^1H and ^{13}C Nuclear Magnetic Resonance Identification of the Products of the Reaction of *NN*-Dialkylformamide Dimethyl Acetals with Secondary Amines

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Eight reactions of *NN*-dialkylformamide dimethyl acetals with secondary amines have been followed by means of ^1H n.m.r. The reaction products were not only other amide acetals but also ester aminals and orthoamides. Therefore secondary amines exchanged the amine moiety and the methoxy group of the amide acetal. The relative concentrations of products at equilibrium have been estimated. The ^{13}C chemical shifts for substrates and some products have been reported.

NN-Dialkylformamide acetals are highly reactive and thus widely applied in the organic synthesis of, for example, amidines or enamines.[1,2] Simchen *et al.*[3] synthesized some *NN*-dialkylformamide dialkyl acetals (amide acetals) and bis-dialkylaminoalkoxymethanes (ester aminals), their purity has been checked by means of ^1H n.m.r., and the chemical shifts have been reported. The ease of exchange of one alkoxy group for another is important in the synthetic utility of amide acetals. It has been shown that not only methoxy groups but also the methine proton of *NN*-dimethylformamide dimethyl acetal (DMF DMA) exchanged with MeOD and kinetic parameters have been calculated.[4,5]

The amine moiety of the amide acetal can be exchanged for another thus giving the new amide acetal.[1] In this process other reaction products and the mechanism of amino-group exchange have not been reported.

DMF DMA was expected to react with secondary amines according to reaction (A) and to yield the new amide acetal. If the amine exchanged one methoxy group in the molecule of amide acetal, an ester aminal would appear in the mixture, according to reaction (B). The exchange of the second methoxy group would give orthoamide [reaction (C)].

$$Me_2NCH(OMe)_2 + HNR_2 \rightleftharpoons R_2NCH(OMe)_2 + Me_2NH \quad (A)$$

$$Me_2NCH(OMe)_2 + HNR_2 \rightleftharpoons Me_2NCH(OMe)NR_2 + MeOH \quad (B)$$

$$Me_2NCH(OMe)NR_2 + HNR_2 \rightleftharpoons Me_2NCH(NR_2)_2 + MeOH \quad (C)$$

Thus, with two amines, Me_2NH and R_2NH, present in the reaction mixture, *i.e.* with $R^1_2NH \neq R^2_2NH$, nine different compounds of three types (*i.e.* amide acetal, ester aminal, orthoamide) might be expected as the products of the reaction of amide acetal with secondary amine. It seemed interesting, therefore, to check whether, with the secondary amines studied, all these products actually appear in the reaction mixture.

Experimental

^1H N.m.r. spectra were recorded at 80 MHz on a Tesla BS 487 C spectrometer equipped with a variable-temperature probe. $(Me_3Si)_2O$ (HMDS) as a reference and one of the substrates were placed in the n.m.r. sample tube, another substrate was added from a syringe and the spectra were immediately recorded. The reaction pathway, *i.e.* the disappearance of the signals of substrates and the appearance of those of products, was therefore followed directly.

The starting molar ratio of amide acetal to amine was 1:1 and the volume of the reaction mixture 0.5 cm^3. The yields of products were calculated from the integrated signal areas relative to those of the initial concentration of amide acetal.

After ^1H n.m.r. measurement the samples were diluted with $CDCl_3$ (with 1% Me_4Si) to provide the deuterium lock and the ^{13}C n.m.r. spectra were recorded on a JEOL FX 90 Q 22.50 MHz spectrometer.

500—1 500 scans were accumulated for proton-noise-decoupled ^{13}C spectra, a 8 μs pulse with a repetition time of 1.1 s, a spectral width of 4 000 Hz, and 8k data points were utilized for the accumulation of interferograms, which were then Fourier transformed with a JEOL 980 computer.

The ^{13}C and ^1H chemical shifts were accurate to within 0.04 and 0.01 p.p.m., respectively.

Dimethylamine was commercial grade and used without further purification. Amide acetals were synthesized according to known procedures.[3] Amines and amide acetals were distilled in dry nitrogen directly before use.

Results and Discussion

In this paper the reactions of *NN*-dialkylformamide acetals of general formula $R_2N\text{-}CH(OMe)_2$ (*NN*-dimethylformamide, *N*-formylmorpholine, and *N*-formylpiperidine dimethylacetal) with some secondary amines (*N*-methylaniline, morpholine, pyrrolidine, piperidine, dimethylamine) have been studied by means of n.m.r.

The ^1H chemical shifts of substrates and products are collected in Table 1 and the yields of products in Table 2. The signals of acetals (**1**)—(**4**), MeOH, and Me_2NH have been identified by adding these substances to the reaction mixture and observing the increase of the intensities of the respective signals.

In the spectrum of products from reaction (2) the aminal (**6**) was easy to assign because it had a 2:1 intensity ratio of the signals for NMe_2 and OMe and this ratio was constant during the whole reaction and independently of the initial concentration of amine or amide acetal. In order to assign other products two additional reactions have been carried out, *i.e.* that of *N*-formylmorpholine dimethyl acetal with morpholine [in the spectrum of the reaction mixture three signals appeared in the OMe region, a decreasing signal for acetal (**3**), increasing signals for aminal (**9**) and of MeOH] and that of DMF DMA with dimethylamine [the product was aminal (**7**) with a constant NMe_2:OMe signal intensity ratio of 4:1]. In the spectrum of products of reaction (3) the aminal (**5**) should have an NMe_2:OMe signal intensity ratio of 2:1, but the OMe signal at δ 3.26 was stronger than expected. The reaction of *N*-formylpiperidine dimethyl acetal with piperidine showed that its product, the aminal (**8**), had the same chemical shift of the OMe group as the aminal (**5**). The yield of (**5**) has been

Table 1. ^{1}H[a] and ^{13}C n.m.r. chemical shifts from Me_4Si of amide acetals, ester aminals, and orthoamides

Compound	Formula	Amide acetals[b] $R_2NCH(OMe)_2$ with R_2N	Chemical shift ^{1}H (δ)			Chemical shift [δ(p.p.m.)] ^{13}C					
			CH	OMe	NMe	CH	OMe	NMe	CH_2 in amino part α	β	γ
(1)	$C_5H_{13}NO_2$	Me_2N	4.30	3.19	2.18	113.17	53.23	37.49			
(2)	$C_8H_{17}NO_2$	Pip	4.29	3.19		113.22	53.18		46.64	25.87	25.14
(3)	$C_7H_{15}NO_3$	Mor	4.28	3.21		112.22	52.84		46.42	66.87	
(4)	$C_7H_{15}NO_2$	Pyr	4.38	3.26		113.25	53.18		46.68	24.23	
		Ester aminals[b] $R^1_2NCH(OMe)NR^2_2$ with									
		R^1_2N / R^2_2N									
(5)	$C_9H_{20}N_2O$	Me_2N / Pip	3.55	3.30	2.21						
(6)	$C_8H_{18}N_2O_2$	Me_2N / Mor	c	3.34	2.28						
(7)	$C_6H_{16}N_2O$	Me_2N / Me_2N	3.53	3.30	2.24	111.14	57.26	39.75			
(8)	$C_{12}H_{24}N_2O$	Pip / Pip	3.58	3.30		110.79	57.34		49.11	26.27	25.40
(9)	$C_{10}H_{20}N_2O_3$	Mor / Mor	c	3.38		109.66	57.99		48.46	67.01	
		Orthoamides[b] $(R_2N)_3CH$ R_2N									
(10)	$C_7H_{19}N_3$	Me_2N	3.04		2.34	108.85		41.36			
(11)	$C_{16}H_{31}N_3$	Pip	3.11								
(12)	$C_{13}H_{25}N_3O_3$	Mor	3.09								

[a] Calculated from the relation: $\delta_{Me_4Si} = \delta_{(Me_3Si)_2O} + 0.04$. [b] Me_2N = dimethylamino, Pip = piperidino, Pyr = pyrrolidino, Mor = morpholino. [c] The $O(CH_2)_2$ multiplet of morpholine is in the region δ 3.41—3.66.

Table 2. Yields of reaction products of *NN*-dialkylformamide dimethyl acetals with secondary amines

Reaction	Substrates: Acetal	Substrates: Amine	Time (min)	Temp. (°C)	Yields (%) of: Amide acetals (1)	(2)	(3)	(4)	Aminals (5)	(6)	(7)	(8)	(9)	Orthoamides (10)	(11)	(12)
(1)	(1)	Pyrrolidine	30	30				0								
			60	90				48			1					
(2)	(1)	Morpholine	20	30			0			10	4		10			
			20	90			28			10	4		10			
(3)	(1)	Piperidine	20	30		15			18		7	5				
(4)	(3)	Dimethylamine	20	30	13					15	9		5			
(5)	(1)	Dimethylamine	2	30							45			1		
(6)	(2)	Piperidine	18	30								46			16	
(7)	(3)	Morpholine	26	30									24			18

estimated from its NMe_2 signal area, and the yield of (**8**) from the difference of the OMe area.

In the spectra of products of reactions (6) and (7) the signal for MeOH was greater than should result from the exchange of one OMe group, indicating that the exchange of the methoxy groups of the amide acetal went further, *i.e.* to orthoamide (**11**) or (**12**). The yields of these compounds were calculated from the excess of the MeOH signal, because the CH signals of orthoamides were too small for reliable estimation of integrated areas.

In the ^{1}H n.m.r. spectra of the mixture of DMF DMA with *N*-methylaniline the NH signal of amine is shifted by 0.62 p.p.m. downfield with respect to its position in the spectrum of pure *N*-methylaniline, thus indicating that the hydrogen-bonded complex of amine with the oxygen and/or nitrogen lone pair of DMF DMA is formed. The formation of *N*-formyl-*N*-methylaniline dimethyl acetal did not take place, however, even on heating to 110 °C. Neither the intensity changes nor the signals of any product were observed.

The ^{1}H chemical shifts observed for the four amide acetals (Table 1) are almost the same; for ester aminals also the differences are small. The chemical shift of CH group is δ *ca.* 4.3, for amide acetals, δ 3.5 for aminals, and δ 3.0 for orthoamides, and thus a significant upfield shift of the CH signal is observed when exchanging methoxy for amino. Some regularities can be observed in the chemical shifts of OMe groups, *i.e.* with a decreasing number of OMe groups in the molecule the downfield signal shift of remaining OMe takes place.

For reactions (1) and (5)—(7) the ^{13}C n.m.r. spectra were recorded for the mixtures after equilibrium was achieved. The yield of products estimated from ^{1}H n.m.r. was > 20% and thus the time-consuming accumulation of ^{13}C n.m.r spectra for these samples could be avoided. The ^{13}C spectra of acetals (**1**)—(**4**) and of secondary amines were recorded separately as an aid in assignment.

The chemical shifts of the carbon CH in acetals are δ 112—113 p.p.m., in aminals δ 110—111 p.p.m., and in orthoamides δ 107—108 p.p.m.; with the exchange of methoxy for amino an

upfield shift of *ca.* 2 p.p.m. in the CH signal and a downfield shift of remaining OMe signal (*ca.* 53 in amide acetals and 57 p.p.m. in aminals) were observed.

The downfield shift of the NMe_2 signal can be observed in both the ^{13}C and ^{1}H n.m.r. spectra of the amine moiety when the order amide acetals → ester aminals → orthoamides is considered. The downfield shifts can be seen also for NCH_2 *i.e.* α-carbons, and for β(γ)-carbons, but the differences in ^{13}C chemical shifts are smaller.

Five distinct ester aminals were found in the reaction mixtures. Only three orthoamides were identified because of their low concentration and thus the low intensity of CH signals. The existence of these products confirmed, therefore, the occurrence of reactions (B) and (C). However, other reactions, for example rapid aminal–aminal equilibration, cannot be excluded. It is worth mentioning that the identification of products in the usual manner, for example, separation by distillation, is difficult to carry out because volatile products such as Me_2NH and MeOH leave the mixture during heating and the composition is changed. The appearance of ester aminals and orthoamides in significant concentrations (Table 2) explains the fact that the yield of transamination reaction is lower than 70%.[1]

The reactivity of the five amines studied toward DMF DMA increases as follows: *N*-methylaniline (does not react), pyrrolidine (no aminals, new acetal appeared at high temperature), morpholine (aminals at 30 °C, new acetal at high temperature), piperidine (aminals and acetal at 30 °C), dimethylamine (reaction reaches equilibrium after 2 min).

No simple correlation between reactivity and the pK_a values of the above amines is found because these values increase in the order *N*-methylaniline (3.49), morpholine (7.77), dimethylamine (9.56), piperidine (9.59), and pyrrolidine (9.77).[6]

The steric bulk of the amine can explain the smaller reactivity of piperidine when compared with dimethylamine because the pK_a values of both are similar.

Further studies on the kinetics and mechanisms of these reactions are in progress.

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