LACTAM ACETALS

IX.* DEUTERIUM EXCHANGE IN THE 1-METHYL-2-ARYLIMINOLACTAM SERIES

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The rate of deuteration of 1-methyl-2-aryliminolactams depends on the electronic character of the substituent in the benzene ring and on the size of the lactam ring. Deuterium exchange proceeds at the highest rate in piperidine derivatives that have electron-donor substituents in the benzene ring.

It is known [2, 3] that lactam ethers exist in solution in tautomeric equilibrium with the corresponding α-alkoxyenes (A ⇄ B), and this prototropic transformation can be realized only by means of stripping of a proton from the 3-position of the molecule

A B

TABLE 1. 2-Arylimino Derivatives of 1-Methyllactams

Compound	Temp., °C	Reaction time, h	mp or bp (mm), °C	n_D^{20}	Empirical formula	Found, %		Calc., %		Yield, %
						C	H	C	H	
Ia	60	1	163—164 (5mm)	1,5876	$C_{12}H_{16}N_2O$	70,5	7,9	70,6	7,8	79
IIa	60	1,5	76,0—76,5 a	—	$C_{13}H_{18}N_2O$	71,7	8,3	71,6	8,3	81
IIIa	40	2,5	84—86 b	—	$C_{14}H_{20}N_2O$	71,8	8,5	72,4	8,6	88
IIIb	40	3	158—159 (2mm)	1,5733	$C_{14}H_{20}N_2$	77,7	9,3	77,8	9,3	87
IIIc	20	3	147—148 (5mm)	1,5818	$C_{13}H_{18}N_2$	76,5	8,7	77,2	8,9	90
IIId	20	3	68—69 b	—	$C_{13}H_{17}N_2Cl$	66,1	7,3	66,1	7,2	69

[a] From hexane. [b] From petroleum ether.

TABLE 2. PMR Spectra (chemical shifts, ppm)

Compound	H^3	H^4	H^5	H^6	H^7	N-CH_3	Ar	p-OCH_3	p-CH_3
Ia	2,33	1,91	3,37	—	—	2,92	6,77	3,73	—
IIa	2,17	1,67		3,26	—	2,95	6,71	3,72	—
IIIa	2,35	1,63			3,44	3,05	6,60 d 6,80 d	3,74	—
IIIb	2,45	1,63			3,44	3,05	6,60 d 6,80 d	—	3,74
IIIc	2,39	1,62			3,41	3,05	6,65 d 6,88 t 7,28 t	—	—
IIId	2,36	1,65			3,45	3,05	6,62 d 7,02 d	—	—
IIIe	2,44	1,68			3,50	3,09	6,80 d 8,09 d	—	—

*See [1] for communication VIII.

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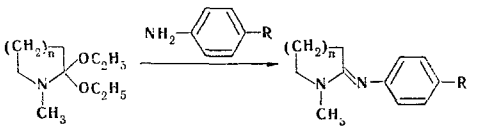
TABLE 3. Deuterium Exchange-Rate Constants in CD_3OD

Temp., °C	70	70	70	70	70	70	25	25	25	25	40
Compound	Ia	IIa	IIIa	IIIb	IIIc	IIId	IIIe	IIa	IIa+NH_3	IIa+quinuclidine	IIa+H_2SO_4	IIIa	IIIa
$K \cdot 10^{-5}$ sec^{-1}	13,025± ±0,838	51,634± ±4,78	6,176± ±0,163	2,484± ±0,224	1,098± ±0,069	0,661± ±0,066	0,239± ±0,028	0,575± ±0,071	1,790±0,151	1,545±0,099	1,816±0,114	0,133± ±0,013	0,907± ±0,173

Inasmuch as the electron-acceptor interaction (on the C_3 atom) of the imino ether and the amidine groupings is similar, one might expect that the protons attached to C_3 in amidines, which are readily obtained from lactam acetals [4], will also be sufficiently labile. This in turn creates the prerequisite for electrophilic substitution in the 3-position.

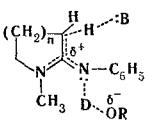
In this connection, the rate of deuteration in the presence of a large excess of CD_3OD was investigated for 1-methyl-2-aryliminolactams Ia, IIa, and IIIa-e, which were obtained from the diethyl acetals of N-methylbutyro-, valero-, and caprolactams (Table 1), by measurement of the integral intensities of the signals of the protons attached to C_3 in the PMR spectra (Table 2).* The rate constants were calculated from the first-order equation† by the method of least squares (see Table 3). It was found that the amidine with a six-membered ring (IIa) is deuterated at the highest rate. The rate of deuteration in the series of amidines IIIa-e depends substantially on the character of the substituent in the aromatic ring and decreases on passing from electron donors to electron acceptors.



I-III

I a n=1, R=OCH_3; II a n=2, R=OCH_3; III a-e n=3, a R=OCH_3; b R=CH_3; c R=H; d R=Cl; e R=NO_2

The dependence $\log K = 0.045 - 0.976\sigma_i - 1.52\sigma_R$ with multiple correlation coefficient $R = 0.964$ and $S_0 = 0.19$ was obtained by correlation of the rate constants obtained with the σ_i and σ_R constants. The low ρ_i and ρ_R values indicate that charged ions are absent in the transition state. The substantial contribution to the interaction of the conjugation effect makes it possible to represent the activated complex as follows (B is a solvent molecule or a second amidine molecule):



IV

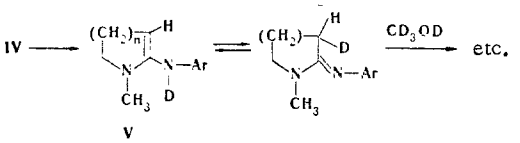
Correspondingly, electron-acceptor substituents should lower the stability of the activated complex and thereby decrease the rate of deuterium exchange; this is actually observed. The step that limits the rate of the reaction is detachment of a proton from the 3-position. The activation parameters for deuteration of amidine IIIa were obtained from data on the rate constants of the process at various temperatures (Table 3): $E^{\neq} = 17.21 \pm 0.05$ kcal/mole^{-1}; $\log A = 11.81 \pm 0.013$; $\Delta H^{\neq} = 16.62 \pm 0.05$ kcal/mole^{-1}; and $\Delta S^{\neq} = -6.5 \pm 0.057$ cal/mole^{-1} deg^{-1}. The relatively low activation entropy is in good agreement with the proposed structure of the transition state. As CD_3OD approaches the C_3 atom in the step involving the formation of the activated complex, with simultaneous detachment of a proton, one should have expected considerably larger $\Delta S^{\neq}$ values. On the basis of the preceding, it is possible to explain the change in the rate of deuterium exchange of amidines as a function of the size of the ring. Inasmuch as the protons are not in a shielded conformation only in the six-membered ring, the approach of base B to the protons attached to the C_3 atom in this case is less sterically hindered than in the case of five- and seven-membered amidines.

Deuterium exchange of protons in the 3-position of amidines I-III may be accelerated in the presence of basic or acidic catalysts. In the first case, the accelera-

*The integral intensity of the protons attached to C_3 was assumed to be one at the start of the recording.

†A pseudo first-order reaction is confirmed by the linear dependence of $\ln (C_0 - C)$ on time; $r > 0.96$, $S_0^2 = 0.07$-0.0006.

tion is achieved due to the effective interaction of the base with the hydrogen atom attached to C_3, while in the second case, acceleration is achieved by protonation of the N_2^1 atom and corresponding facilitation of detachment of protons from the 3-position of the molecule. This sort of examination corresponds to the general concepts of the mechanism of acid-base catalysis (for example, see [5]). The detachment of a proton from C_3 during the simultaneous addition of a deuteron to N'_2 may also not be accompanied by the addition of deuterium to form the C_3–D bond; this should lead to the appearance of enediamine tautomeric form V.



V

The data obtained do not exclude the assumption that the investigated amidines exist in tautomeric equilibrium with enediamines V. However, this equilibrium is almost completely shifted to favor the amidines, inasmuch as the signals of the enamine form are not detected in the PMR spectra in CD_3O_3 (see Table 2).

EXPERIMENTAL

The PMR spectra were recorded with a JNM-4H-100 spectrometer with tetramethylsilane as the internal standard.

1-Methyl-2-(p-anisidylimino)pyrrolidone (Ia). A 3.46-g (0.02 mole) sample of N-methylpyrrolidone diethyl acetal in 10 ml of dry chloroform was added to 2.46 g (0.02 mole) of p-anisidine in 15 ml of dry chloroform, and the mixture was stirred at 60° for 1 h. The solvent was evaporated, and the residue was distilled to give 2.6 g (79%) of Ia with bp 163-164° (5 mm). Compounds IIa and IIIa-d (see Table 1) were similarly synthesized from the appropriate acetals. Compound IIIe was previously described in [4].

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