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AN *ab initio* STUDY OF PROTONATION AND ALKYLATION OF AMINOPYRIDINE

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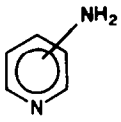
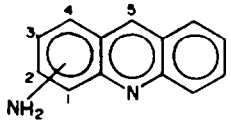
Abstract—STO-3G *ab initio* calculations show that the first site of protonation in 2-, 3- and 4-aminopyridines is the cyclic nitrogen, whatever the position of the amino group. There is an excellent linear relationship between the calculated proton affinities and the experimental pK_a values ($r = 0.995$). The protonation site is also confirmed by $\pi \rightarrow \pi^*$ transition energy variations as a function of position of the amino-group due to protonation; these effects are connected with the MO structures. Basicity and reactivity in alkylation reveal lone pair localization.

While investigating the redox reaction of heterocyclic amines with tetracyanoquinodimethane (TCNQ) and hydroquinone which led to radical salt (Scheme 1), it was found that solid state properties of the resulting salts depend essentially on the starting amine structure.[1] Salts obtained from 2- and 3-aminopyridines have a metallic behavior in contrast to 4-aminopyridine. One reason could be a change of the protonation site along the series. Either the ring nitrogen atom or the amino group nitrogen atom.



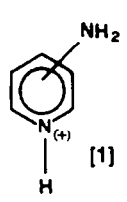
In the case of 2- and 3-aminopyridines, protonation on the ring nitrogen atom is suggested as it involves bathochromic shifts on the lowest $\pi \rightarrow \pi^*$ transition of 13 and 27 nm respectively;[2] if it involved the extracyclic one, hypsochromic shift would have been expected.[2-4] For protonation of the 4-aminopyrinine, as a very small hypsochromic shift is observed[2] the situation is rather complex and difficult to assess. Protonation on an extracyclic nitrogen atom has been already proposed for 1, 2, 3 or 4-aminoacridines but in position 5 the cyclic nitrogen



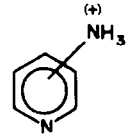
seems to be protonated first by comparison of UV spectrum of 5-aminoacridine and 9-aminoanthracene.[5]

Quantum mechanical calculations of the electronic structure of aminopyridines and their cations have been reported,[6,7] indicating a ring nitrogen protonation for all cases. Meanwhile, these calculations cannot take into account the amine basicities by evaluation of proton affinities, and do not predict UV spectra correctly for neutral aminopyridines.

First we calculated, using a minimal basis set STO-3G,[8] the two protonated systems **1** and **2** in order to appreciate which one of the two is the more stable.



[1]

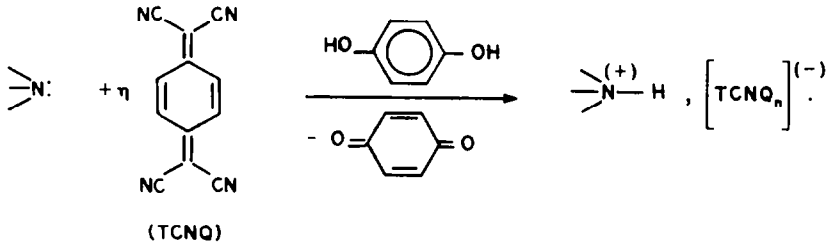


[2]

As *ab initio* molecular calculations at the minimal basis set STO-3G level[8] have been successful in reproducing the experimental gas phase energies (relative proton affinities) for a variety of proton transfer equilibria,[9-11] we now describe calculations for aminopyridines and their monocations. The protonation energy (+ also defined as the negative proton affinity[12]) corresponds, in the gas phase, to the following reaction:

$$[B\text{–}H]^+ \rightleftharpoons B + H^+$$

We then calculated the protonation energies ΔE_{prot} for protonation of aminopyridines either at the cyclic N_1 **1** or at the extracyclic N_{72} by taking the differences between



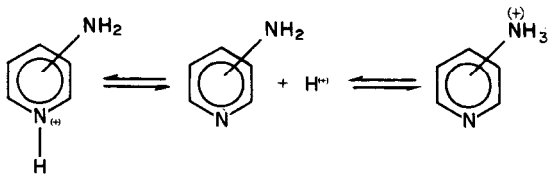
(TCNQ)

Scheme 1.

the total energies of **B** and the total energies of **1** or **2**:

$$\Delta E_{prot}\,\mathbf{1} = E_{\mathbf{B}}^{tot} - E_{\mathbf{1}}^{tot}$$

$$\Delta E_{prot}\,\mathbf{2} = E_{\mathbf{B}}^{tot} - E_{\mathbf{2}}^{tot}$$



1 B 2

(a = unsubstituted; b = 2–NH_2; c = 3–NH_2; d = 4–NH_2)

These values can be tentatively correlated with the observed pK_a values.

From the calculated molecular orbitals, we tried to confirm the protonation effect on the lowest transition shifts.

Protonation sites of aminopyridines

Relative stabilities of the two protonated species. Results of the *ab initio* calculation (E_{tot}) and the differences of stabilities between the protonated species in position 1 and 7 $\{\Delta E = E_1^{tot} - E_2^{tot}\}$ are given in Table 1.

For pyridine, the employed geometry parameters come from X-ray data.[13] For aminopyridines, their ring structures are taken identical to that of pyridine with standard parameters for NH_2 groups[14] and postulating a sp_3 hybridation of the extracyclic N atom as in aniline.[15,16] For the protonated species, we assume the ring structure being unchanged. When the ring nitrogen is protonated, the planarity around it is taken as suggested by previous calculations[17] with a N^+–H bond length of 1.043 Å, optimized value in $CH_2{=}NH_2^+$, very close to the 1.04 Å found by Jordan.[18] In the tetrahedral protonated aminogroups, the C–N^+ bond length is calculated as 1.51 Å, value optimized in $CH_2{=}CH{-}NH_3^+$, and N^+–H ones as 1.044 Å.[19]

For each pair of cations, the calculated ΔE values indicate that systems **1** are more stable than cations **2**. These results confirm the Konishi previous calculations[6] using a semiempirical method for valence electron system.[7] Calculations are in agreement with the conclusions obtained from UV data for monoprotonation of aminopyridines.[2–5]

Correlation between aminopyridine pK_as and the calculated protonation energies. The basicity of aromatic heterocycles can be related to the protonation energy ΔE_{prot} of a base so far as the entropy of protonation is constant or proportional to the protonation energy.[21–23]

$$pK_a \propto \Delta E_{prot}$$

The ΔE_{prot} values against the pK_a ones given in Table 1 are plotted in Fig. 1.

Figure 1 shows a very good linear relationship between the observed pK_{a1} values and the calculated ΔE_{prot} for monoprotonation on the cyclic nitrogen N_1.[24] On the other hand, there is no such a relationship if we consider the ΔE_{prot} for protonation on the extracyclic nitrogen atom N_7. This clearly indicates that the ring nitrogen is involved in the first protonation.

It is noteworthy to point out, as shown several times, the existence of a good parallelism between the relative proton affinities in the gas phase and amine basicities in solution.[25,26] It was also shown a relationship between pK_a and the delocalized bond energy ΔE_π of the heterocyclic compound.[27] This good agreement between calculated ΔE_{prot} values and observed pK_a ones is consistent with the fact, reported by Elliott and Mason[28] that the variation in the pK_a's is primarily due to enthalpy changes rather than entropy changes. With the Gaussian 70 program with a minimal basis set STO-3G, we get a very good linear relationship (r = 0.995) though a ASMO-SCF treatment leads to a discrepancy between ΔE_{prot} and pK_a values.[6] As the assumed geometries are the same for Ref. 6 and us, this good correlation observed is due to a much better parametrization of the program used here.

As previously noticed[29–32] the net electronic charges are not adequate neither to predict the different basicities, since $q_{N_7} > q_{N_1}$ (see Table 1) nor to take into account the relative basicities since q_{N_1} sequence is different from the pK_a one. It has also been shown[32] that it exists a good linear correlation between the n orbital energy and the experimental proton affinities.

Transition energies in aminopyridines and their cations

Up to now, the only experimental fact for the first site of protonation of aminopyridines comes from UV observations. As STO-3G calculations give good results for predicting the protonation site and the basicity scale, one can wonder if it works as well to take into account of the transition energies of the neutral molecules and their monoprotonated corresponding ones. Therefore, we have to evaluate the lowest UV transition, i.e. the difference energies $\Delta\epsilon$ between the HOMO and the LUMO of the π systems:

$$\Delta\epsilon = \epsilon_{\pi^*} - \epsilon_{\pi}.$$

Neutral molecules. In Table 2 are listed the energy levels ϵ_π and ϵ_{π^*} of highest occupied π molecular orbitals and the lowest unoccupied π^* ones. We also report the calculated $\Delta\epsilon$, and, for sake of comparison, we indicate the λ_{max} observed values.[2,33]

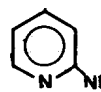
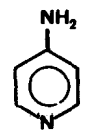
As shown in Fig. 2, it appears a good agreement between the calculated transition energies and the reciprocal of the experimental λ_{max} values (r = 0.971).

So the $\Delta\epsilon$ calculated values obtained for the two lowest $\pi \rightarrow \pi^*$ transitions are predict quite well the observed effects on λ_{max} according to the substituents position[34] in contrast with the previous calculations.[6]

Monoprotonated systems. In Table 2, we also give the π and π^* energy levels of the pyridinium and aminopyridinium **1** and the calculated $\Delta\epsilon$ values with the observed λ_{max}.[2,33] The same parameters are given for the N_7 protonated species **2**. As already noticed for neutral species, we observed a very good relationship (r = 0.966) between calculated $\Delta\epsilon$ and the experimental ones figured by $1/\lambda_{max}$ values (see Fig. 3). We should notice that such a linear relationship is not observed if we consider the first protonation site to be nitrogen atom 7.

Protonation effect on the transition energy changes. From comparison of the calculated $\Delta\epsilon$ values for neutral species **B** and monoprotonated ones **1** or **2** it appears that (a) if the first protonation occurs at the extracyclic N_7 atom, a hypsochromic effect should be expected since calculated $\Delta\epsilon$ is increased by protonation[35] (for instance $\Delta\epsilon$ = 0.498 a.u. for **Bb** and 0.532 a.u. for **2b** (b) if it occurs at the cyclic N_1 atom, a bathochromic effect could be

Table 1. Calculated energies of neutral (E_B) and protonated species E_1 and E_7; protonation energies; experimental pKa and net total changes of aminopyridines

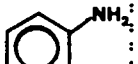
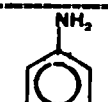
B =	E^{tot}_B (in a.u.)[a]	E^{tot}_1 and E^{tot}_2 (in a.u.)	$\Delta E = E^{tot}_1 - E^{tot}_2$ (in kcal/moles)	$\Delta E_{prot} = E^{tot}_B - E^{tot}_1$ or 2 (in a.u.)	$pKa^{b)}$ 20° C	net total charge densities in B q_{N_1}	q_{N_7}
 a	-243.63378[c]	1a -244.07121[d]	-	1a 0.43743	5.23	-0.238	-
 b	-297.95789	1b -298.40296 2b -298.38228	-12.98	1b 0.44507 2b 0.42439	6.86	-0.272	-0.402
 c	-297.95223	1c -298.39236 2c -298.36582	-16.65	1c 0.44013 2c 0.41359	5.98	-0.228	-0.400
 d	-297.95287	1d -298.40575 2d -298.37101	-21.80	1d 0.45288 2d 0.41814	9.17	-0.258	-0.400

a)1 a.u. = 627.5 kcal/mole.
b)pKa_1 values for the first protonation (20).
c) total energy = −243.6158 a.u. according to (18)
d)total energy = −244.0626 a.u. according to (18).

Table 2. Observed λ_{max} values for neutral and monoprotonated substituted aminopyridines.[2,33] and the corresponding calculated Transition Energies $\Delta\epsilon = \epsilon_\pi^* - \epsilon_\pi$ (in a.u.)

	NEUTRAL SPECIES B				MONOPROTONATED SPECIES						
						on N_1 atom			on N_7 atom		
	λ_{max} (nm)	ϵ_π	ϵ_π^*	$\Delta\epsilon_B$	λ_{max} (nm)	ϵ_π	ϵ_π^*	$\Delta\epsilon_1$	ϵ_π	ϵ_π^*	$\Delta\epsilon_2$
 a	252	-0.302	0.240	0.542	254.5	-0.533	-0.046	0.487	—	—	—
 b	288	-0.255	0.243	0.498	300	-0.478	-0.027	0.451	-0.488	0.044	0.532
 c	288	-0.256	0.242	0.498	315	-0.464	-0.040	0.424	-0.484	0.049	0.533
 d	265	-0.263	0.251	0.514	263	-0.491	-0.020	0.471	-0.481	0.038	0.519

Table 3. UV shifts related to C_π and C_π^* atomic coefficients

				
C_{π,N_1}	0.541	0.278	0.158	0.471
C_{π^*,N_1}	0.644	0.588	0.625	0.628
$\Delta\lambda_{exp}$ (nm)	+ 2.5 (33)	+ 12 (2)	+ 27 (2)	- 2 (2)

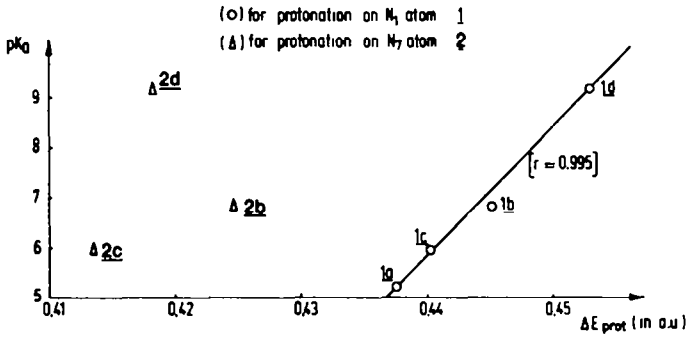


Fig. 1.

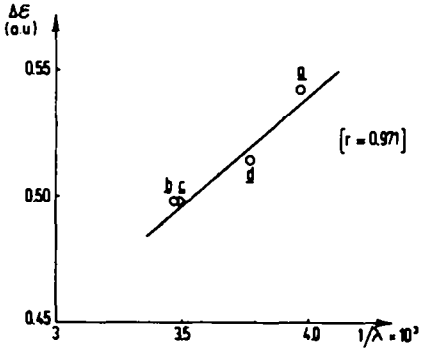


Fig. 2.

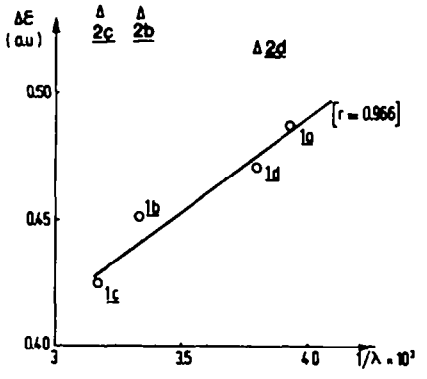


Fig. 3.

predicted since $\Delta\epsilon$ is decreased by protonation (for instance $\Delta\epsilon = 0.498$ a.u. for **2b** and 0.451 a.u. for **1b**).

Consequently, the observed bathochromic effects on λ_{1max} positions[2] argue for the N cyclic protonation.[37] This bathochromic effect (i.e. the π and π^* become energetically closer when the molecules are protonated) is due to a more important stabilisation of the π^* molecular orbital vs the π one. It is known that the effect of protonation on all molecular orbitals is to stabilize them and it is much more effective when the orbitals are more localized.[6, 38, 39]

Calculations show that in neutral species the MO atomic coefficients on the N_1 atom is greater in the π^* MO compared to the π one (see Table 3) inducing a greater stabilization of the π^* MO and therefore the batochromic effect. We should notice that this effect is much greater as the magnitude of the coefficients in π^* and π are more different.

Such an explanation is also consistent with the hypsochromic effect observed for the second protonation of 3-aminopyridine.[3] This effect could be foreseen when considering the MO atomic coefficients on N_7 atom in monocation **2c** as they have greater value in the π than in the π^* orbital (0.593 in π versus 0.047 in π^*).

We may quote here that it can be easy, in the same way, to justify the protic solvent effects on the $n \rightarrow \pi^*$ and $\pi \rightarrow \pi^*$ transitions of the α-enones.[40] As an n orbital is more localized than π^* one an hypsochromic effect occurs on the $n \rightarrow \pi^*$ transition, while the π^* is more localized on oxygen atom than the π orbital,[41] a bathochromic effect is expected and observed[40] on the $\pi \rightarrow \pi^*$ transition.

Regioselectivity of the alkylation of aminopyridines

In protonation we have been dealing with a thermodynamic process. We now investigate a kinetic process considering the alkylation of aminopyridines. These species can be considered as ambident nucleophiles which are able to react either by the cyclic N_1 atom or by the extracyclic N_7 atom. From a general point of view, regioselectivity can be either under charge control or orbital control.

(i) *Under charge control* reaction could be expected on the extracyclic N_7 atom since the total charge density is greater on N_7 atom than on N_1 atom (see Table 1).

(ii) *Under orbital control* two ways of approaching the aminopyridines can be envisaged: (a) π attack which would be the frontier orbital controlled reaction[42] as π MO is the frontier orbital HOMO. The π approach on N_1 atom implies the complete loss of aromaticity when bond making is developing while the π approach on N_7 atom implies a less important loss of resonance energy. Consequently the better π approach should occur at N_7 atom. (b) a σ attack of N_1 lone pair along the N_1C_4 axis, which is a subjacent orbital controlled reaction. Previous calculations concerning the approach of the proton on pyridine[43] have concluded to a preferential σ attack versus the π one (in gas phase the calculated difference is about 80 kcal/mol) due to the loss of aromaticity in the π approach. As the n orbital is much more localized than the π one on atom N_7, σ attack on N_1 is *under orbital overlap control*[42] while π attack on N_7 is *under orbital energy gap control.*

As it exists a linear Hammett relationship for 22 substituted pyridines without deviation for NH_2 groups[44], experiments suggest that the cyclic nitrogen N_1 is always

the attacking site of alkyl iodides[44,45] or of acrylic derivatives.[46] Consequently, alkylation of aminopyridines are overlap control reaction underlying thus the great importance of π energy loss in this case. An immediate consequence of this orbital control lies in the fact that the Mentschukin reaction rates should be enhanced as the LUMO orbital energy levels of the electrophile is low lying: C–I > C–Br > C–Cl > C–F.[47] This reactivity order is actually the experimental one.[48] For some generalization of this aspect of the reactivity, it seems to us that acylations may be treated by the same way.[49]

CONCLUSION

Considering thermodynamic equilibrium of protonation, STO-3G *ab initio* calculations suggest that the first protonation site of 2-, 3- and 4-aminopyridines remain the cyclic nitrogen whatever NH_2 position is. A very good linear relationship (r = 0.995) is observed between experimental pK_a's and calculated proton affinities if the N_1 atom is involved, confirming thus the protonation site and the reliance of the STO-3G computation for this type of problem. We point out that basicity and reactivity are not connected to charge densities on nitrogen atoms since N_7 atoms bear a more important negative charge than N_1 atoms. So, we have, classically, to consider that the *n* orbital localization is a determinant factor as the N_1 cyclic lone pair is much more localized than the N_7 extracyclic one which is conjugated with the π system. To the most localized lone pair corresponds the most basic aminopyridine. These calculations allow also to justify the experimental arguments in favour of the N cyclic protonation (i.e. bathochromic shifts on λ_{1max} for the lowest $\pi \rightarrow \pi^*$ UV transitions, whereas hypsochromic shifts should have result from N_7 protonation); these effects are connected with the relative magnitude on atomic coefficients in π and π^* MO at the protonation site.

Considering alkylation of aminopyridines, we are led to conclude to overlap controlled reaction as cyclic N_1 is always the attacking site. Such a σ approach is due to the great localization of the lone pair on N_1 atom.

These results show that, in order to explain the previous observation about metallic properties of radical salts (Scheme 1), the difference of behaviour of 4-aminopyridines vs 2- and 3-aminopyridines is not due to a difference in protonation site.

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[24]This proportionality between ΔE_{prot} and pK_a values indicates that relative proton affinities are well described while the absolute ΔE_{prot} values are overestimated in regard of the experimental data; a best fit between calculated and experimental values would have been obtained by the use of the isodesmic reaction.[9,10]
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[34]If we attribute the second transition to $\pi \rightarrow \pi_2^*$ transitions, either calculated $\Delta\epsilon_2 = \epsilon_{\pi_2^*} - \epsilon_\pi$ and experimental λ_{2max} values are poorly dependent on the amino position: $\Delta\epsilon_2$ is slightly decreased from 0.519 to 0.518 and 0.517 a.u. while λ_{2max} increased from 231 to 232 and 233 nm. This shows a nice agreement between calculation and experiment.
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