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Semiempirical (AM1) Studies of Possible and Preferred Site(s) of Porotnation in the Gas Phase for Polyfunctional Nitrogen Bases: N^1, N^1-Dimethyl-N^2-azinylformamidines[1)]

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Proton affinities for seven polyfunctional nitrogen bases (N^1,N^1-dimethyl-N^2-azinylformamidines) containing one amidine moiety and one, two or three nitrogen atoms in *ortho*-, *meta*-, and/or *para*-positions of the heterocyclic six-membered group have been predicted by semiempirical AM1 method. The preferred site(s) of protonation and exceptionally high gas-phase basicity of N^1, N^1-dimethyl-N^2-azinylformamidines containing 2-azinyl group *anti*periplanar to the functional carbon atom in the amidine moiety have been discussed. The effects of one group on the basicity of the other one have been compared with those found for the corresponding model amidines and azines.

Investigations of the proton transfer reactions in the gas phase have been carried out for many monofunctional organic acids and bases[2,3)] and numerous data (thermodynamic parameters: $\Delta G°$,$\Delta H°$) of these reactions have been compiled.[4)] However there are only a few data for polyfunctional compounds. Some exceptions are amino acids and peptides.

Recent experimental studies on the gas-phase basicities of N^1, N^1-dimethylamidines,[5)] (Me_2N–CR=NX, R = H, alkyl, aryl, NMe_2, X = H, alkyl, heteroalkyl, aryl) together with the theoretical calculations[6)] have indicated the possibilities of determination of the preferred site(s) of protonation and the substituent effects for compounds containing the amidine moiety.

These results encourage us to study the proton transfer reactions for more complicated polyfunctional N^1, N^1-dimethyl-N^2-azinylformamidines containing the nitrogen heterocycle and amidine moieties.[7)] Both frameworks are often present in biological macromolecules. N^1, N^1-Dimethyl-N^2-azinylformamidines are also found as strong neutral organic bases.[8)]

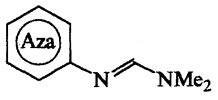
For our studies we have chosen 7 derivatives (Scheme 1, FDMP* Aza, **1**—**7**). To avoid the prototropic tautomerism in the amidine moiety, they contain two methyl groups at the amino nitrogen atom. Compounds **1**—**3** (N^1, N^1-dimethyl-N^2-pyridylformamidines) are the simplest examples of N^1, N^1-dimethyl-N^2-azinylformamidines. They contain only one amidine and 2-, 3-, and 4-azinyl group, respectively. In **1** and **2** the rotational isomerism of the aryl group may take place. This isomerism may influence the gas-phase basicity of each group. For this reason, compounds **4** and **6** (N^1, N^1-dimethyl-N^2-pyrimidinylformamidines) containing one amidine and 1,3-diazin-2-yl and -5-yl groups have also been considered. For **4** and **6** the rotational isomerism is absent. Compound **5** [N^1, N^1-dimethyl-N^2-(4-pyrimidinyl)-formamidine] with 1,3-diazin-4-yl group has been chosen to compare directly the effect of the amidine moiety on the gas-phase basicity of the nitrogen atoms in 1,3-diazine being in the same molecule. Since **5** displays the rotational isomerism of the aryl group, compound **7** [N^1, N^1-dimethyl-N^2-(1,3,5-triazin-2-yl)formamidine] has also been taken into account.

We use the semiempirical (AM1) method. This method has successfully been applied for prediction of the gas-phase basicities (as *PA*) for different carbon, nitrogen and oxygen bases.[9)] AM1 calculations supply also information on the geometry of neutral and protonated forms and the preferred site(s) of protonation. As model compounds we have chosen series of the corresponding formamidines and azines (Scheme 1, FDMP*X and AZA*X) for which the AM1 calculations have already been carried out.[6a,9—11)]

Results and Discussion

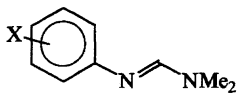
Most Stable Structures of N^1, N^1-Dimethyl-N^2-azinylformamidines and Their Ions. For our investigations of the geometry of neutral and protonated forms of at the AM1 level, E configuration on the C=N double bond in the amidine moiety has been chosen for all N^1, N^1-dimethyl-N^2-azinylformamidines **1**—**7**, as for the model formamidines[6a)] (FDMP*X). Moreover, for **1**, **2**, and **5**, two conformations (**a** and **b**) have been considered for neutral and protonated forms (Scheme 2). Due to lone pair/lone pair repulsion in conformation **a**, structures **1a**, **5a**, **1a**-Am, **5a**-Am, and **5a**-4-Aza are not stable enough. Therefore only a local minimum for each structure has been found. Selected geometrical parameters (bond lengths and angles) obtained for the neutral molecule and the corresponding amino, imino, and aza

N^1,N^1-Dimethyl-N^2-azinyl-formamidines



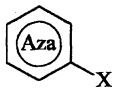
FDMP*Aza

Model formamidines



FDMP*X

Model azines



AZA*X

1 2-azinyl
2 3-azinyl
3 4-azinyl
4 1,3-diazin-2-yl
5 1,3-diazin-4-yl
6 1,3-diazin-5-yl
7 1,3,5-triazin-2-yl

Scheme 1.

protonated forms are given in Table 1.

Comparison of the data from Table 1 shows that the position and number of the nitrogen atoms in a heterocycle have significant influence only on the twist of the aryl group (see dihedral A^2–C^1–N^7=C^8 and A^6–C^1–N^7=C^8 in Table 1, where A is the carbon or nitrogen atom). The other angles and bond lengths change little in the neutral, amino, and imino protonated forms, and are of the same order of magnitude as for the model formamidines (FDMP*X).[6a]

For the aza protonated forms (**4**-2-Aza, **5**-Aza, **7**-Aza) it is interesting to mention that the C=N double bond in the amidine group is almost the same or even considerably longer than the C–N single bond. A similar effect is found for the X-protonated structures of model amidines with X = COMe and NO_2.[6a] In the literature there are only a few examples of amidines in which the equalization of the CN bond lengths in the amidine moiety as a result of substituent effects has been observed.[12] All examples represent some kind of so-called "push-pull" molecules, in which electron donating effects of the amino group are transmitted by resonance through the the imino group to an electron accepting substituent X, directly linked to the imino nitrogen atom or separated by a phenyl ring. In N^1, N^1-dimethyl-N^2-azinylformamidines protonated on the nitrogen atom of azinyl group, the electron accepting effects of the azonium group ($\sigma_{m,p} > 2$)[13] are three times higher than the NO_2 group ($\sigma_m = 0.71$, $\sigma_p = 0.78$).[14] For FDMP*4-NO_2, it was found that the C=N double bond is a little shorter than the C–N single bond.[15] Thus, for aza protonated N^1, N^1-dimethyl-N^2-azinylformamidines, the equalization of the CN bond lengths may be expected.

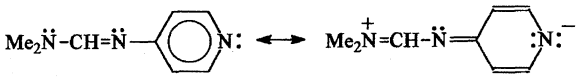
Possible and Preferred Site(s) of Protonation in N^1, N^1-Dimethyl-N^2-azinylformamidines. N^1, N^1-Dimethyl-N^2-azinylformamidines **1**—**7** can be treated as polyfunctional nitrogen bases. They contain the amidine moiety with two nitrogen atoms, the amino and imino, and additionally the nitrogen atom(s) in the heteroaromatic ring. Thus three sites of protonation (the amino, imino, and aza nitrogen atoms) are possible for **1**—**3**. For **4**—**7** there are one or two additional nitrogen atoms in the heteroaromatic ring. Therefore, four or five sites of protonation (the amino, imino, and two or three aza nitrogen atoms) are possible.

The possible conjugation of the lone pair of electrons on the amino nitrogen atom with the π electrons of the imino group in the amidine moiety (Eq. 1) decreases the basicity of the amino nitrogen atom and increases the basicity of the imino nitrogen atom. This means that the imino nitrogen atom should be the most preferred site of protonation in the moiety.

$$Me_2\ddot{N}–CH=\ddot{N}X \longleftrightarrow Me_2\overset{+}{\ddot{N}}=CH–\overset{-}{\ddot{N}}X \quad (1)$$

However, for N^1, N^1-dimethyl-N^2-azinylformamidines, the n–π conjugation effect in the amidine moiety may be transmitted to the nitrogen atom(s) in the heterocycle. This so-called "push-pull" effect may increase the basicity of the aza nitrogen atom. The stronger effect may be observed for **1** (Eq. 2), **3** (Eq. 3), **4**, **5**, and **7** with the aza nitrogen atom(s) in *ortho*- and/or *para*-position. For these derivatives, the aza nitrogen atom may be the most preferred site of protonation.

(2)



(3)

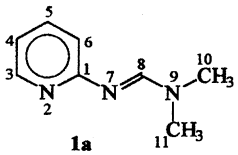
Semiempirical (AM1) calculations make possible the prediction of the gas-phase basicity of each site in polybasic N^1, N^1-dimethyl-N^2-azinylformamidines **1**—**7**. For this reason, the heats of formation ($\Delta_f H°$) have been calculated for all neutral, amino, imino, and aza protonated structures given in Scheme 2. Obtained results are summarized in Table 2.

The proton affinities (as *PA*) corresponding to the protonation on each possible site (the amino, imino, and aza nitrogen atoms) in compounds **1**—**7** have been predicted using Eq. 4. In calculations, the same conformation for neutral and protonated forms has been considered. Such treatment will make it possible to identify other effects such as lone pairs repulsion, rotation or chelation of proton. Obtained *PA* values are listed in Table 3.

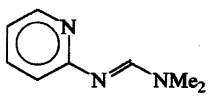
$$PA = \Delta_f H°(B) + \Delta_f H°(H^+) - \Delta_f H°(BH^+) \quad (4)$$

The first comparison of the calculated *PA* values shows that for all N^1, N^1-dimethyl-N^2-azinylformamidines **1**—**7** the amino nitrogen atom is the least basic site. The difference

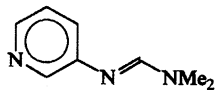
Neutral forms



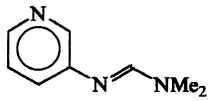
1a



1b



2a



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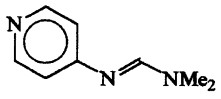
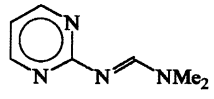
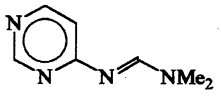


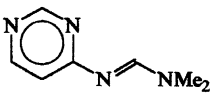
3



4



5a



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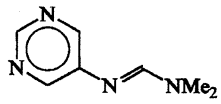
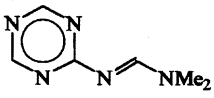
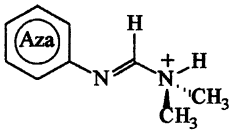


6



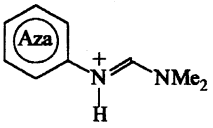
7

Amino protonated forms



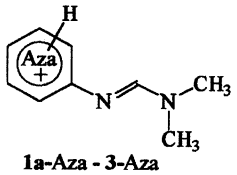
1a-Am - 7-Am

Imino protonated forms

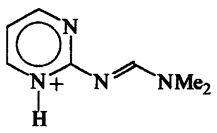


1a-Im - 7-Im

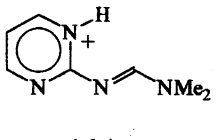
Aza protonated forms



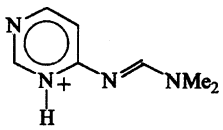
1a-Aza - 3-Aza



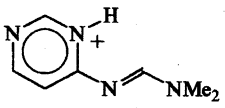
4-2-Aza



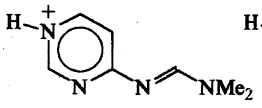
4-6-Aza



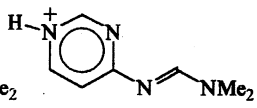
5a-2-Aza



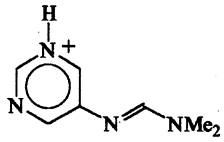
5b-2-Aza



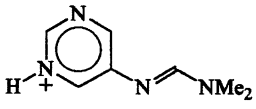
5a-4-Aza



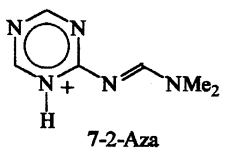
5b-4-Aza



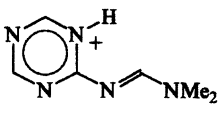
6-5-Aza



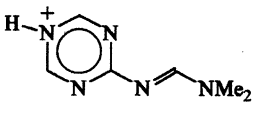
6-3-Aza



7-2-Aza



7-6-Aza



7-4-Aza

Scheme 2.

Table 1. Selected Geometrical Parameters (AM1) in the Gas Phase for N^1, N^1-Dimethyl-N^2-azinylformamidines **1**—**7** and Their Ions from Scheme 2

Structure	Symmetry	Bond lengths [Å]		Angles in degrees					
		$C^8=N^7$	C^8-N^9	$N^7=C^8-N^9$	$C^1-N^7=C^8-N^9$	$A^2-C^1-N^7=C^8$	$A^6-C^1-N^7=C^8$	$N^7=C^8-N^9-C^{10}$	$N^7=C^8-N^9-C^{11}$
A. Neutral forms									
1a	C1	(1.306)[a]	(1.402)[a]	(124.3)[a]	(−171.0)[a]	(−124.9)[a]	(59.7)[a]	(−152.5)[a]	(−8.4)[a]
1b	C1	1.312	1.395	123.3	−173.8	−172.9	7.9	−155.7	−6.3
2a	C1	1.308	1.400	124.2	−172.1	−150.4	33.0	−149.7	−5.0
2b	C1	1.308	1.400	124.2	−171.9	−149.7	33.9	−150.2	−4.9
3	C1	1.308	1.398	124.2	−172.0	−148.2	35.3	−150.9	−4.9
4	C1	1.311	1.393	123.3	−176.2	−143.6	−40.3	−158.8	−8.9
5a	C1	(1.306)[a]	(1.398)[a]	(124.0)[a]	(−170.7)[a]	(−120.2)[a]	(65.1)[a]	(−155.0)[a]	(−9.3)[a]
5b	C1	1.316	1.388	123.1	−174.0	−172.2	8.8	−159.7	−5.7
6	C1	1.310	1.396	124.1	−171.9	−152.3	31.5	−152.0	−5.2
7	C1	1.316	1.385	123.2	−171.6	−149.0	34.7	−158.0	−3.6
B. Amino protonated forms									
1a-Am	C1	(1.282)[a]	(1.496)[a]	(118.7)[a]	(−178.8)[a]	(172.8)[a]	(−7.4)[a]	(−63.3)[a]	(61.3)[a]
1b-Am	C1	1.287	1.495	119.6	−179.9	−179.9	0.1	−60.6	64.3
2a-Am	C1	1.287	1.492	119.5	−179.9	−179.4	0.7	−59.6	65.2
2b-Am	C1	1.287	1.492	119.5	−179.9	−179.0	1.1	−59.8	65.0
3-Am	C1	1.284	1.494	119.5	−179.8	−174.9	5.7	−60.4	64.4
4-Am	C1	1.284	1.495	119.2	−178.9	−148.7	33.8	−61.7	62.9
5a-Am	C1	(1.281)[a]	(1.497)[a]	(118.8)[a]	(−179.8)[a]	(175.7)[a]	(−4.6)[a]	(−64.7)[a]	(59.8)[a]
5b-Am	C1	1.286	1.495	119.6	180.0	179.6	−0.5	−61.6	63.3
6-Am	C1	1.288	1.491	119.5	−179.9	−179.4	0.7	−59.2	65.6
7-Am	C1	1.284	1.494	119.4	178.5	136.4	−46.8	−66.5	62.1
C. Imino protonated forms									
1a-Im	C1	1.348	1.346	125.7	175.5	−131.7	49.8	176.3	−2.8
1b-Im	C1	1.350	1.347	125.3	179.8	178.8	−1.3	179.8	−0.1
2a-Im	C1	1.347	1.347	125.9	179.7	−136.2	45.4	179.5	−0.7
2b-Im	C1	1.348	1.347	125.9	−179.4	−138.5	43.1	179.5	−0.5
3-Im	C1	1.348	1.346	125.8	−179.9	−144.8	36.6	180.0	−0.2
4-Im	C1	1.352	1.345	124.9	180.0	179.9	−0.1	180.0	0.0
5a-Im	C1	1.351	1.344	125.5	176.5	−140.7	40.7	177.6	−1.9
5b-Im	C1	1.354	1.344	125.3	179.9	179.3	−0.7	179.9	−0.1
6-Im	C1	1.350	1.346	125.8	−179.9	−135.8	49.1	179.4	−0.7
7-Im	C1	1.357	1.342	124.9	180.0	179.9	−0.1	180.0	0.0
D. Aza protonated forms									
1a-2-Aza	C1	1.342	1.351	122.5	−172.8	−163.7	19.7	−175.0	2.3
1b-2-Aza	C1	1.340	1.352	122.5	−171.3	−159.6	24.6	−171.7	2.6
2a-3Aza	C1	1.335	1.358	122.7	−174.7	−165.3	18.0	−174.4	1.4
2b-3-Aza	C1	1.333	1.358	122.8	−173.0	−159.7	24.6	−171.6	1.5
3-4-Aza	C1	1.345	1.350	122.6	−170.3	−166.5	16.8	−172.8	3.3
4-2-Aza	C1	1.355	1.346	121.9	179.5	179.5	−0.7	−179.7	−0.1
4-6-Aza	C1	1.340	1.350	122.4	−168.2	−149.0	36.7	−169.4	3.4
5a-2-Aza	C1	1.348	1.347	122.4	−172.1	−167.4	15.6	−175.2	2.5
5b-2-Aza	C1	1.346	1.347	122.4	−169.8	163.2	20.8	−172.2	3.3
5a-4-Aza	C1	(1.349)[a]	(1.347)[a]	(122.4)[a]	(−166.4)[a]	(−162.9)[a]	(21.2)[a]	(−170.7)[a]	(4.2)[a]
5b-4-Aza	C1	1.360	1.345	121.9	177.7	178.3	−2.2	178.8	−0.7
6-3-Aza	C1	1.339	1.355	122.6	−175.4	−168.4	14.4	−176.0	1.5
6-5-Aza	C1	1.338	1.355	122.7	−173.6	164.4	19.4	−173.5	1.8
7-2-Aza	C1	1.362	1.342	121.8	179.0	179.0	−0.9	179.5	−0.2
7-6-Aza	C1	1.348	1.345	122.3	−164.8	−164.8	29.6	−169.4	4.6
7-4-Aza	C1	1.366	1.341	121.8	164.8	164.8	−11.8	173.4	−4.2

a) Value obtained with use of the HyperChem program.

Table 2. Heat of Formation ($\Delta_fH°$ in kcal mol^{-1}) Calculated at AM1 Level for Neutral, Amino, Imino, and Aza Protonated Forms of N^1, N^1-Dimethyl-N^2-azinylformamidines **1**—**7** from Scheme 2

Structure	$\Delta_fH°$	Structure	$\Delta_fH°$	Structure	$\Delta_fH°$	Structure	$\Delta_fH°$
1a	(69.7)[a]	**1a**-Am	(232.4)[a]	**1a**-Im	202.5	**1a**-2-Aza	203.2
1b	65.0	**1b**-Am	224.6	**1b**-Im	198.7	**1b**-2-Aza	204.1
2a	63.5	**2a**-Am	225.2	**2a**-Im	200.8	**2a**-3-Aza	206.1
2b	63.4	**2b**-Am	225.1	**2b**-Im	200.5	**2b**-3-Aza	207.1
3	63.5	**3**-Am	227.9	**3**-Im	201.7	**3**-4-Aza	200.6
4	83.2	**4**-Am	246.2	**4**-Im	216.6	**4**-2-Aza	217.6
						4-6-Aza	226.8
5a	(80.3)[a]	**5a**-Am	(249.1)[a]	**5a**-Im	219.0	**5a**-2-Aza	218.0
5b	75.5	**5b**-Am	241.1	**5b**-Im	214.8	**5b**-2-Aza	218.9
						5a-4-Aza	(222.4)[a]
						5b-4-Aza	214.1
6	74.4	**6**-Am	239.6	**6**-Im	216.3	**6**-3-Aza	222.5
						6-5-Aza	223.2
7	95.3	**7**-Am	264.2	**7**-Im	234.6	**7**-2-Aza	234.1
						7-6-Aza	243.6
						7-4-Aza	237.8

a) Value obtained with use of the HyperChem program.

Table 3. Proton Affinities (*PA* in kcal mol^{-1}) Predicted for Each Site in N^1, N^1-Dimethyl-N^2-azinylformamidines **1**—**7** (Scheme 2) by AM1 Method

Proton transfer reaction	*PA*(Am)	Proton transfer reaction	*PA*(Im)	Proton transfer reaction	*PA*(Aza)	*PA*(Im)−*PA*(Am)	*PA*(Im)−*PA*(Aza)
1a-Am→**1a**	(204.6)[a]	**1a**-Im→**1a**	(234.6)[a]	**1a**-2-Aza→**1a**	(233.9)[a]	30.1	0.7
1b-Am→**1b**	207.6	**1b**-Im→**1b**	233.4	**1b**-2-Aza→**1b**	228.1	25.8	5.3
2a-Am→**2a**	205.5	**2a**-Im→**2a**	229.9	**2a**-3-Aza→**2a**	224.6	24.4	5.3
2b-Am→**2b**	205.5	**2b**-Im→**2b**	230.1	**2b**-3-Aza→**2b**	223.6	24.6	6.6
3-Am→**3**	202.8	**3**-Im→**3**	229.0	**3**-4-Aza→**3**	230.1	26.2	−1.1
4-Am→**4**	204.2	**4**-Im→**4**	233.8	**4**-2-Aza→**4**	232.9	29.5	0.9
				4-6-Aza→**4**	223.6		10.2
5a-Am→**5a**	(198.4)[a]	**5a**-Im→**5a**	(228.8)[a]	**5a**-2-Aza→**5a**	(229.7)[a]	30.4	−0.9
5b-Am→**5b**	201.6	**5b**-Im→**5b**	228.0	**5b**-2-Aza→**5b**	223.8	26.4	4.1
				5a-4-Aza→**5a**	(225.1)[a]		3.7
				5b-4-Aza→**5b**	228.6		−0.7
6-Am→**6**	202.0	**6**-Im→**6**	225.4	**6**-3-Aza→**6**	219.1	23.4	6.3
				6-5-Aza→**6**	218.4		7.0
7-Am→**7**	198.3	**7**-Im→**7**	227.9	**7**-2-Aza→**7**	228.4	29.6	−0.5
				7-6-Aza→**7**	218.9		9.0
				7-4-Aza→**7**	224.6		3.3

a) Value obtained with use of the HyperChem program.

between the *PA* values (ca. 20—30 kcal mol^{-1}) calculated for protonation at the imino and amino nitrogen atom is of the same order of magnitude as that found for series of model compounds FDMP*X.[6a] This confirms the n–π conjugation in the amidine moiety (Eq. 1). The higher ΔPA values (ca. 30 kcal mol^{-1}) are obtained for isomers containing the aza nitrogen atom(s) in *ortho*-position(s) (for **1a**, **4**, **5a**, and **7**) for which the lone pair/lone pair repulsion takes place. The smaller ΔPA values (ca. 20—25 kcal mol^{-1}) are found for derivatives with the aza nitrogen atom(s) in *meta*-position (for **2** and **6**).

The differences between the *PA* values for the imino and aza nitrogen atoms are considerably smaller ($\leq\pm10$ kcal mol^{-1}). Taking into account the different average errors for *PA* calculations found for the model series of amidines[6a] (FDMP*X, −1.3 kcal mol^{-1}) and pyridines[9—11] (−5.3 kcal mol^{-1}), we can draw the following conclusions:

The imino group seems to be more basic than the aza nitrogen only for compounds **2** and **6** containing one and two aza nitrogen atoms in *meta*-position of the heterocyclic group, respectively. The corrected *PA* value of the imino group (Table 4) is higher by ca. 1—3 kcal mol^{-1} than that of the corresponding nitrogen atoms in a heterocycle. The difference is still too small to establish the favored site of protonation.

The nitrogen atom in heterocycle seems to be more basic than the imino group for the other derivatives (**1**, **3**—**5** and **7**) containing one, two, and three aza nitrogen atoms in *ortho*- and/or *para*-position(s) of the heterocycle.

The gas-phase basicity of the 2-azinyl group depends on

Table 4. Proton Affinities (*PA* in kcal mol^{-1}) Corrected for N^1, N^1-Dimethyl-N^2-azinylformamidines **1**—**7** (Scheme 2) on the Basis of the *PA* Values Predicted by AM1 Method (Table 3) and the Average Errors for *PA* Calculations Found for the Model Series of FDMP*X (−1.3 kcal mol^{-1})[6a] and Pyridines (−5.3 kcal mol^{-1})[9—11]

Proton transfer reaction	*PA*(Im)	Proton transfer reaction	*PA*(Aza)	*PA*(Im)−*PA*(Aza)
1a-Im→**1a**	235.9	**1a**-2-Aza→**1a**	239.2	−3.3
1b-Im→**1b**	234.7	**1b**-2-Aza→**1b**	233.4	1.3
2a-Im→**2a**	231.2	**2a**-3-Aza→**2a**	229.9	1.3
2b-Im→**2b**	231.4	**2b**-3-Aza→**2b**	228.9	2.5
3-Im→**3**	230.3	**3**-4-Aza→**3**	235.4	−5.1
4-Im→**4**	235.1	**4**-2-Aza→**4**	238.2	−3.1
		4-6-Aza→**4**	228.9	6.2
5a-Im→**5a**	230.1	**5a**-2-Aza→**5a**	235.0	−4.9
5b-Im→**5b**	229.3	**5b**-2-Aza→**5b**	229.1	0.2
		5a-4-Aza→**5a**	230.4	−0.3
		5b-4-Aza→**5b**	233.9	−4.6
6-Im→**6**	226.7	**6**-3-Aza→**6**	224.4	2.3
		6-5-Aza→**6**	223.7	3.0
7-Im→**7**	229.2	**7**-2-Aza→**7**	233.7	−4.5
		7-6-Aza→**7**	224.2	5.0
		7-4-Aza→**7**	229.9	−0.7

the conformation of the aryl group. The 2-azinyl group *anti*periplanar to the functional carbon atom in the amidine group is more basic than that *syn*periplanar. For **1**, **4**, **5**, and **7**, the difference between the *PA* values of the 2-azinyl group *anti*periplanar and *syn*periplanar is equal to 5.8, 9.3, 5.9, and 9.5 kcal mol^{-1} respectively. That the values for **4** and **7** are almost double those for **1** and **5** may be explained by the planar structure found for the aza nitrogen protonated form (**4**-2-Aza and **7**-2-Aza in Table 1). For this form an intramolecular hydrogen bonding[2b] may be more easily formed (see below).

The 2-azinyl group *anti*periplanar is also more basic than the 4-azinyl group in compounds containing both the 2- and the 4-aza nitrogens in the same molecule (**5a** and **7** by 4.6 and 3.8 kcal mol^{-1}, respectively).

The difference between the corrected *PA* values (Table 4) for the 2-azinyl *anti*periplanar or 4-azinyl group and for the imino group is higher for **1**, **4**, **5**, and **7** (ΔPA ca. 3÷5 kcal mol^{-1}) than that for the 3-azinyl and imino group observed for **2** and **6** (ΔPA ca. −1÷−3 kcal mol^{-1}). Taking into account the wide range of errors for *PA* calculations for pyridines[10,11] (−1÷−11 kcal mol^{-1}), however, it is not evident which site is favored for protonation in the gas phase.

The 2-azinyl group *syn*periplanar is less basic than the 4-azinyl group in **5b** and **7** (by 4.8 and 5.7 kcal mol^{-1}, respectively). Its corrected *PA* value is close to or smaller than that of the imino group in **1b**,**4**,**5b**, and **7** (by 1.3, 6.2, 0.2, and 5.0 kcal mol^{-1},respectively). The higher difference found for **4** and **7** may result from the enhancement of basicity of the imino group in the almost planar structure (**4**-Im and **7**-Im) due to a chelation of proton by two nitrogen atoms[2b] and/or a relief of lone pair/lone pair repulsion in the neutral base upon protonation[16] (see below).

Gas-Phase Basicity of N^1, N^1-Dimethyl-N^2-azinylformamidines. Since the choice of the most basic site is not clear, N^1, N^1-dimethyl-N^2-azinylformamidines **1**—**7** can be considered as formamidines with the electron-accepting azinyl group(s) as substituent(s) or as azines with the electron-donating N=CH–NMe$_2$ group as substituent. In both cases, effects of substituents on the gas-phase basicity of the possible site of protonation can be estimated by comparison of the *PA* values calculated for N^1, N^1-dimethyl-N^2-azinylformamidines (Table 3) with those for the corresponding model compounds, formamidines[6a,b](FDMP*X) and azines[9—11] (AZA*X).

Comparison of the calculated *PA*(Im) values for **1**—**7** and reference base,[6a] FDMP*H, gives substituent effects of the aza nitrogen atom(s) on the basicity of the imino nitrogen atom in the amidine moiety [δPA(Im)]. Comparison of the calculated *PA*(Aza) values for **1**—**7** and pyridine[9] gives substituent effects of the amidine moiety on the basicity of the aza nitrogen [δPA(Aza)]. Obtained results are summarized in Tables 5 and 6. Effects of selected substituents, electron-accepting groups (X=4-COMe, CN, CF$_3$, and NO$_2$) in model

Table 5. Comparison of the Gas-Phase Substituent Effects (in kcal mol^{-1}) of the Aza Group on the *PA* Values of the Amidine Group (the Imino Nitrogen Atom) in N^1, N^1-Dimethyl-N^2-azinylformamidines (FDMP*Aza, **1**—**7**) and the Corresponding Model Formamidines (FDMP*X)[6a]

FDMP*Aza	δPA(Im)	FDMP*X	δPA(Im)
1a	0.2	X : H	0
1b	−1.0		
2a	−4.5	4-COMe	− 3.7
2b	−4.3		
3	−5.4	4-CN	− 6.1
4	−0.6		
5a	−5.6	4-CF$_3$	− 7.3
5b	−6.4		
6	−9.0	4-NO$_2$	−11.1
7	−6.5		

formamidines[6a] and electron-donating groups (X=NH_2 and NMe_2) in model azines[9—11] on the calculated *PA*(Im) and *PA*(Aza) values have also been given in Tables 5 and 6, respectively.

The calculated gas-phase aza effects [δPA(Im) in Table 5] for N^1, N^1-dimethyl-N^2-azinylformamidines **1**—**7** treated as formamidines are close to those found for FDMP*X with typical electron-accepting groups (X=4-COMe, CN, CF_3, and NO_2). Exceptions are the 2-azinyl group in **1** which seems to be a weakly electron-donating for the 2-azinyl *anti*periplanar conformation **a** and a weakly electron-accepting group for the 2-azinyl *syn*periplanar conformation **b**, and the 1, 3-diazin-2-yl group in **4** which seems to be a weakly electron-accepting group. All effects of the nitrogen atoms of azine are more or less additive.

The calculated gas-phase substituent effects of the amidine moiety (N=CH–NMe_2) for compounds **1**—**7** treated as azines [δPA(Aza) in Table 6] are considerably higher than those of the NH_2 group in the corresponding model azines. They are close to those of the NMe_2 group (except derivatives with the 2-azinyl *anti*periplanar group). In solution, these effects have been found to be higher than for the NH_2 group and smaller than for the NMe_2 group.[8,17,18]

Comparison of the δPA(Aza) values for FDMP*Aza, AZA*NH_2, and AZA*NMe_2 (Table 6) shows that the substituent effects of the amidine, NH_2 and NMe_2 groups are differently transmitted to the nitrogen atom(s) in 2-, 3- or 4-azinyl group. The 2- and 4-azinyl group in comparison to the 3-azinyl group are more favored for the NH_2 and NMe_2 than for the N=CH–NMe_2 group for derivatives containing one aza nitrogen (**1**—**3**). Additional nitrogen atom(s) in the heterocycle decrease both the basicity of azines and of N^1, N^1-dimethyl-N^2-azinylformamidines considered as azines, and the effects observed for azines are higher.

Exceptions are observed for derivatives with the 2-azinyl *anti*periplanar group [**1a**(2-Aza), **4**(2-Aza), **5a**(2-Aza), and **7**(2-Aza)]. For **1a**(2-Aza) the effects of the amidine moiety are considerably higher than for **3**(4-Aza) with the 4-azinyl group. For the other [(**4**(2-Aza), **5a**(2-Aza), and **7**(2-Aza)] these effects are only reduced by the additional aza nitrogen in the heterocycle. The exceptional substituent effects of the 2-azinyl group in AZA*NH_2 and AZA*NMe_2 are not observed. In azines the substituent effects of the amine moiety (NH_2 and NMe_2) in 2-Aza are smaller than those in 4-Aza.

For a derivative with a 2-azinyl *syn*periplanar group [**1b**(2-Aza)], the δPA(Aza) value is smaller by 2 kcal mol^{-1} than for the corresponding derivative with 4-azinyl group [**3**(4-Aza)]. The decrease of basicity of **1b**(2-Aza) may result from a difference in stabilization of the neutral and protonated forms. In the neutral molecule, an intramolecular hydrogen bonding between the 2-azinyl *syn*periplanar group and the hydrogen atom at the functional carbon in the amidine moiety may additionally stabilize the conformation **b** (Chart 1). This extra interaction disappears during protonation.

A similar effect (but reduced by the additional aza nitrogen atom in the heterocycle) may be observed for other derivatives with the 2-azinyl *syn*periplanar group [**4**(6-Aza), **5b**(2-Aza), and **7**(6-Aza)]. Taking into account the weak acidity of the hydrogen atom at the functional carbon atom in the amidine moiety, we think that such kind of intramolecular stabilization in the neutral molecule is not so strong as the chelation effect of proton by two nitrogen atoms of almost the same basicity in monoprotonated derivatives with the

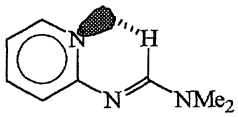
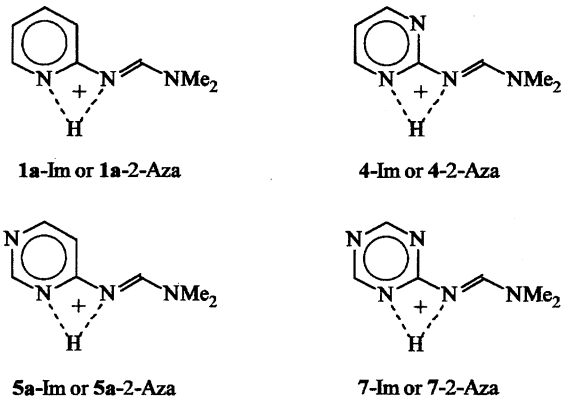


Chart 1.

Table 6. Comparison of the Gas-Phase Substituent Effects (in kcal mol^{-1}) of the Amidine Group on the *PA* Values of the Aza Group in N^1, N^1-Dimethyl-N^2-azinylformamidines (FDMP*Aza, **1**—**7**) and the Corresponding Model Azines (AZA*NH_2 and AZA*NMe_2); Pyridine Used as the Reference Base[9]

FDMP*	δPA(Aza)	Reference	AZA*NH_2	δPA(Aza)	Reference	AZA*NMe_2	δPA(Aza)	Reference
1a (2-Aza)	18.8	This work	2-Aza	7.6	10	2-Aza	11.3	10
1b (2-Aza)	13.0	This work						
2a (3-Aza)	9.5	This work	3-Aza	4.4	10	3-Aza	7.0	10
2b (3-Aza)	8.5	This work						
3 (4-Aza)	15.0	This work	4-Aza	12.0	10	4-Aza	14.8	10
4 (2-Aza)	17.8	This work	2(or 6)-Aza	(2.2)[a]	This work	2(or 6)-Aza	(6.9)[a]	This work
4 (6-Aza)	8.5	This work						
5a (2-Aza)	14.6	This work	2-Aza	(2.0)[a]	This work	2-Aza	(6.4)[a]	This work
5a (4-Aza)	10.0	This work	4-Aza	(7.0)[a]	This work	4-Aza	(10.5)[a]	This work
5b (2-Aza)	8.7	This work						
5b (4-Aza)	13.5	This work						
6 (3-Aza)	4.0	This work	3(or 5)-Aza	(−1.9)[a]	This work	3(or 5)-Aza	(1.0)[a]	This work
6 (5-Aza)	3.3	This work						
7 (2-Aza)	13.3	This work	2(or 6)-Aza	(−4.1)[a]	This work	2(or 6)-Aza	(1.2)[a]	This work
7 (6-Aza)	3.8	This work						
7 (4-Aza)	9.5	This work	4-Aza	(1.6)[a]	This work	4-Aza	(6.3)[a]	This work

a) Calculated with use of the HyperChem program.



Scheme 3.

2-azinyl *anti*periplanar group [**1a**(2-Aza), **4**(2-Aza), **5a**(2-Aza), and **7**(2-Aza)].

Exceptionally high basicity of the 2-azinyl *anti*periplanar group observed for compounds **1a**(2-Aza), **4**(2-Aza), **5a**(2-Aza), and **7**(2-Aza) may be explained by an intramolecular hydrogen bonding in the imino or aza protonated forms and/or by a relief of lone pair/lone pair repulsion in the neutral base upon protonation (Scheme 3).

N^1, N^1-dimethyl-N^2-azinylformamidines **1**, **4**, **5**, and **7** with their exceptionally high basicity can be compared with so-called "proton sponges", for which an enhancement of basicity has been observed not only in the gas phase but also in solution.[19] Although N^1, N^1-dimethyl-N^2-azinylformamidines differ from typical "proton sponges" by their conformational flexibility, the formation of an intramolecular hydrogen bonding in the protonated forms seems to be similar.

Computational Details

AM1 calculations for N^1, N^1-dimethyl-N^2-azinylformamidines **1**—**7** were performed using the SPARTAN (at the University of California, Irvine) and/or the HyperChem programs (at the Agricultural University, Warszawa).[20]

Geometrical parameters and heats of formation (as $\Delta_f H°$) in the gas phase at 298.15 K were found for all neutral, imino, amino and aza protonated forms given in Scheme 2. Proton affinties (as *PA*) were obtained from the calculated $\Delta_f H°$ values for the corresponding neutral and protonated forms and the experimental $\Delta_f H°$ value for proton, similarly as proposed by Dewar and Dieter.[9]

The HyperChem program gives systematically the $\Delta_f H°$ values which are slightly smaller (by ca. 0.2—0.3 kcal mol^{-1}) than those from the SPARTAN program. However both programs give almost the same *PA* values (the differences are not higher than $\pm$0.1 kcal mol^{-1}).

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