Amidines. Part 20.[1] Rates of Reaction of *N,N*-Dialkylformamide Acetals with Substituted Anilines

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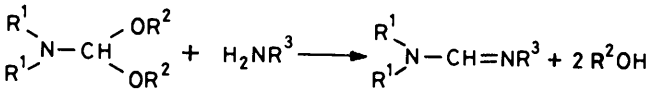
Rates of reaction of seven *N,N*-dialkylformamide acetals $R^1_2N-CH(OR^2)_2$ with a series of anilines substituted on the phenyl ring have been measured in benzene, methanol, chloroform, and tetrahydrofuran by use of a g.l.c. method. In each case studied reaction is irreversible and obeys a second-order kinetic equation. Reaction rates correlate with Hammett σ constants for substituents on the phenyl ring of the aniline molecule. On the basis of the kinetic data, the mechanism of reaction is discussed.

Dialkyl acetals of *N,N*-dialkylformamide react readily with various compounds containing active hydrogen,[2] and have therefore been used for preparative purposes. One of the best known such reactions is that with primary amino groups, giving an amidine (Scheme 1). This reaction occurs with primary amines,[3–6] carboxamides,[4,6–8] sulphonamides,[6] and other compounds containing an NH_2 group.[4,6,9,10] Dimethylformamide dimethyl acetal is widely used as a derivatization reagent for g.l.c. analysis of compounds containing NH_2 groups.[11–14] It is particularly convenient for analysis of amino acids, as simultaneously with the formation of a dimethylaminomethyleneamino group ($Me_2N-CH=N-$) from the amino group, methylation of the carboxy group occurs.[11]



Scheme 1.

The rate of this reaction has not been studied previously, although Scoggins[12] reported that reaction with primary amines is complete within no more than 10 min. It can be assumed, however, that the reaction rate depends on the structure of both reagents as well as on the reaction conditions. Thus the question arises as to how far the reaction rate depends on substituents in the amide acetal, on the structure of the product, and on the solvent; studies of such factors could provide information relevant to the possibility of selective derivatization of polyfunctional compounds.

We have undertaken a systematic study of factors controlling both the course and the rate of the reactions of amide acetals with various compounds. We report here an investigation of rates of reaction of *N,N*-dialkylformamide acetals containing various *N*- and *O*-substituents substituents with anilines containing *m*- or *p*-substituents in the phenyl ring, in solvents most commonly used for derivatization with amide acetals.

Experimental

Materials.—Amide acetals were prepared by Bredereck's procedure[15] from the corresponding *N,N*-dialkylformamides. The substituted anilines were all commercial samples of analytical grade, dried over barium oxide, and redistilled before use. Their purity, as adjudged by g.l.c., was over 99%. All solvents were thoroughly dried before use: benzene over sodium, methanol by boiling with magnesium methoxide, chloroform over calcium chloride, and tetrahydrofuran over lithium aluminium hydride.

Kinetics.—Reactions of amide acetals with unsubstituted aniline were followed kinetically by g.l.c. Typical concentrations of the substrates were: [aniline] 0.05M, [amide acetal] 1.0M, [standard] 0.05M; reaction volume 5 ml. Reactions were carried out at 25.0 ± 0.1 °C under dry argon (passed through 4 Å molecular sieves). In each experiment, ten samples (each 0.2 ml) were taken at 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) and ethanol (0.5 ml) if necessary for homogenization, the concentration of the N^1,N^1-dialkylformamidine formed was determined.

Competitive reactions of an amide acetal with aniline and a substituted aniline were followed kinetically also by the g.l.c. method. Concentrations of the substrates were: [aniline] 0.5M, [substituted aniline] 0.5M, [amide acetal] 0.05M; total volume 2 ml. Reactions were carried out at 25.0 ± 0.1 °C. After 4 h water (0.1 ml) was added to the reaction mixture to hydrolyse unchanged amide acetal; then the ratio of concentrations of amidines formed was determined.

Quantitative Determinations.—For quantitative analysis a Chromatron GCHF 18.3.4 gas chromatograph with a flame-ionization detector was used, equipped with a 3 m × 3 mm (int. diam.) column filled with 15% GE SE-30 silicone gum rubber on Chromosorb W AW (60—80 mesh); column temperature 240 °C, injection port 360 °C, and detector 350 °C; carrier gas nitrogen at 30 ml min^{-1}.

Retention indices of the compounds studied, determined under these conditions, are given in other papers.[16,17]

Concentrations of amidines formed were determined by the internal standard method (with n-dodecane or n-hexadecane as standard). Relative molar responses[18] were determined for each compound separately using authentic samples.

Results and Discussion

Measurement Conditions.—The following precautions were taken to ensure reliability and reproducibility of the results. In order to stop the reaction and thus avoid errors caused by increased reaction rate in the injection port of the chromatograph, each sample taken from the reaction mixture before analysis was treated with an excess of water. Amide acetals are hydrolysed almost instantaneously,[19] but hydrolysis of amidines under these conditions is undetectable. Errors due to differences of sampling and injected volumes were eliminated by the use of the internal standard, the concentration of which in the reaction mixture was constant. As standards, inert high-boiling normal hydrocarbons were chosen.

Each rate constant was determined from two experiments using different ratios of reagent concentrations. In each experiment at least nine samples were taken at various time

intervals, and concentrations of products in each sample were determined as mean values from at least three g.l.c. analyses.

Relative rate constants were determined from two parallel experiments; the ratios of product concentrations were determined as mean values from at least five g.l.c. analyses of each sample.

Reaction Rates.—It might be expected that the rate of reaction of an amide acetal with a primary amine would depend on *N*- and *O*-substituents of the amide acetal and on *N*-substituents of the amine. For this study we selected amide acetals containing various *N*- and *O*-alkyl substituents. As primary amines we used derivatives of aniline containing various *m*- or *p*-substituents of known Hammett constant.

In all cases studied reaction was irreversible and the sole products (as indicated by g.l.c.) were the corresponding N^1,N^1-dialkyl-N^2-phenylformamidine[20,21] and the alcohol R^2OH. In all cases studied the reaction obeyed a second-order kinetic equation, first-order with respect to aniline and to amide acetal. The calculated rate constant was not changed by changing the ratio of concentrations of the reagents. Rate constants calculated with confidence intervals at the significance level of 0.05 for reaction of dimethylformamide dimethyl acetal with aniline in our solvents commonly used for syntheses are given in Table 1. It is clear that the reaction depends on the nature of the solvent; in methanol it proceeds fifteen times faster than in chloroform.

Reactions of amide acetals with various *N*- and *O*-substituents provide further information. Rate constants for the reactions of aniline with various amide acetals are summarized in Tables 2 and 3. The rate constants for dimethylformamide acetals containing various *O*-alkyl substituents increase in the order R^2 = methyl, benzyl, ethyl, isopropyl. The sequence is the same as observed in the reaction of these acetals with deoxybenzoin by Arnold and Kornilov.[22] They concluded that reactivity is determined largely by the size of the alkoxy group.

Comparison of rate constants of *N*-substituted amide acetals (Table 3) reveals a new feature. A small but discernible increase of rate constant in the order *N*,*N*-dimethyl-, *N*,*N*-pentamethylene, *N*,*N*-hexamethylene-formamide acetal may be satisfactorily explained by an increase of polar effects of *N*-substituents. However, the greater than four-fold increase in the case of the amide acetal containing a morpholine moiety indicates that here some additional effects are involved.

Relative rate constants (k_i/k_0) were obtained from competitive reactions. In such reactions at low conversions (below 10%) the ratio of concentrations of the products is equal to the ratio of reaction rate constants,[23] and their logarithms can be directly correlated with Hammett σ constants.

The logarithms of the relative rate constants for the dialkyl acetals of dialkylformamides studied are summarized in Table 4. The rate constants obey the Hammett equation. The parameters are given in Table 5. The magnitude of the ρ value indicates that the transition state in the rate-determining step is polar. Its sign suggests that in the reaction aniline is a nucleophilic reagent.

Similarities between the parameters of corresponding Hammett equations (Table 5) indicate that for all acetals studied, including the acetal containing the morpholine moiety, the reaction mechanism is the same. It can be formulated as in Scheme 2.

As indicated by the sign of the calculated ρ values in the first step S_N2-type nucleophilic attack of aniline on the carbon atom of the amide acetal occurs. This step is rate-determining. As a result a salt of an ester aminal (C) is formed; thus the rate of

Table 1. Rate constants ($dm^3\ mol^{-1}\ s^{-1}$) of reaction of dimethylformamide dimethyl acetal with aniline at 25.0 °C

Solvent	10^5k
Methanol	12.25 ± 0.82
Tetrahydrofuran	2.78 ± 0.27
Benzene	2.07 ± 0.12
Chloroform	0.80 ± 0.16

Table 2. Rate constants ($dm^3\ mol^{-1}\ s^{-1}$) of reaction of dialkyl acetals of *N*,*N*-dimethylformamide Me_2N–$CH(OR^2)_2$ with aniline at 25.0 °C

	10^5k	
R^2	In benzene	In chloroform
Me	2.07 ± 0.22	0.80 ± 0.16
CH_2Ph	2.73 ± 0.48	0.87 ± 0.17
Et	17.50 ± 3.50	6.52 ± 0.58
Pr^i	17.83 ± 2.67	15.15 ± 1.63

Table 3. Rate constants ($dm^3\ mol^{-1}\ s^{-1}$) of reaction of dimethyl acetals of *N*,*N*-dialkylformamides $R^1{}_2N$–$CH(OMe)_2$ with aniline at 25.0 °C in benzene

$R^1{}_2N$	10^5k
Me_2N	2.07 ± 0.22
Piperidino	3.40 ± 0.63
$[CH_2]_6N$	4.02 ± 0.55
Morpholino	18.00 ± 2.00

Table 4. Values of $\log(k_i/k_0)$ for reaction of dialkyl acetals of *N*,*N*-dialkylformamides $R^1{}_2N$–$CH(OR^2)_2$ with substituted anilines $X_iC_6H_4NH_2$ at 25.0 °C

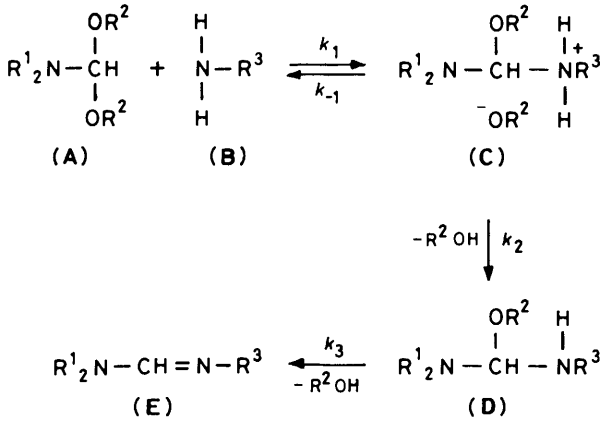
	$R^1{}_2N$ =	Me_2N				Piperidino	$[CH_2]_6N$	Morpholino
	OR^2 =	OMe	OMe	OEt	OPr^i	OMe	OMe	OMe
X_i	Solvent =	Methanol	Benzene	Benzene	Benzene	Benzene	Benzene	Benzene
p-OMe		0.97 ± 0.04	0.98 ± 0.05	0.98 ± 0.03	0.98 ± 0.08	0.93 ± 0.03	0.92 ± 0.05	0.79 ± 0.09
p-Me		0.49 ± 0.03	0.42 ± 0.01	0.43 ± 0.03	0.42 ± 0.03	0.52 ± 0.02	0.40 ± 0.02	0.43 ± 0.08
m-Me		0.18 ± 0.04	0.11 ± 0.02	0.09 ± 0.01	0.10 ± 0.02	0.13 ± 0.01	0.10 ± 0.02	0.00 ± 0.04
m-OMe		−0.15 ± 0.05	−0.13 ± 0.01	−0.12 ± 0.02	−0.12 ± 0.01	−0.13 ± 0.03	−0.15 ± 0.01	−0.22 ± 0.10
p-Cl		−0.66 ± 0.03	−0.42 ± 0.04	−0.52 ± 0.03	−0.44 ± 0.02	−0.40 ± 0.03	−0.38 ± 0.03	−0.56 ± 0.07
p-Br						−0.52 ± 0.03	−0.47 ± 0.03	−0.69 ± 0.05
m-Cl		−0.98 ± 0.07	−0.73 ± 0.06	−0.83 ± 0.03	−0.78 ± 0.05	−0.82 ± 0.01	−0.73 ± 0.02	−0.91 ± 0.10
m-Br						−0.86 ± 0.02	−0.78 ± 0.04	−1.05 ± 0.10
m-NO_2[a]		−1.77 ± 0.10	≤ −1.8	≤ −1.8	≤ −1.8	≤ −1.8	≤ −1.8	≤ −1.8
p-NO_2[a]		−1.84 ± 0.10	< −1.8	≤ −1.8	≤ −1.8	≤ −1.8	≤ −1.8	≤ −1.8

[a] For $R^1 = R^2$ = Me in $CHCl_3$ or THF, $\log(k/k_0) \leq -1.8$.

Table 5. Regression parameters obtained for rate constants in benzene with σ values[26]

$R^1{}_2N$	OR^2	ρ	r
Me_2N	OMe	−2.41 ± 0.68	0.972
Me_2N	OEt	−2.59 ± 0.66	0.977
Me_2N	OPr^i	−2.48 ± 0.67	0.973
Piperidino	OMe	−2.52 ± 0.35	0.988
$[CH_2]_6N$	OMe	−2.30 ± 0.40	0.981
Morpholino	OMe	−2.60 ± 0.33	0.990
Me_2N	OMe	−2.61 ± 0.26[a]	0.994

[a] In methanol.



Scheme 2.

reaction in methanol would be expected to be higher than that in benzene or chloroform. Further support for this interpretation is provided by the increase of reaction rate constant with the increase of the volume of the OR^2 alkoxy group. This increase is well explained in terms of the release of steric hindrance, as postulated by Arnold and Kornilov.[22] The possibility of formation of an ester aminal has been previously raised for the reaction of dimethyl acetals of dialkylformamides with secondary amines.[24]

The next, fast step is abstraction of a proton from the salt by an alkoxy group. The last step is irreversible elimination of an alcohol molecule, to give the amidine (E).

On the basis of the proposed mechanism a kinetic equation can be derived. The rate of formation of the aminal salt (C) from an amine (B) and a dialkyl acetal (A) is determined by equation

$$d[(C)]/dt = k_1[(A)][(B)] - (k_{-1} + k_2)[(C)] \quad (1)$$

(1), The rate of aminal (D) formation is given by equation (2),

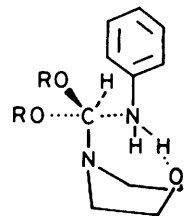
$$d[(D)]/dt = k_2[(C)] - k_3[(D)] \quad (2)$$

and the formation of amidine (E) by equation (3). Intermediates

$$d[(E)]/dt = k_3[(D)] \quad (3)$$

(C) and (D) are highly unstable, and their concentrations in the reaction mixture are very low (undetectable by ^1H n.m.r.). Therefore steady-state treatment[25] may be applied, giving equation (4).

$$d[(E)]/dt = \frac{k_1k_2}{k_{-1} + k_2}[(A)][(B)] = k_{obs}[(A)][(B)] \quad (4)$$



Scheme 3.

Equation (4) implies that in the case when k_{-1} [decomposition of aminal salt (C) to reagents] is negligible with respect to k_2 [formation of aminal (D) from (C)], the overall reaction rate k_{obs} is equal to k_1. Otherwise it is determined by equation (4). In both cases the reaction obeys the second-order equation. The agreement of the results obtained with equation (4) provides additional support for the proposed mechanism.

The high rate constant for the amide acetal containing a morpholine moiety may be explained according to the proposed mechanism by assuming that in this case a hydrogen-bonded complex (Scheme 3) is formed. This may facilitate reaction in two ways. First, in such complexes the amino nitrogen atom is kept close to the functional carbon atom of the amide acetal, *i.e.* the reaction centre. Secondly, 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 dialkylformamide dialkyl acetals with primary amines is irreversible; the sole products are amidines and the corresponding alcohols. The reaction obeys the second-order kinetic equation (4), being first-order with respect to both reagents. Rate constants obtained indicate that reaction is not instantaneous, despite the claims of Scoggins[12] and of some manufacturers of derivatization reagents; it occurs at a definite rate. Considerable differences in rate constants, even between substituted anilines, entitle one to expect that selective derivatization of only one of two non-equivalent NH_2 groups will be possible, if reaction conditions are properly adjusted.

Acknowledgements

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