scheme 8).



Scheme 8

In such a complex the amino nitrogen atom is kept close to the functional carbon atom of the amide acetal, *i.e.* the reaction centre, thus attack in this atom is facilitated, as required by the mechanism (a). Therefore, even for weakly basic amines, such as nitroanilines, deviations from a Hammett-type relation are not observed. Moreover, the hydrogen bond causes an increase of electron density on the atom to which the hydrogen atom is covalently bonded, *i.e.* in this case the amino nitrogen atom, which is the active site of the nucleophile. In both these ways the reaction rate should be increased without change of mechanism.

Conclusions

The reaction of *N*,*N*-dialkylformamide dialkyl acetals with primary amines in pyridine is irreversible and the sole products are amidines and the corresponding alcohols. The reaction obeys second-order kinetics, being first order with respect to both reagents. Rate constants indicate that even in pyridine the reaction is not instantaneous (despite the claims of some manufacturers of derivatization reagents) but instead occurs at a definite rate.

The proposed mechanism allows an explanation of the changes in the reaction course, depending on both the substituents in the amide acetal and amine, and on the solvent.

The results obtained indicate that pyridine has little influence on the rate of reaction of amide acetals with strongly and moderately basic NH_2 groups, but it can be the most convenient solvent for reaction with NH_2 groups of low basicity, because in these cases it causes a significant increase in the reaction rates.

Acknowledgements

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