Heterocycles. CII. Barriers to Rotation in Some N'-Heteroaryl N,N-Dimethylformamidines

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The free energies of activation about the =CH-NMe$_2$ bond in N'-heteroaryl N,N-dimethylform-amidines have been found in the range from 15.6 kcal/mole to 23 kcal/mole.

There has been a continuing interest in the barrier to rotation about the C-N bond in amides, thioamides and ureas (1,2), but for substituted formamidines, activation parameters for hindered rotation only for N'-t-butyl- (3) and some N'-aryl-N,N-dimethylformamidines (4,5,6) have been established.
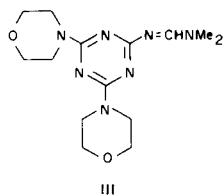
In this paper rotational barriers in formamidines bearing some heterocyclic residues have been studied by nmr technique.
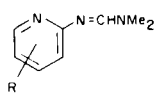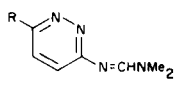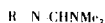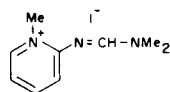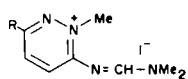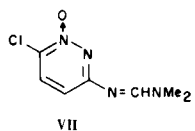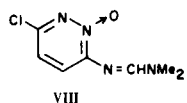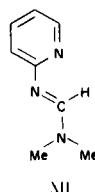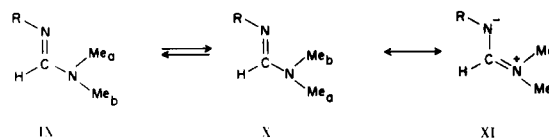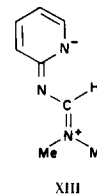

All compounds (Table I) were prepared from the corresponding aminoheterocycles and N,N-dimethylformamide dimethylacetal. For purposes of correlation an aliphatic (IVa) and phenylsubstituted derivative (IVb) are included.

Pyridyl and pyridazinyl formamidines are quaternized at the ring nitrogen giving compounds Va-d and VIa,b. The structure of these compounds follows from an inde-

TABLE I

N,N-Dimethyl-N'-substituted Formamidines

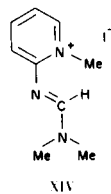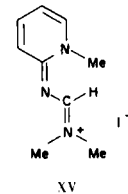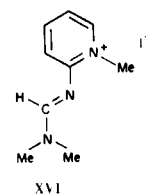| Com-pound	Mp (°C) or bp (°C/mm)	Nmr date: chemical shift (τ) and coupling constants J (Hz) (a) N=CH, N-(CH₃)₂	other proton resonances	Formula		C	H	N
Ia		A (295) 1.6 (s) 6.8 (s), 6.90 (s)	3.20 (ddd, H₃), 2.55 (ddd, H₄), 3.25 (ddd, H₅), 1.9 (ddd, H₆); J₃,₄ = 7.5, J₄,₅ = 7.5, J₃,₅ = 3.0, J₃,₆ = 1.0, J₄,₆ = 2.5, J₅,₆ = 5.6.					
Ib	229-231/760	A (295) 1.65 (s) 7.0 (s), 7.1 (s)	2.7 (dd, H₄), 3.3 (dd, H₅), 2.08 (dd, H₆); 7.75 (s, 3-CH₃); J₄,₅ = 7.5, J₅,₆ = 4.5, J₄,₆ = 1.5.	C₉H₁₃N₃	Calcd. Found	66.22 66.19	8.03 8.18	25.75 25.64
Ic	58-63; 100/3	A (295) 1.60 (s) 7.0 (s), 7.1 (s)	3.14 (s, H₃), 3.3 (d, H₅). 2.0 (d, H₆), 7.8 (s, 4-CH₃); J₅,₆ = 6.0.	C₉H₁₃N₃	Calcd. Found	66.22 66.51	8.03 7.89	25.75 25.91
Id	62-7; 100/3	A (295) 1.65 (s) 7.0 (s), 7.1 (s)	3.4 (d, H₃), 2.7 (dd, H₄), 2.08 (d, H₆), 7.85 (s, 5--CH₃); J₃,₄ = 8.7, J₄,₆ = 2.2.	C₉H₁₃N₃	Calcd. Found	66.22 66.15	8.03 7.87	25.75 26.21
IIa	42-6	A (302) 1.59 (s) 6.93 (s), 7.03 (s)	3.12 (dd, H₄), 2.78 (dd, H₅), 1.40 (dd, H₆); J₄,₅ = 9.0, J₅,₆ = 4.5, J₄,₆ = 2.0.	C₇H₁₀N₄	Calcd. Found	55.98 55.68	6.71 7.03	37.31 36.94
IIb	115 (b)	A (297) 1.62 (s) 6.97 (s), 7.05 (s)	2.96 (d, H₄), 2.55 (d, H₅); J₄,₅ = 9.4.	C₇H₉ClN₄	Calcd. Found	45.55 46.00	4.91 5.17	30.34 30.34
III	202-204 (b)	A (303) 1.20 (s) 6.82 (s), 6.98 (s)	5.85 (CH₂ of the morpho-line substituents).	C₁₄H₂₃N₇O₂	Calcd. Found	52.30 52.26	7.27 7.40	33.88 33.76
IVa	110-112/760	A (295) 2.75 (s) 7.3 (s)	7.0 (t, -CH₂N=), 9.2 (t, CH₃CH₂CH₂-), 8.65 (qt, CH₃CH₂CH₂); J_{CH₂CH₃} = 6.75, J_{CH₂CH₂} = 6.75.	C₆H₁₄N₂	Calcd. Found	63.11 63.13	12.36 12.60	24.53 24.71
IVb	231-232/760	B (273) 2.90 (s) 7.28 (s)	3.25 (m, C₆H₅).	C₉H₁₂N₂	Calcd. Found	72.94 72.45	8.16 8.38	18.90 18.82
Va	196-197 (c)	A (301) 1.45 (s) 6.70 (s), 6.85 (s)	2.4 (dd, H₃), 2.05 (ddd, H₄), 2.88 (ddd, H₅), 1.6 (dd, H₆), 4.1 (s, 1-CH₃); J₃,₄ = 8.25, J₃,₅ = 1.5, J₄,₅ = 6.75, J₄,₆ = 1.6, J₅,₆ = 6.75.	C₉H₁₄IN₃	Calcd. Found	37.20 36.99	4.84 5.03	14.25 14.35
Vb	177-178 (c)	A (301) 1.75 (s) 6.80 (s), 6.87 (s)	1.87 (dd, H₄), 2.75 (dd, H₅), 1.5 (dd, H₆), 6.1 (s, 1-CH₃), 7.70 (s, 3-CH₃); J₄,₅ = 7.5, J₄,₆ = 0.5, J₅,₆ = 6.0.	C₁₀H₁₆IN₃	Calcd. Found	39.42 38.91	5.25 5.19	13.83 13.53
Vc	273-274 (c)	A (299) 1.50 (s) 6.75 (s), 6.88 (s)	2.5 (d, H₃), 3.0 (dd, H₅), 1.7 (d, H₆), 6.1 (s, 1-CH₃), 7.63 (s, 4-CH₃); J₃,₅ = 1.5, J₅,₆ = 6.75.	C₁₀H₁₆IN₃	Calcd. Found	39.42 39.32	5.25 5.35	13.83 13.64
Vd	247-248 (c)	A (299) 1.60 (s) 6.80 (s), 6.90 (s)	2.58 (d, H₃), 2.12 (dd, H₄), 1.8 (d, H₆), 6.15 (s, 1-CH₃), 7.75 (s, 5-CH₃); J₃,₄ = 9.0, J₄,₆ = 2.5.	C₁₀H₁₆IN₃	Calcd. Found	39.42 39.60	5.25 5.47	13.83 13.45
VIa	192-193 (d)	A (299) 1.55 (s) 6.80 (s), 6.94 (s)	2.26 (d, H₄), 1.85 (dd, H₅), 0.75 (d, H₆), 5.67 (s, 2-CH₃); J₄,₅ = 9.2, J₅,₆ = 6.0.	C₈H₁₃IN₄	Calcd. Found	32.89 33.21	4.48 4.85	19.18 18.90
VIb	178-179 (d)	A (302) 1.13 (s) 6.63 (s), 6.76 (s)	1.70 (d, H₅), 1.80 (d, H₄), 5.96 (s, 2-CH₃); J₄,₅ = 9.4.	C₈H₁₂ClN₄	Calcd. Found	29.52 29.43	3.71 3.65	17.21 17.26
VII	153-154 (b)	A (305) 1.7 (s) 6.85 (s), 6.97 (s)	3.27 (d, H₄), 2.12 (d, H₅); J₄,₅ = 8.2.	C₇H₉ClN₄O	Calcd. Found	41.92 (e)	4.52	27.94 27.81
VIII	123-124 (b)	A (305) 1.2 (s) 6.90 (s), 7.0 (s)	2.77 (d, H₄), 2.13 (d, H₅); J₄,₅ = 8.2.	C₇H₉ClN₄O	Calcd. Found	41.92 (e)	4.52	27.94 27.95

(a) Solvents: A = DMSO-d₆, B = CS₂. Temperature (in °K) at which recording was made is given in parenthesis. (b) crystallized from ethyl acetate. (c) crystallized from ethanol. (d) crystallized from ethyl acetate and ethanol, 1:3. (e) The recorded mass spectrum corresponds to the formula.

pendent synthesis starting from the corresponding quaternized aminopyridines or aminopyridazines and N,N-dimethylformamide dimethylacetal.

All compounds under investigation exhibit in the tem-

perature range between -110° and +180° temperature dependent nmr spectra with typical coalescence patterns which are associated with the slow interconversion of IX and X. Since there is only one coalescence present, no

TABLE II

Activation Parameters for N'-Heteroaryl N,N-Dimethylformamidine
(in DMSO-d_6)

Compound	T_c (°K)	$\Delta\nu$ (cps)	k_c (s^{-1})	ΔG (kcal/mole)
Ia	305	4	8.9	16.6
	278	1.35	3.0	15.6 (a)
Ib	301	3.75	8.3	16.4
	290	3.0	6.0	15.8 (a)
Ic	312	5.7	12.6	16.7
	295	3.3	7.55	16.1 (a)
Id	308	5.25	11.7	16.6
	303	7.5	16.6	16.0 (a)
IIa	331	9.75	21.6	17.4
IIb	349	10.5	23.2	18.4
III	351	8.03	17.8	18.6
IVa	247.5	7.5	16.6	13.0
IVb	279.5	5.25	11.6	14.9
Va	431	8.25	18.3	23.0
Vb	394	6.75	15.0	21.1
Vc	431	8.3	18.4	22.4
Vd	426	6.8	15.1	22.8
VIa	434	8.03	17.8	23.1
VIb	>467	7.5	16.6	>25.2
VII	370	7.5	16.5	19.7
VIII	359	6.0	13.2	19.3

(a) In Carbon Disulfide.

TABLE III

N,N-Dimethyl-N'-(5-methylpyridyl-2)formamidine in
Various Solvents (0.368 molal concentration)

Solvent	DC, (a) ϵ	μ (D) (a)	T_c (°K)	$\Delta\nu$ (cps)	$\Delta G^{\ddagger}$ (kcal/mole)
CS$_2$	2.6	0	303	7.5	16.0
CD$_3$COCD$_3$	20.7	2.7	306	6.0	16.3
CD$_3$OD	32.6	1.65	312	6.0	16.1
CD$_3$CN	37.5	3.5	296	4.0	16.2
CD$_3$SOCD$_3$	48.5	3.9	308	5.25	16.6

(a) Taken for nondeuterated solvents from C. Reichardt: Lösungsmittel Effekte in der organischen Chemie, Verlag Chemie, 1969. DC = dielectric constant; μ = dipole moment; T_c = coalescence temperature; $\Delta\nu$ = the maximum chemical shift difference of two methyl signals (in Hz).

evidence for the existence of more than one isomer was obtained. It is possible to show that electron donating groups decrease $\Delta G^{\ddagger}$ while electron-wtihdrawing groups increase it. The additional π bonding in the resonance structure XI in the ground state should also account for an increase in the rotational barrier around the CH-N (CH$_3$)$_2$ bond. Since a nitrogen atom in an aromatic nucleus is known to be a strong electron withdrawer from the ortho and para positions, one can expect an increase in the barrier in N'-heteroaryl N,N-dimethyl substituted formamidines in comparison to N'-aryl substituted ones. However, if we are taking into consideration that $\Delta G^{\ddagger}$ values increase from $\Delta G^{\ddagger}$ = 13.0 kcal/mole (R = propyl) and 14.9 kcal/mole

(R = phenyl) to about 18 kcal/mole (R = pyridazinyl-3) and over 23 kcal/mole (R = 2-methylpyridazinylium-3) (Table II), one can conclude that some other resonance structures, such as XIII and XV must also be highly contributing. This reveals, that double bond character of the C-N bond is adequately increased. According to Pauling (7) a barrier of about 21 kcal/mole should correspond approximately to 40% double bond character.

The importance of the solvent has been demonstrated in the measurement of rotational barriers by high resolution nmr spectroscopy. For example, for $N.N$-dimethylacetamide the rotational barrier increases from approximately 12 kcal/mole in neat liquid to 24.7 kcal/mole in formamide

(8). As evident from the Table III, solvent polarity has practically no influence on the magnitude of $\Delta G^{\ddagger}$ values. The traces of acid have no effect on the coalescence temperature, but the addition of base results in the decomposition products.

Compounds of the types XII, XIV are most probably in the *anti* configuration. Evidence for this configuration was obtained from the absence of the nuclear Overhauser effect for compound Vb and from X-ray studies (9), excluding, thus, the alternative *syn* configuration, as XVI. The same is valid also for the corresponding quaternized compounds.

Finally, it should be mentioned that in the case of the two isomeric *N*-oxides, VII and VIII, only in the case of VIII is a downfield shift for the methine proton observed which also may be explained by the proximity of N-O and -CH= group as encountered in the *anti* configuration (as XII or XIV).

EXPERIMENTAL

Melting points were determined on a Kofler micro hot stage. Nmr spectra were recorded on a JOEL JNM-C-6OHL spectrometer (tetramethylsilane as internal standard), equipped with a custom-built variable temperature probe.

General procedure for the Preparation of N,N-Dimethyl-N'- substituted Formamidines.

A mixture of the corresponding amine (0.01 mole) and N,N- dimethylformamide dimethylacetal (1.2 g.) was heated under reflux for 1 hour. Eventual unreacted reagent was distilled off, the residue was treated with ethyl acetate (1 ml.) and the product was filtered off and purified by distillation *in vacuo* or crystallization. The synthesized compounds, their analytical and nmr data are listed in Table I. Yields were 54-90 %. The synthesis of compounds Ia (10) and IVb (11) (b.p. 231-232°) were reported previously.

General Procedure for the Synthesis of Quaternized N,N-dimethyl-N'-substituted Formamidines.

The corresponding formamidine (0.005 mole), methanol (10 ml.) and methyl iodide (1 g.) were heated under reflux for 3 hours. The solvent was distilled off and after addition of ethyl acetate (2 ml.) the product was filtered off. It was then dissolved in hot acetic acid, the acid was distilled *in vacuo* and the residue was suspended in ethyl acetate (1 ml.), filtered and crystallized. The

compounds obtained, their analytical and nmr data are listed in Table I.

Kinetic Measurements.

Temperature measurements are accurate to Tc = ± 0.5° and the measurement of $\Delta \nu$ was accurate to ± 0.5 Hz. We assign thus an average experimental error of ± 5 % to $\Delta G^{\ddagger}$ of each rate constant. The rate constant k_c is based upon comparison of observed spectral lines of pairs of coalescing signals at the temperature T_c where the two lines just coalesce to a broad singlet. The free energies of activation, $\Delta G^{\ddagger}$, for stereomutation were determined at the T_c from the Gutowsky-Holm equation, $k_c = \pi/\sqrt{2}$. $\Delta \nu$ and the Eyring equation (1). The validity of using these equations for determined k_c has been discussed recently. It has been found that values for k_c obtained by complete line shape analysis for equally intense coalescing singlets are within 20% of the rates obtained using the approximate equation (12).

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(9) An X-ray analysis of compound, performed by I. Leban, is in accord with the proposed configuration. An angle of 21,13° was observed betweeen the plane of the pyridazine ring and the -N=CHN atoms of the side chain. A detailed report on this structure analysis will be published elsewhere.

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