Studies on the Tautomerism of 2-Anilinopyridine and Related Heterocycles

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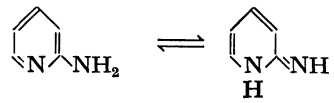
2-(*N*-Methylanilino) and 1-methyl-2-phenylimino derivatives of pyridine and quinoline were prepared as models for the amino and the imino tautomers of 2-anilino-pyridine and -quinoline. The ultraviolet, infrared and NMR spectra of these compounds were compared with those of the model compounds. The spectral data show that the amino tautomers are by far preferred in various solvents. The pK_a measurement on 1-methyl-2-phenylimino-1,2-dihydropyridine allows the assumption of the tautomeric equilibrium constant.

Tautomerism of aminopyridines has long been studied by several investigators, and earlier researches, mostly by chemical means, was summarized by Angyal *et al.*[1] 2-Aminopyridine is proved to exist as amino- (**1a**) by comparing its ultraviolet spectrum with those of 1-methyl-2-pyridoneimine and 2-dimethylaminopyridine,[2] and M. J. Cook *et al.*[3] have determined the tautomeric equilibrium constant between **1a** and **1b**.



(**1a**) (**1b**)

The infrared spectroscopic studies affirmed the above conclusion,[4,5] and the dipole moment[6] and mass spectrometric[7,8] investigations were also carried out. Molecular orbital calculations[9] have predicted that the amino tautomer is more stable than the imino one.

As to anilinopyrines Cook *et al.* have recently discussed their tautomeric behavior on the basis of the ultraviolet spectra.[10] On the other hand, Bell[11] and Rud'ko[12] measured the infrared spectra of a series of substituted 2-anilinopyridines and assumed the existence of the imino tautomers. The present authors have investigated on the splittings of the N–H stretching absorptions of 2-anilino-pyridines and -lepidines, and assigned them to the rotational isomers.[13] The possibility of the tautomeric equilibrium is rejected on the basis of the fact that 3-carboline, which can exist as tautomers but not as rotational isomers, show only a single symmetric N–H stretching band. The present report deals with the tautomerism of 2-anilinopyridine and related heterocycles by means of ultraviolet, proton magnetic resonance and molecular orbital theoretical approaches, and excludes the presence of the considerable amounts of the imino tautomers.

Experimental

Preparation of Materials. *2-Anilinopyridine and Its Methyl Derivatives*: 2-Anilinopyridine (**2**) and 2-(*N*-methylanilino)-pyridine (**3**) are known substances, and prepared by the condensation of 2-chloropyridine with aniline or *N*-methylaniline according to the procedures reported previously.

1-Methyl-2-phenylimino-1,2-dihydropyridine (1-methylpyridone phenylimine) (**4**), the model of the imino tautomer, was prepared by the following procedure. In a sealed tube, 11.4 g of 2-chloropyridine and 28.4 g of methyl iodide were heated for 3 h at 130 °C to produce 2-iodo-1-methylpyridinium iodide. The product of this methylation procedure depends on the reaction temperature, and 2-chloro-1-methylpyridinium iodide is obtained when the reaction is run at room temperature for 24 h. The 2-chloro and 2-iodo methiodides were identified by the different chemical shifts (δ: 4.40 and 4.48, respectively) of *N*-methyl protons. The iodo-methiodide thus obtained was condensed with aniline by heating it with an excess of aniline for 1 h at 100 °C. The crude 1-methyl-2-anilinopyridinium iodide was recrystallized from chloroform. Brownish yellow needles with mp 175—178 °C (decomp.). Yield: 55%. The same iodide was obtained by reacting 2-anilinopyridine with methyl iodide.

The elimination of hydrogen iodide to produce the anhydrobase (**4**) was accomplished by reacting freshly prepared silver oxide. The crude anhydrobase was obtained almost quantitatively and then it was extracted with cyclohexane and recrystallized from hexane. Yellow prisms with mp 70.5 °C. Found: C, 78.50; H, 6.61; N, 15.31%. Calcd for $C_{12}H_{12}N_2$: C, 78.23; N, 6.57; N, 15.20%. MS, *m/e* 184 (parent peak).

2-Anilino-4-methylquinoline[16] *and Its Methyl Derivatives*: 2-(*N*-methylanilino)-4-methylquinoline (**6**) is a hitherto unknown substance and prepared by a similar procedure with 2-anilino-4-methylquinoline. A mixture containing 5.3 g of 2-chloro-4-methyl-quinoline, 3.9 g of *N*-methylaniline, 4.3 g of anhydrous potassium carbonate and a few drops of pyridine was heated for 4 h at 140 °C. The reaction mixture was digested with 50 ml of 30% aqueous K_2CO_3 solution. Then, the product was extracted with chloroform and distilled under reduced pressure. Recrystallization from hexane gave yellow prisms. Yield; 58% mp, 81 °C. Found: C, 81.95; H, 6.51; N, 11.52%. Calcd for $C_{17}H_{16}N_2$: C, 82.22;, H, 6.49; N, 11.28%. 1,4-Dimethyl-2-phenylimino-1,2-dihydroquinoline (1-methyl-2-lepidone phenylimine) (**7**) was prepared similarly to 1-methyl-2-phenylimino-1,2-dihydropyridine. The final product was recrystallized from hexane to give yellow prisms. Overall yield from 2-chloro-4-methylquinoline is 9.2%. Mp, 112 °C. Found: C, 82.43; H, 6.63; N, 11.35%. Calcd for $C_{17}H_{16}N_2$: C, 82.22; H, 6.49; N, 11.28%. MS, *m/e* 248 (parent peak).

Measurements of the Spectra. Ultraviolet spectra were measured with a Hitachi EPS-3T recording spectrophotometer in various solvents. The solvents were purified in the following way. Chloroform and carbon tetrachloride were carefully distilled immediately before use, and water was distilled at least twice. The others were commercially available spectrograde ones. NMR spectra were measured with a JEOL JNM C60-H high resolution spectrometer and,

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Table 1. The ultraviolet spectra

Compound	Solvent	λ_{max} (nm)	ε_{max} (cm mol l^{-1})	Compound	Solvent	λ_{max} (nm)	ε_{max} (cm mol l^{-1})
2-Anilinopyridine (**2**)	C_6H_{12}	300—310 sh	7000		CH_3OH	320	7500
		275	18600			260	8500
	CH_3CN	305—310 sh	7500		H_2O	318	10200
		273	21100			250	7900
	CH_3OH	310—315 sh	7000	2-Anilino-4-methyl-quinoline (**5**)	C_6H_{14}	360	9400
		273	19700			345	10600
2-(*N*-Methyl-anilino)pyridine (**3**)	C_6H_{12}	293	10900		$CHCl_3$	355	9600
		243	11200			347 sh	9300
	CH_3CN	310—315	6500		CH_3OH	355	8300
		285	9300			349	8700
		240	9200	2-(*N*-Methyl-anilino)-4-methyl-quinoline (**6**)	C_6H_{14}	358 sh	8200
	CH_3OH	310	5900			346	9200
		282	8000		$CHCl_3$	360 sh	8000
		241	9000			350	8600
1-Methyl-2-pyridone phenylimine (**4**)	C_6H_{12}	373	4100		CH_3OH	356 sh	6900
		280	11900			347	7300
	CCl_4	374	4200	1,4-Dimethyl-2-phenylimino-1,2-dihydro-quinoline (**7**)	C_6H_{14}	383	8900
		283	11800		CCl_4	383	7800
	CH_3CN	366	4800		$CHCl_3$	378	9400
		285	11300		CH_3OH	370	10700
	$CHCl_3$	366	5900				
		288	13500				
	$HCO(CH_3)_2$	370	5500				
		288	12800				

sh: shoulder.

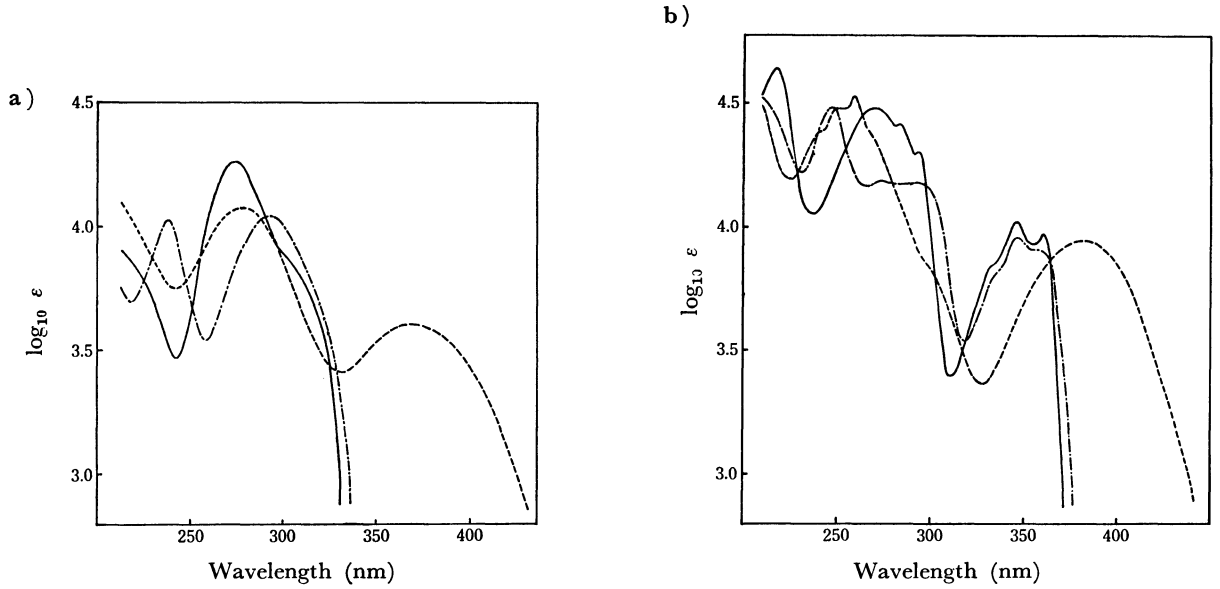


Fig. 1. The ultraviolet spectra of a) 2-anilinopyridine (**2**) [——] and its *N*-methyl derivatives (**3**) [—·—] and (**4**) [----]; b) 2-anilino-4-methylquinoline (**5**) [——] and its *N*-methyl derivatives (**6**) [—··—] and (**7**) [----].

when necessary, $Eu(fod)_3$ was used to separate the overlapping signals. Infrared spectra were obtained by employing a Hitachi Model 225 grating infrared spectrometer. Besides the usual 4000—400 cm^{-1} region spectra in potassium bromide pellets, the 1700—1600 cm^{-1} region ($\nu_{C=N}$ region) spectra were measured in various solvents of a wide range of polarity, including both protic and aprotic ones. Mass spectra were determined with a Hitachi RMU-6L mass spectrometer.

Results and Discussion

Ultraviolet Spectra and MO Calculations. The ultraviolet absorption maxima of 2-anilinopyridine, 2-anilino-4-methylquinone and their *N*-methyl derivatives are given in Table 1 and some typical spectra of them are illustrated in Fig. 1. As recognized at a glance of Fig. 1, the spectra of 2-anilinopyridine and

Table 2. The results of MO calculations[25]

a) Total π-Electronic and Transition Energies.

Compound			Amino-form	Imino-form
2-Anilino-pyridine	E_π	HMO(β_0)	20.0374	19.9436
		PPP(eV)	−625.8672	−624.5931
	ΔE[a]	HMO($-\beta_0$)	1.4958	1.0243
		PPP(eV)	4.9228	4.3306
			(251.8 nm)	(286.3 nm)
2-Anilino-quinoline	E_π	HMO(β_0)	25.7376	25.7350
		PPP(eV)	−886.7434	−886.0459
	ΔE[a]	HMO($-\beta_0$)	1.1756	0.9080
		PPP(eV)	4.5632	3.9081
			(271.7 nm)	(317.2 nm)

b) Bond Orders.

Bond	2-Anilinopyridine		2-Anilinoquinoline	
	Amino-form	Imino-form	Amino-form	Imino-form
N(exo)-C(2)	0.3416	0.7213	0.3304	0.6382
N(1)-C(2)	0.6201	0.4696	0.6645	0.4587
C(2)-C(3)	0.6291	0.3672	0.5677	0.4999
C(3)-C(4)	0.6797	0.8650	0.7835	0.7786
C(4)-C(5 or 10)	0.6534	0.4187	0.5418	0.4909
C(5)-C(6) [or C(9)-C(10)]	0.6741	0.8403	0.5221	0.5487
C(6 or 9)-N(1)	0.6487	0.4321	0.5385	0.4168
C(5)-C(10)[b]	—	—	0.5605	0.5821
C(5)-C(6)[b]	—	—	0.7196	0.6994
C(6)-C(7)[b]	—	—	0.6076	0.6289
C(7)-C(8)[b]	—	—	0.7192	0.6919
C(8)-C(9)[b]	—	—	0.5620	0.6042
N(exo)-C(1′)	0.2875	0.3134	0.2873	0.3123
C(1′)-C(2′)	0.6371	0.6186	0.6371	0.6202
C(2′)-C(3′)	0.6728	0.6777	0.6728	0.6772
C(3′)-C(4′)	0.6626	0.6586	0.6626	0.6591

a) The lowest π-π^* transitions are given. b) Bonds in the carbocyclic ring of quinoline nucleus.

2-anilino-4-methylquinoline are similar to those of the corresponding 2-(*N*-methylanilino) derivatives and different considerably from those of the 1-methyl derivatives. This tendency is quite general when the spectra in aprotic solvents (given in Table 1) are compared. This suggests that 2-anilinopyridines (**2**) exist as amino tautomers at least in these solvents. Results of MO calculations on these tautomers are in accordance with the observations. In all cases, the amino structure is estimated to be more stable than the imino structure irrespective of the calculation methods.

The imino model compounds **4** and **7** possess intense bands at longer wavelengths. They are located at 372 and 383 nm, respectively in inert nonpolar solvents, and assigned to the π-π^* electronic transitions of the iminodiene chromophores from their intensities and locations. The imino tautomers are predicted to possess iminodiene characters judging from the bond alternation in the heterocyclic rings (as shown in the bond order values in Table 2). Considerable destablization of the imino tautomer might arise from

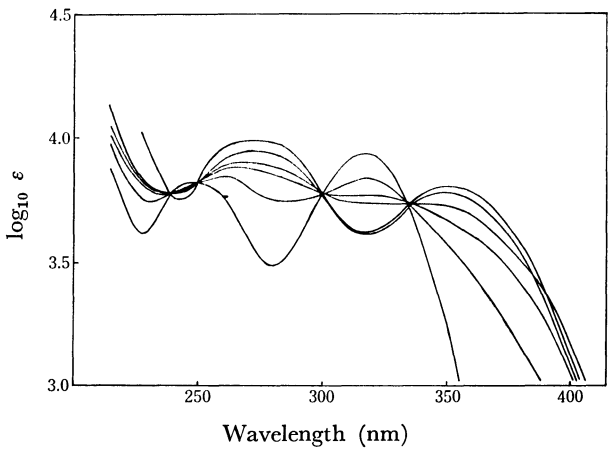


Fig. 2. The ultraviolet spectra of 1-methyl-2-phenyl-imino-1,2-dihydropyridine at various pH's.

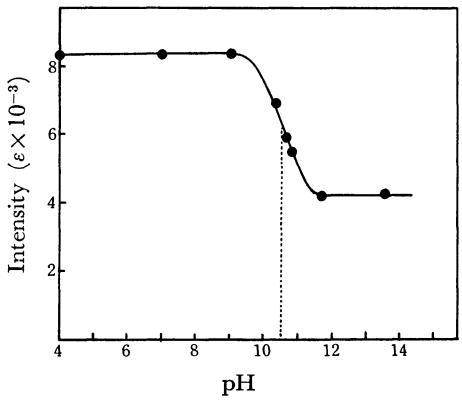


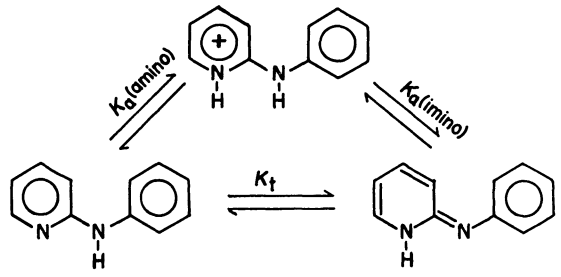
Fig. 3. The pH dependence of the intensity of the 318 nm-band of the anhydrobase (**4**).

the loss of aromaticity in the heterocyclic ring. The lowest π-π^* transition from the destablized ground state to the "aromatic" excited state should shift to the longer wavelength, and this actually occurs in the spectra of the imino model compounds **4** and **7**.

The absorption patterns of 2-anilinopyridine and 2-anilino-4-methylquinoline are similar to those of the corresponding amino model compounds **3**, **6**, and rather insensitive to the nature of the solvent. However, the lowest π-π^* bands of the 1-methyl derivatives **4** and **7** shift towards longer wavelengths with increase in the polarity of the solvents. By far larger hypsochromic shifts are observed when protic solvents are used for the measurement of the former imino compound, and this is assumed to arise from its protonation in this solvents. The anhydrobase (**4**) is expected to be enough basic to capture the hydroxylic protons from the protic solvents (alcohols and water). Existence of the acid-baseq euilibrium is assertained by observing the isosbestic points at 335, 300, and 249 nm in its ultraviolet spectra measured at different pH's (shown in Fig. 2).

Then, the ionization constant, pK_a, of the anhydrobase (**4**) is determined from the pH dependence of the ultraviolet spectra. Thus, the intensity of the its 318 nm peak is plotted against pH, and pK_a of **4** is estimated to be 10.5 from the curve shown in Fig. 3. The tauto-

meric equilibrium constant between the amino and the imino forms of 2-anilinopyridine is estimated according to the scheme proposed by Angyal *et al.*[1] for the estimation of the pK_a of 2-aminopyridine.



(**2a**) (**2b**)

If the pK_a's of the both forms (**2a** and **2b**) are known, the tautomeric equilibrium constant K_t is easily obtained by the following equation.

$$K_t = \frac{[\mathbf{2a}]}{[\mathbf{2b}]} = \frac{K_a(\text{amino})}{K_a(\text{imino})}$$ [17]

Since the K_a values of the amino and the imino tautomers could not be determined separately by any means, those of the model compounds are used instead for the calculation of the tautomeric equilibrium constant. The K_a values of **3** (6.0×10^{-6}) is comparable to that of 2-anilinopyridine (1.4×10^{-6}) itself. Moreover, the effect of *N*-methyl substitution is not serious upon the pK_a values of pyridone and its thio analogs,[18-20] the above assumption might be permissible. The K_t is then calculated to be 2×10^5. As expected, the predominance of the amino form is again proved.

NMR Spectra. The NMR spectra of the heterocyclic ring protons of 2-anilinopyridine, 2-anilino-4-methylquinoline and their *N*-methyl derivatives are given in Table 3. The assignments of the signals are based on the comparison with those of analogous heterocycles and on their lanthanide induced shifts.

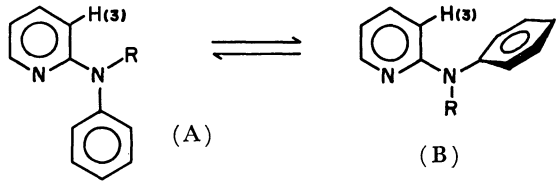
As described in the preceding part of this report, a considerable decrease in aromaticity is predicted to the heterocyclic part of the imino tautomer. Jackman *et al.*[21] have assumed the low field shift by the "ring current" of aromatic ring structure to be 1.55 ppm, and have estimated the aromaticity of pyridones. The ring current theory has been criticized by several authors.[22] However, the chemical shift serves doubtlessly as an index for aromaticity, since there exists a close relationship between aromaticity and diamagnetic susceptibility. The heterocyclic protons of the imino compounds **4** and **7** resonate at remarkably higher fields. The high field shift of 0.95 ppm (in average) in the 2-anilinopyridine series corresponds to 41% of aromaticity if evaluated by Jackman's method, and loss of aromaticity is again significant. In 2-anilino-4-methylquinoline series, the high field shift is about half of that in the 2-anilinopyridine series. The loss of aromaticity is considerably less. This is in accordance with the fact that the anhydrobase (**7**) of the anilinoquinoline series is a weaker base with lesser extent of bond alternation.

Table 3. The NMR spectra (δ ppm in $CDCl_3$)

Compound	H(3)	H(4) or CH_3	H(5)	H(6)	N-CH_3
(**2**)	7.25	7.44	6.65	8.14	—
(**3**)	6.54	a)	6.47	8.16	3.47
(**4**)	6.35	a)	5.69	7.16	3.47
(**5**)	6.78	2.53	—	—	—
(**6**)	6.49	2.38	—	—	3.54
(**7**)	6.31	2.21	—	—	3.70

a) The H(4) signals of these compounds cannot be separated from the phenyl signals even when the shift reagent was added.

When compared with those of the parent anilino derivatives, the 3-H of the heterocyclic part resonates at a higher field in 2-(*N*-methylanilino) derivatives. As described in a previous paper of the present authors,[13] 2-anilinopyridines can exist either of the rotational isomers (A) or (B).



(A) (B)

In 2-anilino-pyridine and -4-methylquinoline, the rotamer (A) is somewhat more stable than the rotamer (B) probably because of the steric hindrance between the hydrogen atom at 3-position (3-H) and the phenyl. When the substituent R is methyl, the CH_3–H(3) interaction in conformer (A) prevent the planar arrangement of the heterocyclic ring and exocyclic nitrogen.[23] This enforces to take a twisted conformation about the exocyclic C_2–N bond which have larger double bond charactor than the N–Ph bond. On the other hand, the conformer (B) can still be coplanar by the sacrifice of the N–Ph coplanarity. Thus, the conformer (B) might become more favorable when the substituent on the anilino nitrogen is changed from hydrogen to methyl. In this conformation, the 3-H lies just above the phenyl ring and is subject to its diamagnetic effect which produce a high field shift.

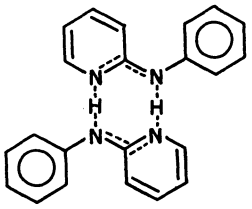
Infrared Spectra. The tautomerism will affect profoundly the N–H stretching and the C=N stretching modes of vibration in the infrared region. The ν_{NH} spectra were discussed in the previous paper of the present authors.[13]

1-Methyl-2-pyridoneimine absorbs intensely at 1652 cm^{-1} and this band is assigned to the C=N stretching mode of vibration. 2-Anilinopyridine also has a weak absorption at 1650 cm^{-1} in the solid state, and Rud'ko *et al.* have concluded the existence of the imino tautomer. Thus, the spectra in the $\nu_{C=N}$ region are measured for a series of compounds investigated, and tabulated in Table 4. The absorption which appears at 1645 cm^{-1} is tentatively assigned to the C=N stretching mode; since it is very intense in the spectra of the imino model compound (**4**). As the solution spectra of 2-anilinopyridine shows no absorption in this region, this compound is supposed to take solely the amino form. However, since 2-anilinopyridinium salts have also the 1645 cm^{-1} bands (as shown in Table 4), the weak 1645 cm^{-1} band of 2-anilinopyridine in the solid state cannot necessarily related to the presence of

Table 4. The infrared spectra in the 1700 to 1600 cm^{-1} region

Compound	Medium	ν_{max} (cm^{-1})	ε_{max} (cm $mol\ l^{-1}$)
(**2**)	KBr(solid)	1645	weak
	CCl_4	—	—
(**3**)	KBr(solid)	—	—
	CCl_4	—	—
(**4**)	KBr(solid)	1645	strong
	C_6H_{12}	1644	1200
	CCl_4	1644	1200
	CH_3CN	1645	1100
	$CHCl_3$	1644	960
		1652	620
	CH_3OH	1646	620
1-Methyl-2-anilino pyridinium iodide	KBr(solid)	1642	strong
	$CHCl_3$	1647	650
	CH_3OH	1647	60
(**5**)	KBr(solid)	1612	medium
(**6**)	KBr(solid)	1614	medium
(**7**)	KBr(solid)	1637	strong

a small amount of the imino tautomer. At present, the participation of a strongly hydrogen bonded dimeric structure (**2d**) also explains the infrared spectra, rather more adequately, since a remarkably lower NH stretching frequency is observed in the solid spectra of (**2**).



(**2d**)

In conclusion, 2-anilinopyridine (**2**) and 2-anilino-4-methylquinoline (**5**) exist as the amino tautomers. In solutions, the tautomeric equilibria are so preferable to the amino tautomers that no indications to the coexistence of the imino tautomer is obtained. Tautomeric equilibria in solids are not thoroughly studied; however, it is evident that the amino tautomer is by far more predominant than the imino tautomer.

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