^{1}H Nuclear Magnetic Resonance Study of the Kinetics of the Reaction of *N,N*-Dialkylformamide Dimethyl Acetals with Secondary Amines

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Rate constants and activation parameters ($\Delta G^{\neq}$, $\Delta H^{\neq}$, $\Delta S^{\neq}$) for the reactions of *N,N*-dialkylformamide dimethyl acetals with four secondary amines have been estimated by ^{1}H n.m.r. spectroscopy. The reactions are reversible and obey a second-order kinetic equation. Substitution of one methoxy group of the amide acetal by the amine entity is found to give ester aminals which are subject to decomposition ($\Delta G^{\neq}$ 92—103 kJ mol^{-1}). A transamination reaction yields a new amide acetal at higher temperatures ($\Delta G^{\neq}$ 115 kJ mol^{-1}). On the basis of the kinetic data, the mechanism of these reactions is discussed.

Earlier studies[1,2] of the reactions of *N,N*-dialkylformamide dimethyl acetals [$R_2NCH(OMe)_2$] with secondary amines (R'_2NH) showed that the amide acetal may exchange either the amine entity or the methoxy group.

With substrates which have different amine entities, several amide acetals and ester aminals were identified in the reaction mixtures by ^{1}H and ^{13}C n.m.r. spectroscopy.[3]

Experimental

^{1}H N.m.r. spectra were recorded at 80 MHz on a Tesla BS 487C spectrometer equipped with a variable-temperature probe. The stability of temperature was ±1 °C.

The volume of a sample in the n.m.r. tube was 0.5 cm^3. In order to keep it constant, suitable amounts of $(Me_3Si)_2O$ (HMDS) as solvent and reference have been used in the course of studies with different ratios of substrates. HMDS and one of the substrates (the secondary amine) were placed in the n.m.r. sample tube and heated or cooled to the desired temperature, then the second substrate was added from a syringe and the spectra were immediately recorded. There was about 1 min lapse between mixing and the time at which the spectrum (or integral) was recorded. The concentrations of products have been calculated from the integrated signal areas. Amide acetals were synthesized according to known procedures;[4] morpholine, pyrrolidine, and amide acetals were distilled in dry nitrogen directly before use. Dimethylamine was commercial grade and handled as solution in HMDS.

Results and Discussion

Ester aminals are expected[3] as the main products of the following reactions:

N-formylmorpholine dimethyl acetal (FM DMA) with morpholine (1)

N-formylpiperidine dimethyl acetal (FP DMA) with piperidine (2)

N,N-dimethylformamide dimethyl acetal (DMF DMA) with dimethylamine (3)

according to:

$$R_2NCH(OMe)_2 + R_2NH \underset{k_-}{\overset{k_+}{\rightleftharpoons}} (R_2N)_2CHOMe + MeOH \quad (A)$$

Further exchange of methoxy group gives orthoamide:

$$(R_2N)_2CH(OMe) + R_2NH \rightleftharpoons (R_2N)_3CH + MeOH \quad (B)$$

The yields of orthoamides obtained in a previous paper[3] were calculated from the excess of the MeOH signal because the signal of the CH group was too small for a correct integration and was overestimated. Some amounts of MeOH can appear also as the result of the fast hydrolysis of amide acetal[5] during the long (up to 30 min) reaction time because of trace amounts of water. In the case of reaction (3) between 3—6% of the excess MeOH signal results from the hydrolysis of *N,N*-dimethylformamide. The more reliable yields of orthoamides are below 10% (with respect to the initial concentration of amide acetal) and in the present approach, therefore, the reaction (B) has been neglected. The reaction pathway *i.e.* the disappearance of the signals of amide acetals and the appearance of those of ester aminal and methanol was followed in the temperature range from 293—343 K [reactions (1) and (2)]. In the case of reaction (3) at 281 K the rate of reaction was too small (after 30 min the yield of ester aminal was below 10%) and at a temperature above 303 K the high volatility of dimethylamine (boiling point 280 K) made the estimation of activation parameters less reliable; thus this reaction was studied only at 291 K.

A series of kinetic runs were carried out at the given temperature with the molar ratios of amide acetal to amine equal to 4:1, 2:1, 1:1, 1:2, and 1:4, respectively. The observed dependence of concentrations of ester aminals (determined from the area of their OMe signal) on time were found to be best-fitted, by means of a computer program, to the kinetic equation[6a] for the reversible second-order reaction: $A + B \underset{k_-}{\overset{k_+}{\rightleftharpoons}} C + D$, first-order with respect to both substrates. The initial concentration of the products is equal to $C_0 = D_0 = 0$, but reactants may be present in either stoicheiometric or non-stoicheiometric amounts.

The kinetics with molar ratios of acetal to amine *ca.* 1:1 were repeated 2—3 times at any temperature and the result of the best-fit of k_+, k_- (in the case of data measured at lower temperatures also a fit of c_∞ was necessary) with the highest correlation coefficients (r) were used to estimate the activation parameters (Table). The dependence of the rate constants on temperature (Arrhenius plot) in the reactions studied is shown in Figure 1. The rate constants k_+, k_- increase with an increase in temperature for reaction (1), the formation constant k_+ being slightly greater than the decomposition constant k_-. The obtained rate constants have been used to calculate the free

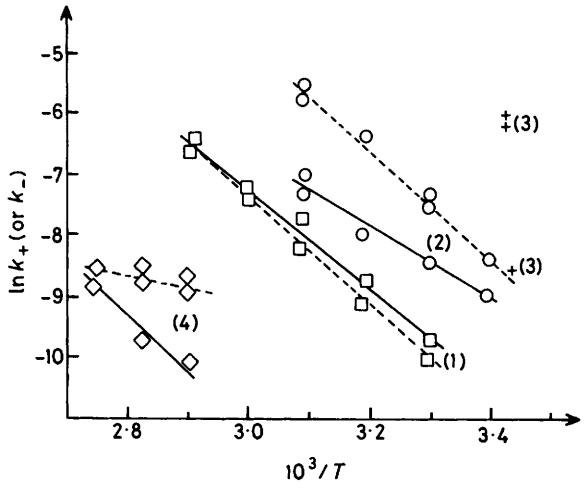


Figure 1. The dependence of rate constants k_+ and k_- (dashed lines) on temperature

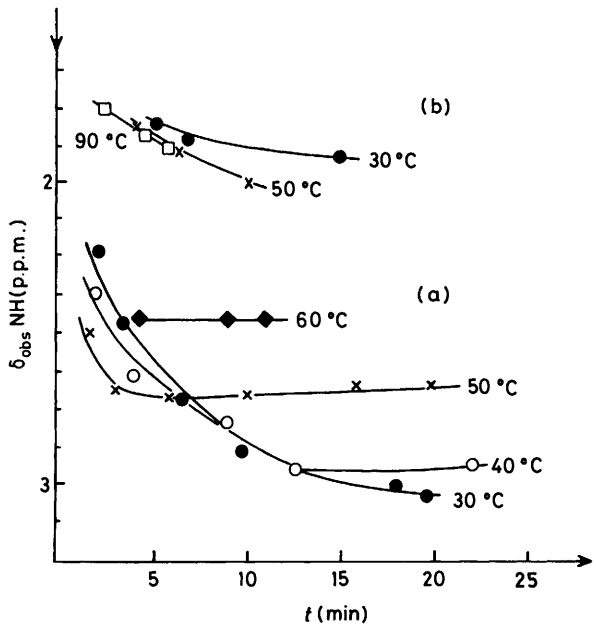


Figure 2. The behaviour of the amine NH signal during the reaction time for reactions: (a) FP DMA with piperidine (2) and (b) DMF DMA with pyrrolidine (4)

energy of activation ($\Delta G^{\neq}$) according to the known expression:[6b]

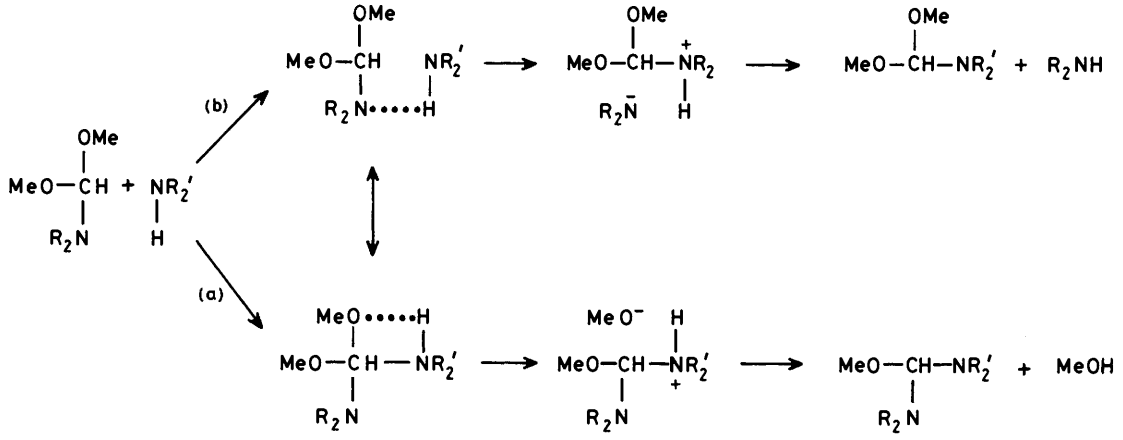
$$\Delta G^{\neq}_{+(-)} = RT[\ln (k_B T h^{-1}) - \ln k_{+(-)}]$$

Further activation parameters, *i.e.* $\Delta H^{\neq}$ and $\Delta S^{\neq}$, have been estimated from the temperature dependence of $\Delta G^{\neq}$: $\Delta G^{\neq} = \Delta H^{\neq} - T\Delta S^{\neq}$. The values obtained for $\Delta H^{\neq}$ and $\Delta S^{\neq}$ are within the range expected for second-order reactions in solution involving an S_N2 mechanism.[7]

The nucleophilic attack of amine on the carbon atom of amide acetal is assumed to be the rate-determining step [see Scheme path (a)]. Further, fast removal of a proton by the methoxy group from the polar intermediate gives the ester aminal. The formation of a salt of an ester aminal as a rate-limiting step has been proposed earlier[8] for the reaction of amide acetals with primary aromatic amines but the presence of an ester aminal as a further intermediate was undetectable by ^{1}H n.m.r. spectroscopy.

The progress of the reaction can also be followed by monitoring the behaviour of the NH signal of amine (Figure 2). The significant (*ca.* 1 p.p.m.) downfield shift of the NH signal during the reaction time takes place in the spectra for all three reactions studied. The observed chemical shift ($\delta_{obs.}$) of this signal is, in fact, the weighted average of δ_{NH} and δ_{OH} because of the fast proton exchange through hydrogen bonds (NH ··· OH or OH ··· NH) between the amine and increasing amounts of methanol.

The position of this signal in the spectra recorded after time sufficient for the reaction to reach equilibrium is dependent on temperature; $\delta_{obs.}$ at 333 K is at higher field than $\delta_{obs.}$ at 323 K because at higher temperatures there are fewer hydrogen bonds in solution (although the concentration of MeOH is greater).



Scheme.

Taking into account that $K = \frac{k_+}{k_-}$, the estimation of equilibrium constants (K) was possible. The dependence of the obtained equilibrium constants on the reciprocal temperature is shown in Figure 3. In the case of reactions (1) and (2) equilibrium constants decrease with the increase in temperature and the enthalpy values of the reaction obtained from the slopes are negative and small (−10.3 and −29.6 kJ mol^{-1},

$$\Delta H = -R[\mathrm{d}(\ln K)/\mathrm{d}(T^{-1})]$$

Table. Rate constants $k_{+(-)}$ ($dm^3\ mol^{-1}\ s^{-1}$) and activation parameters $\Delta G^{\neq}_{+(-)}$ (kJ mol^{-1}), $\Delta H^{\neq}_{+(-)}$ (kJ mol^{-1}), and $\Delta S^{\neq}_{+(-)}$ (J K^{-1} mol^{-1}) for the reactions of *N*,*N*-dialkylformamide dimethyl acetals with secondary amines

Reaction No.	T/K	r	$k_+ 10^{-4}$	$k_- 10^{-4}$	$\Delta G^{\neq}_+$ (±0.6)	$\Delta H^{\neq}_+$	$\Delta S^{\neq}_+$	$\Delta G^{\neq}_-$ (±0.6)	$\Delta H^{\neq}_-$	$\Delta S^{\neq}_-$
	303	0.9971	.605	0.366	98.7			99.9		
		0.9968	.598	0.466	98.7			99.3		
		0.9964	.592	0.317	98.7			100.3		
	313	0.9966	1.588	1.058	99.5			100.5		
(1)	323	0.9970	4.05	3.30	100.2	64.1	−114	100.8	74.3	−84
		0.9971	3.80	2.70	100.4	(±2.5)	(±8)	101.3	(±2.6)	(±8)
	333	0.9980	5.923	6.30	102.4			102.2		
	343	0.9970	14.96	13.9	102.9			103.1		
		0.9948	12.378	12.5	104.4			103.4		
	293	0.9972	1.30	2.216	93.5			92.2		
	303	0.9981	2.20	5.516	95.4			93.1		
		0.9961	2.36	6.466	95.2			92.7		
		0.9970	2.00	5.333	95.6	42.1	−176	93.2	71.3	−71
(2)	313	0.9964	3.383	15.65	97.5	(±3.6)	(±11)	93.5	(±3.0)	(±10)
		0.9960	3.616	17.26	97.4			93.3		
	323	0.9955	8.08	39.16	98.4			94.2		
		0.9940	6.13	32.0	99.1			94.7		
	291	0.9916	1.866	20.50	91.9			86.1		
(3)		0.9910	1.750	17.67	92.1			86.5		
	343	0.9852	0.1817	1.398	115.5			109.7		
		0.9853	0.1840	1.4516	115.4			109.5		
		0.9855	0.1858	1.505	115.4			109.4		
	353	0.9825	0.6183	1.716	115.3	110.2	−15	112.3	14.4	−277
(4)		0.9851	0.585	1.4466	115.5	(±1.6)	(±5)	112.8	(±3.0)	(±9)
	363	0.9907	1.683	2.10	115.7			115.0		
		0.9915	1.635	2.00	115.7			115.1		
		0.9920	1.596	1.983	115.8			115.2		

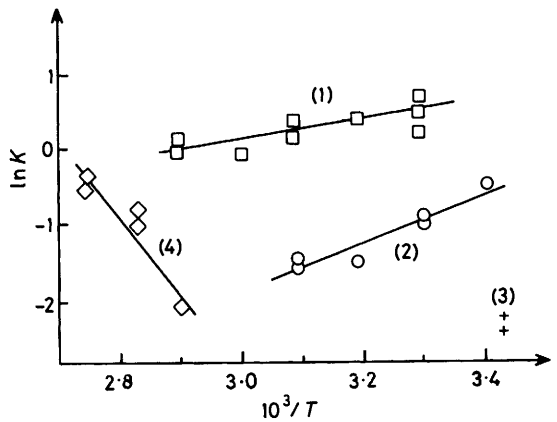


Figure 3. The dependence of equilibrium constants on temperature for reactions (1)—(4)

respectively). Both ester aminals, therefore, decompose at higher temperatures.

No exchange of the methoxy group for amino entity is observed in the case of reaction:

DMF DMA with pyrrolidine (4)

Both reagents have different amine entities and instead of ester aminals, as in reactions (1)—(3), the sole product, besides dimethylamine, is *N*-formylpyrrolidine dimethyl acetal (FP DMA), *i.e.* transamination reaction occurs according to:

$$R_2NCH(OMe)_2 + R'_2NH \underset{k_-}{\overset{k_+}{\rightleftharpoons}} R'_2NCH(OMe)_2 + R_2NH \quad (C)$$

It has been established, as described above, that this reaction also obeys the second-order kinetic equation, first-order with respect to both substrates. The obtained values of rate constants k_+ and k_- and the calculated activation parameters are collected in the Table. At 323 K only trace amounts of the FP DMA appear and the reaction starts at 343 K. The activation parameters $\Delta G^{\neq}_+$, $\Delta H^{\neq}_+$ for formation of this acetal are higher than these for the formation of the ester aminals (Table). The calculated equilibrium constant increases with the increase in temperature (ΔH +95.9 kJ mol^{-1}). The rate-limiting step in its formation is also supposed to involve attack of the pyrrolidine on the carbon atom of acetal [see the Scheme path (b)] to give the polar intermediate. The following fast step should provide elimination of the amine.

It is interesting to note that in the spectra of the reaction mixture a downfield shift of the NH signal has been observed {at 303 K when the reaction does not start it can be explained by the formation of a complex involving NH • • • O or and NH • • • N hydrogen bonds [see the Scheme path (a) and (b)]} together with so drastic an increase of line width that after some first minutes the NH signal is unobservable. This behaviour results probably from the proton exchange through the NH • • • NH hydrogen bonds of both amines (there is no free methanol in the reaction mixture and thus no proton exchange for NH • • • OH).

Reaction(s) of DMF DMA with morpholine has been chosen as an example of one with complex kinetics; both reagents have different amine entities and up to six products were found in the reaction mixture.[3] The question was how to adjust the reaction conditions to obtain higher yields of the acetal FM DMA. The concentrations of two ester aminals {concentration of a third one [$(Me_2N)_2CH(OMe)$] did not exceed 0.1 mol dm^{-3}} and of

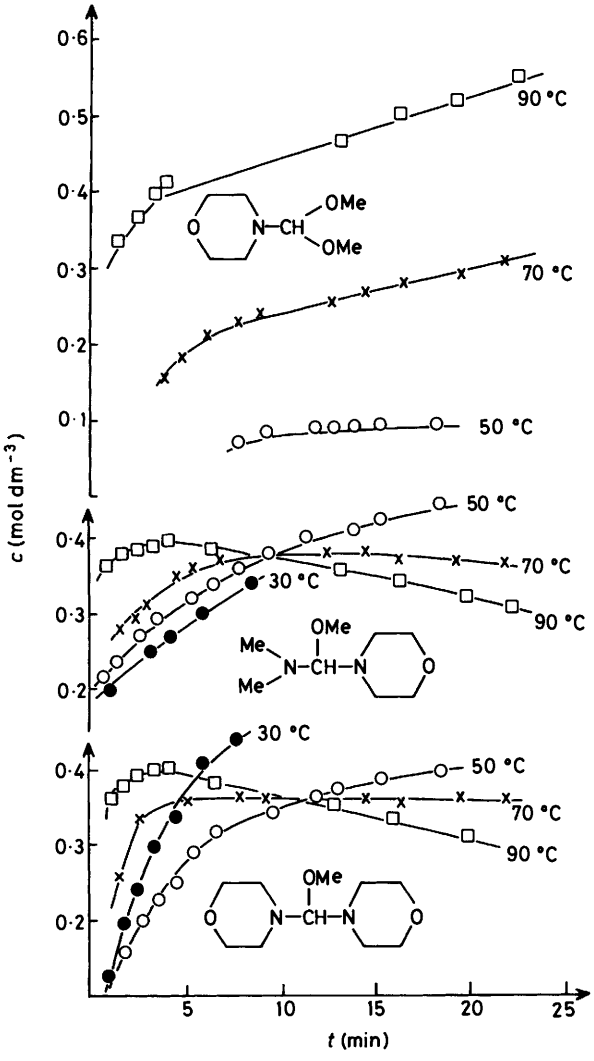


Figure 4. The concentrations of the main products of DMF DMA with morpholine (5) during the reaction at several temperatures

FM DMA during the reaction time at several temperatures is illustrated in Figure 4.

The results obtained as well as those for reactions (1)—(4) allow for the following conclusion: a longer heating time at higher temperatures discourages the formation of the ester aminals while the concentration of the new acetal increases under these conditions. It should be mentioned that the decomposition of ester aminals may not necessarily lead to the formation of amines, amides, and methanol; the possibility of rapid aminal–aminal equilibrations must also be taken into account. An unanswered problem is why dimethylamine and both the amines with six-membered rings (piperidine and morpholine) exchange easily one methoxy group of the acetal thus giving the respective ester aminal while pyrrolidine, with a five-membered ring, fails to do so. The reason probably lies in the specific requirements of the intermediate state because the differences in basicity of amines does not explain[3] the changes in reaction pathways. The problem of steric and other factors determining the mechanism of these reactions as well as the role of hydrogen bonds requires further study.

Acknowledgements

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