Pyridinium-*N*-(2-pyridyl)aminides and related compounds: a theoretical study

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Dedicated to our friend Prof. Julio Alvarez-Builla on the occasion of his 65th anniversary

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Abstract
Seven families of pyridinium-*N*-(heteroaryl)aminides, both azinyl and azolyl, have been studied. For each family, three structures have been considered, the "classical" and two radicals. The transition states corresponding to the rotation of the pyridinium and the heterocycle were calculated at the B3LYP/6-31G* level.

Keywords: Pyridinium-*N*-aminides, pyrazole, isoxazole, 1,2,3-triazole, furazan, B3LYP/6-31G*, MEP

Introduction

The "Heterobetaines group" of the University of Alcalá in Spain, under the direction of Professor Julio Alvarez-Builla, has devoted several papers to pyridinium-*N*-(2-pyridyl)aminides and related compounds.[1-10] These compounds belong to the class of conjugated heterocyclic *N*-ylides.[11-16] Heterocyclic mesomeric betaines have been the subject of extensive investigation, mainly because of their 1,3-dipolar character, which allows them to take part in 1,3-dipolar cycloadditions with various dipolarophiles, thus generating novel five-membered aza heterocycles. As 1,4 dinucleophiles, heterobetaines can react with 1,2-dicarbonyl compounds to give a variety of azonia derivatives possessing a quaternary bridgehead nitrogen. They have also found widespread application in the synthesis of natural products and organic compounds of biological relevance. Amongst the rich reactivity of these compounds, Alvarez-Builla and coworkers discovered that that of azinium-*N*-ylides is controlled by the intramolecular hydrogen-bond (HB) shown in Figure 1.[1,3,5,6] For instance, alkylation occurs exclusively on the exocyclic nitrogen atom (the N^-). However, when a radical is formed, the reactivity is modified and this was attributed to a new HB between the $C^{\cdot}$ and the pyridinium C–H involving a conformational change.[7,9] We will discuss in more detail their paper reporting X-ray data and AM1 calculations.[17]

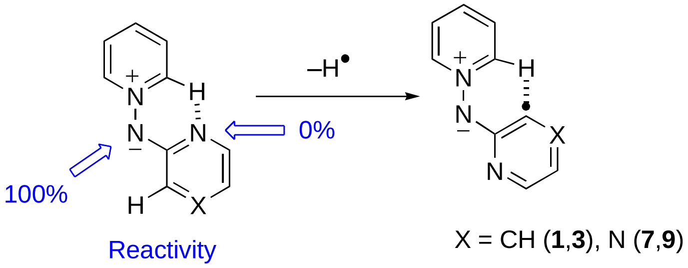


Figure 1. The reactivity of neutral azinium *N*-ylides and their radicals.

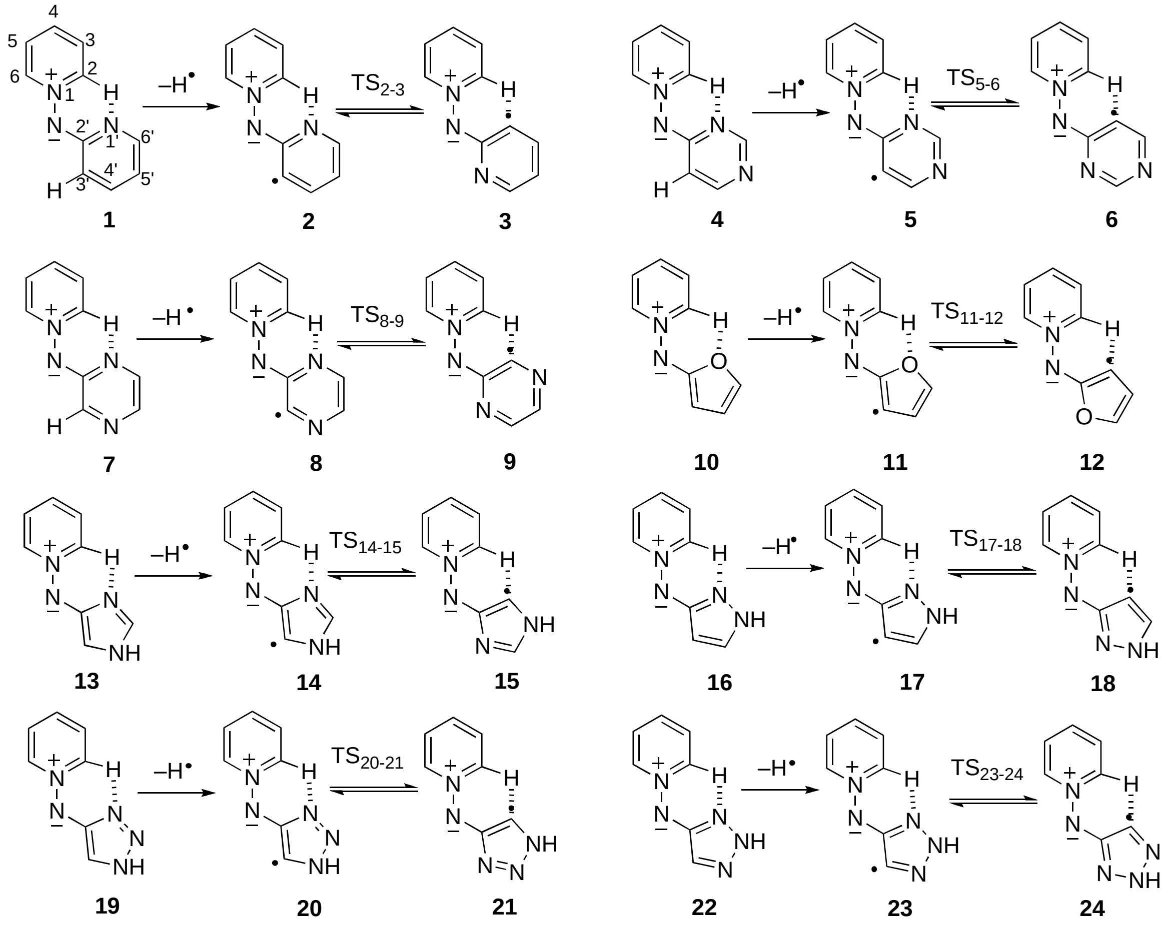


Figure 2. The 21 molecules studied.

We will use the term "neutral" for the closed-shell structures and "radical" for the open-shell ones, although the radicals are also neutral.

Due to our interest in HBs we decided to study these molecules in what concerns their influence on the conformational aspects and the rotation barriers. With this aim we have calculated all the compounds of Figure 2 as well as the transition states connecting them. We have previously studied theoretically pyrazolyl radicals.[18]

Results and Discussion

The energies corresponding to Figure 2, both minima (all real frequencies) and transition states (only one imaginary frequency), are reported in Table 1. All the radicals structures with C_s symmetry present a $^2A'$ electronic configuration while the ones with C_1 symmetry have a ^2A configuration.

We will discuss only the E_{rel} values because those corrected with the ZPE, E_{rel}(+ZPE) are almost identical and strictly proportional.

Table 1. Total energies and ZPE (Hartree), dipole moments (μ, Debye), and relative energies (kJ mol^{-1})

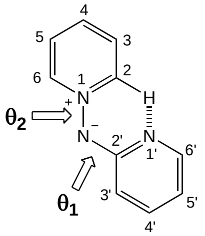
Molecule	E Total	E+ZPE	Dipole	E_{rel}	E_{rel}(+ZPE)
Neutral **1** (pyridine)	–550.67838	–550.50389	2.51	**0.0**	**0.0**
TS(N-C) neutral **1-1**	–550.65617	–550.48259	4.60	58.3	55.9
TS(N-N) neutral **1-1**	–550.66526	–550.49130	5.58	34.4	33.1
Radical **2**	–549.98913	–549.82766	3.03	**0.0**	**0.0**
Radical **3**	–549.98483	–549.82397	4.19	11.3	9.7
TS(N-C) radical **2-3**	–549.97431	–549.81348	3.04	38.9	37.2
TS(N-N) radical **2-2**	–549.97682	–549.81579	6.14	32.3	31.2
TS(N-N) radical **3-3**	–549.97224	–549.81148	7.35	44.4	42.5
Neutral **4** (pyrimidine)	–566.72304	–566.55995	5.76	**0.0**	**0.0**
TS(N-C) neutral **4-4**	–566.70121	–566.53893	7.44	57.3	55.2
TS(N-N) neutral **4-4**	–566.71356	–566.55081	7.92	24.9	24.0
Radical **5**	–566.03250	–565.88230	6.06	**0.0**	**0.0**
Radical **6**	–566.02790	–565.87835	6.89	12.1	10.4
TS(N-C) radical **5-6**	–566.01399	–565.86469	4.47	48.6	46.2

Table 1. Continued

Molecule	E Total	E+ZPE	Dipole	E_{rel}	E_{rel}(+ZPE)
TS(N-N) radical **5-5**	–566.02386	–565.87393	8.31	22.7	22.0
TS(N-N) radical **6-6**	–566.01912	–565.86945	9.46	35.1	33.7
Neutral **7** (pyrazine)	–566.71292	–566.55028	5.22	**0.0**	**0.0**
TS(N-C) neutral **7-7**	–566.69145	–566.52967	4.78	56.4	54.1
TS(N-N) neutral **7-7**	–566.70078	–566.53865	8.05	31.9	30.5
Radical **8**	–566.03464	–565.88489	5.71	**0.0**	**0.0**
Radical **9**	–566.03038	–565.88114	4.07	11.2	9.8
TS(N-C) radical **8-9**	–566.01716	–565.86818	3.50	45.9	43.9
TS(N-N) radical **8-8**	–566.02355	–565.87420	8.46	29.1	28.1
TS(N-N) radical **9-9**	–566.02051	–565.87145	6.94	37.1	35.3
Neutral **10** (pyrazole)	–528.58505	–528.42833	1.56	**0.0**	**0.0**
TS(N-C) neutral **10-10**	–528.57066	–528.41435	2.96	37.8	36.7
TS(N-N) neutral **10-10**	–528.56389	–528.40839	4.43	55.5	52.4
Radica**11**	–527.88392	–527.74001	2.47	**0.0**	**0.0**
Radica**12**	–527.88053	–527.73701	2.71	8.9	7.9
TS(N-C) radical **11-12**	–527.87384	–527.73014	2.96	26.5	25.9
TS(N-N) radical **11-11**	–527.86414	–527.72092	5.38	51.9	50.1
TS(N-N) radical **12-12**	–527.85736	–527.71484	5.74	69.7	66.1
Neutral **13** (isoxazole)	–548.426179	–548.28217	3.15	**0.0**	**0.0**
TS(N-C) neutral **13-13**	–548.407536	–548.26423	6.13	48.9	47.1
TS(N-N) neutral **13-13**	–548.409637	–548.26631	5.17	43.4	41.6

Table 1. Continued

Molecule	E Total	E+ZPE	Dipole	E_{rel}	E_{rel}(+ZPE)
Radica**14**	–547.72456	–547.59314	3.60	**0.0**	**0.0**
Radica**15**	–547.71673	–547.58599	6.19	20.5	18.8
TS(N-C) radical **14-15**	–547.71060	–547.57999	4.31	36.7	34.5
TS(N-N) radical **14-14**	–547.70940	–547.57857	5.84	39.8	38.3
TS(N-N) radical **15-15**	–547.70226	–547.57188	9.14	58.5	55.8
Neutral **16** (2*H*-1,2,3-triazole)	–544.61678	–544.47157	3.69	**0.0**	**0.0**
TS(N-C) neutral **16-16**	–544.60407	–544.45899	3.29	33.4	33.0
TS(N-N) neutral **16-16**	–544.59731	–544.45311	6.79	51.1	48.5
Radical **17**	–543.91696	–543.78532	4.52	**0.0**	**0.0**
Radical **18**	–543.91384	–543.78205	3.07	8.2	8.6
TS(N-C) radical **17-18**	–543.90707	–543.77531	3.81	26.0	26.3
TS(N-N) radical **17-17**	–543.89891	–543.76740	7.78	47.4	47.0
TS(N-N) radical **18-18**	–543.89526	–543.76428	6.54	57.0	55.2
Neutral **19** (furazan)	–564.44101	–564.30916	6.50	**0.0**	**0.0**
TS(N-C) neutral **19-19**	–564.42216	–564.29088	7.78	49.5	48.0
TS(N-N) neutral **19-19**	–564.42543	–564.29418	8.29	40.9	39.4
Radical **20**	–563.74273	–563.62415	7.13	**0.0**	**0.0**
Radical **21**	–563.73428	–563.61655	8.21	22.2	20.0
TS(N-C) radical **20-21**	–563.72779	–563.61014	6.58	39.2	36.8
TS(N-N) radical **20-20**	–563.72825	–563.61020	9.00	38.0	36.6
TS(N-N) radical **21-21**	–563.72142	–563.60383	10.49	55.9	53.4



1

The dihedral angles θ_1 (N1$^+$-N$^-$-C2'-C3') and θ_2 (C2'-N$^-$-N1$^+$-C2) are reported in Table 2.

Table 2. Dihedral angles (in º) of the compounds of Table 1

Molecule	θ_1	θ_2
Neutral **1** (pyridine)	0.0	0.0
TS(N-C) neutral **1-1**	0.0	–180.0
TS(N-N) neutral **1-1**	–92.7	0.3
Radical **2**	0.0	0.0
Radical **3**	0.0	–180.0
TS(N-C) radical **2-3**	–4.4	97.8
TS(N-N) radical **2-2**	–92.6	0.0
TS(N-N) radical **3-3**	–93.1	–180.0
Neutral **4** (pyrimidine)	0.0	0.0
TS(N-C) neutral **4-4**	0.0	–180.0
TS(N-N) neutral **4-4**	–92.3	0.0
Radical **5**	0.0	0.0
Radical **6**	0.0	–180.0
TS(N-C) radical **5-6**	–4.0	96.4
TS(N-N) radical **5-5**	–92.6	0.0
TS(N-N) radical **6-6**	–93.0	–180.0
Neutral **7** (pyrazine)	0.0	0.0
TS(N-C) neutral **7-7**	0.0	–180.0
TS(N-N) neutral **7-7**	–92.2	0.0
Radical **8**	0.0	0.0
Radical **9**	0.0	–180.0
TS(N-C) radical **8-9**	–2.3	92.7
TS(N-N) radical **8-8**	–92.5	0.0
TS(N-N) radical **9-9**	–93.1	–180.0
Neutral **10** (pyrazole)	0.0	0.0
TS(N-C) neutral **10-10**	0.0	–180.0
TS(N-N) neutral **10-10**	92.8	0.0
Radica**11**	0.0	0.0
Radica**12**	0.0	–180.0

Table 2. Continued

Molecule	θ1	θ2
TS(N-C) radical **11-12**	2.3	–93.4
TS(N-N) radical **11-11**	–92.1	–1.6
TS(N-N) radical **12-12**	–91.7	–180.0
Neutral **13** (isoxazole)	0.0	0.0
TS(N-C) neutral **13-13**	–180.0	–180.0
TS(N-N) neutral **13-13**	92.7	0.0
Radica**14**	0.0	0.0
Radica**15**	–13.7	167.1
TS(N-C) radical **14-15**	3.5	–91.7
TS(N-N) radical **14-14**	92.8	0.0
TS(N-N) radical **15-15**	93.2	–180.0
Neutral **16** (2*H*-1,2,3-triazole)	0.0	0.0
TS(N-C) neutral **16-16**	0.0	–180.0
TS(N-N) neutral **16-16**	92.9	0.0
Radical **17**	0.0	–0.1
Radical **18**	0.0	–180.0
TS(N-C) radical **17-18**	–1.5	90.4
TS(N-N) radical **17-17**	–91.9	–2.5
TS(N-N) radical **18-18**	–93.5	176.7
Neutral **19** (furazan)	0.0	0.0
TS(N-C) neutral **19-19**	0.0	–180.0
TS(N-N) neutral **19-19**	–92.7	0.0
Radical **20**	0.0	0.0
Radical **21**	–18.3	161.3
TS(N-C) radical **20-21**	2.9	–89.6
TS(N-N) radical **20-20**	92.8	0.0
TS(N-N) radical **21-21**	93.2	–180.0

In their 1994 paper,**Error! Bookmark not defined.** Alvarez-Builla *et al*. reported the X-ray molecular structure of **1** (LESKEZ)[19] characterized by two dihedral angles, the one involving the C–N bond, θ_1 = 177.5º and the one about the N–N bond, θ_2 = 65.7º, *i.e.* one ring is almost planar but the other is twisted. AM1 calculations were carried out rotating the θ_2 angle, finding that the planar structure (θ_2 = 0º) is the most stable and the barrier to rotation about the N–N bond is 27 kJ mol^{-1}. The calculated dipole moments are 2.6 D (minimum) and 6.4 D (TS). They also reported that the C–H bond (C2–H) involved in the HB is elongated compared with other C–H bonds in **1**.[17]

Dipole moments. Our calculated dipole moments in the case of **1** are 2.51 D for the minimum (compare with 2.6 D) and 5.58 D for the TS corresponding to rotation about the N-N bond (compare with 6.4 D).[17]

Minima. All the minima are planar, including **1**, in agreement with the previous result.[17] We have calculated two minima for the radicals, the N···H and the $C^{\bullet}$···H. In the case of the six-membered rings, the structure with an HB with the lone pair (LP) of the nitrogen atom is more stable than that with an HB to the carbon atom radical by about 11-12 kJ mol^{-1} **2/3**, **5/6**, **8/9**. In pyrazole **11/12** and in 2*H*-1,2,3-triazole **17/18**, the N lone-pair is preferred (8.9 kJ mol^{-1} and 8.2 kJ mol^{-1}, respectively). The replacement of an NH by an O atom (isoxazole and furazan) results in an important increase of these values, 20.5 and 22.2 kJ mol^{-1}, respectively. These effects are not only due to the strength of the hydrogen bonds, other factors, such as stereoelectronic ones, could contribute.

Barriers to the rotation about N-N and N-C bonds (transition states, TS). We have considered two rotations, those about the single N-N and N-C bonds (Figure 3). The barrier calculated for the rotation about the N-N bond in **1** (33-34 kJ mol^{-1}) is close to that calculated at the AM1 level (27 kJ mol^{-1}).[17]

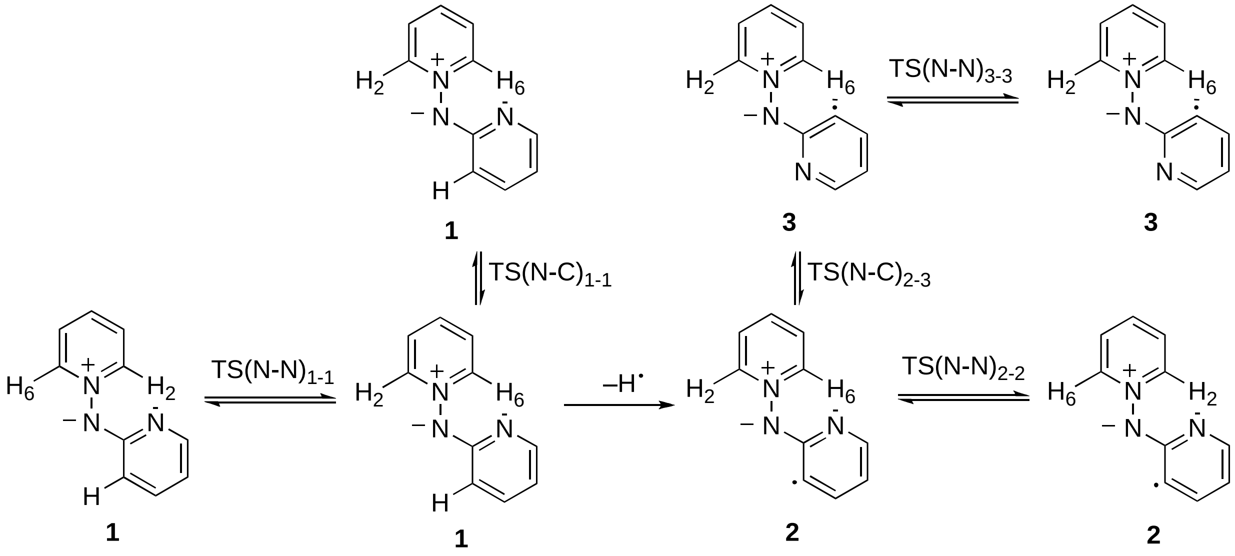


Figure 3. The different TSs illustrated in the case of pyridinium-*N*-(2'-pyridyl)aminide **1**.

The rotations in neutral molecules are all degenerate (identical initial and final states). The fourteen barriers of Table 1 have been represented in Figure 4. Roughly, when a barrier increases, the other decreases [TS(N-N) = (89±10) – (1.00±0.20) TS(N-C), ($R^2 = 0.84$)].

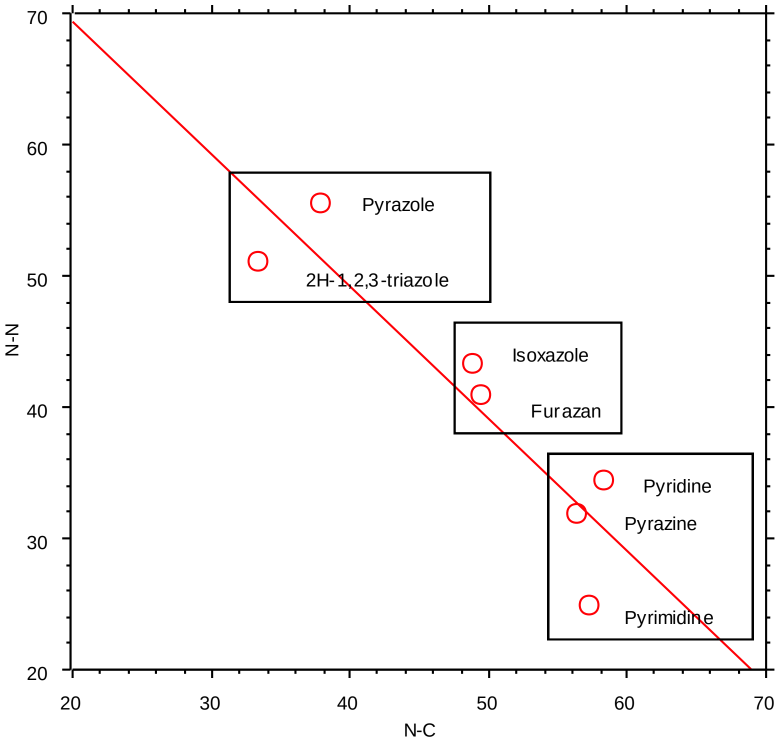


Figure 4. Scattergram of the rotation barriers in neutral molecules (kJ mol^{-1}).

Protons H2 and H6 in **1** are magnetically equivalent (isochrones) because the barrier to the rotation about the N-N bond is low (about 33-34 kJ mol^{-1}).

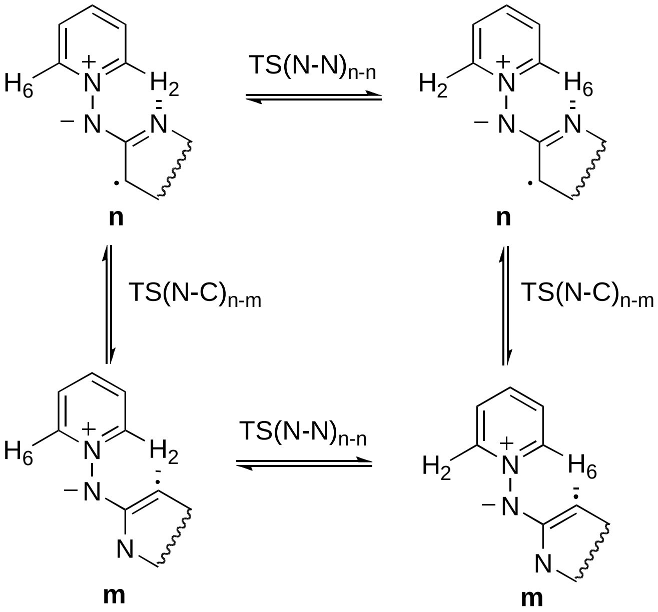


Figure 5. The two different TSs of Figure 6.

In the radicals, there are three barriers, two degenerate (the N-N) and two corresponding to an asymmetric process (the N-C). For the asymmetric one, we have used the barriers from the most stable to the less stable rotamer, see Figures 5 and 6. For instance, in the case of pyrimidine, we have used 22.7 kJ mol^{-1} for the degenerate N-N barrier **5-5** and 45.2 kJ mol^{-1} for the N-C barrier **5-6**, resulting from 48.6 – 12.1 values of Table 1.

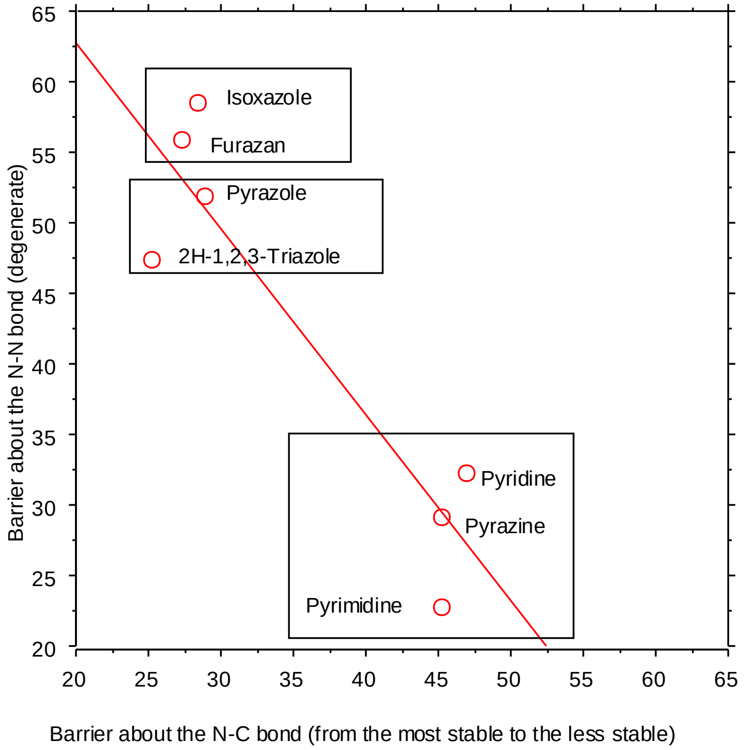


Figure 6. Scattergram of two rotation barriers in radicals **n** and **m**. The trendline corresponds to: N-N barrier = (89±10) – (1.32±0.26) C-N barrier, n = 7, R^2 = 0.84.

Figure 6 shows that both barriers are related and, as in the case of the neutral molecules, when one increases the other decreases, meaning that the partial double bond character of two single bonds (the N–N and the N–C) are related.

Molecular electrostatic potential (MEP). We have calculated the MEP of the three structures of pyridinium-*N*-(2-pyridyl) aminides **1-3** (Figure 7). The radical formation results in an increment of the nucleophilicity of the aminide nitrogen; regarding the pyridine nitrogen, it slightly reduces its nucleophilicity in **2** while it almost doubles its value in **3**. This variation in the electrostatic potential, with the observed changes in the conformational profile, could explain the reactivity differences between **1** and their radical counterparts, **2**/**3**.

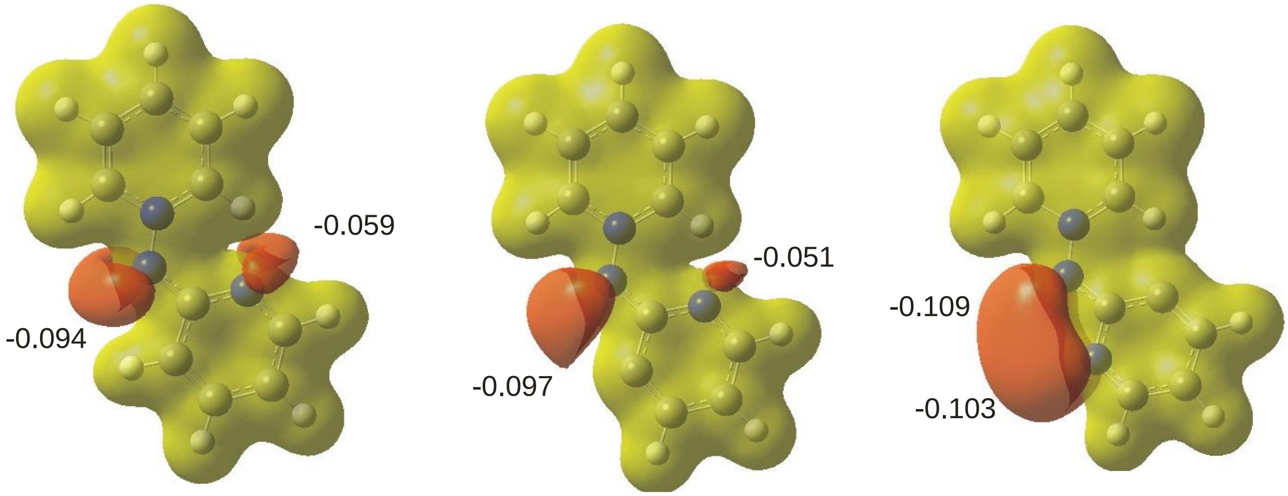


Figure 7. From left to right, MEPs at ±0.04 au of **1**, **2** and **3**. The values of the minima for each negative region are indicated.

Geometry and electron density. The hydrogen removal (radical formation) produces small changes in the affected ring. The variation of the bond distances between the closed shell configuration and the open shell ones ranges between –0.05 and +0.04 Å. The N···H bond distances (Table 3) are shorter in the closed shell configuration than in the corresponding open shell ones, being the C$^{\bullet}$···H bond distance the longest for all the compounds studied here. Contrary to what was reported previously,[17] in our calculations the C-H bond involved in the HB interaction is always shorter (in average 0.002 Å) than the corresponding one that is not involved in this interaction.

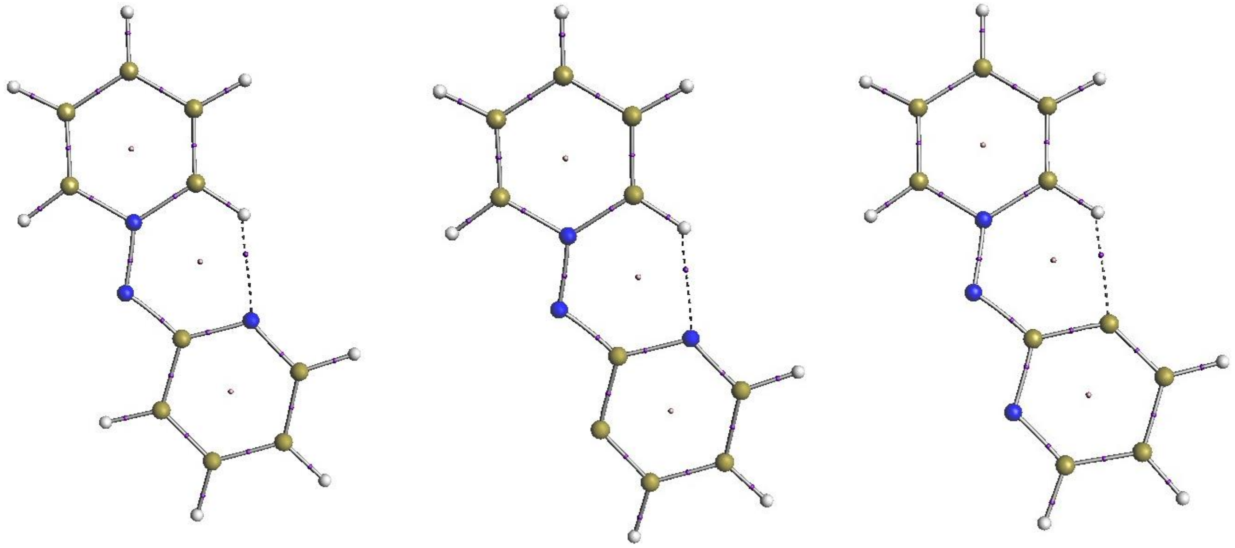
Table 3. Properties of the intramolecular HB: distances in Å and electron density and Laplacian in au

System	N/C$^{\bullet}$···H distance	ρ_{bcp}	$\nabla^2\rho_{bcp}$
1	2.007	0.0301	0.0968
2	2.017	0.0293	0.0948
3	2.044	0.0281	0.0769
4	2.006	0.0300	0.0968
5	2.014	0.0293	0.0951
6	2.042	0.0279	0.0770
7	2.017	0.0293	0.0948
8	2.021	0.0289	0.0941
9	2.060	0.0279	0.0775
10	2.007	0.0275	0.0953
11	2.014	0.0270	0.0940
12	2.070	0.0249	0.0749

Table 3. Continued

System	N/C$^{\bullet}\cdots$H distance	ρ_{bcp}	$\nabla^2\rho_{bcp}$
13	1.980	0.0283	0.0992
14	1.986	0.0279	0.0983
15	2.191	0.0200	0.0685
16	2.029	0.0260	0.0909
17	2.035	0.0257	0.0901
18	2.091	0.0237	0.0739
19	2.008	0.0266	0.0939
20	2.012	0.0263	0.0932
21	2.308	0.0165	0.0637

The topological analysis of the electron density shows in all cases an intramolecular HB critical point (Figure 8). The values of the electron density, ρ_{bcp}, and Laplacian, $\nabla^2\rho_{bcp}$, at the intramolecular HB are typical of this kind of weak interactions.[20] In previous reports, a linear and exponential relationship between ρ_{bcp} and the intermolecular distances has been shown.[21] In the present case, the data are clustered based on the size of the ring attached to the pyridine one (Figure 9). Thus, the five membered ring derivatives show smaller ρ_{bcp} for a similar intermolecular distance than the one obtained in the six membered rings. No significant differences are obtained for the N$\cdots$H and C$^{\bullet}\cdots$H interactions.



1 **2** **3**

Figure 8. Molecular graph based on the electron density. The bond and ring critical points are indicated as well as the bond paths.

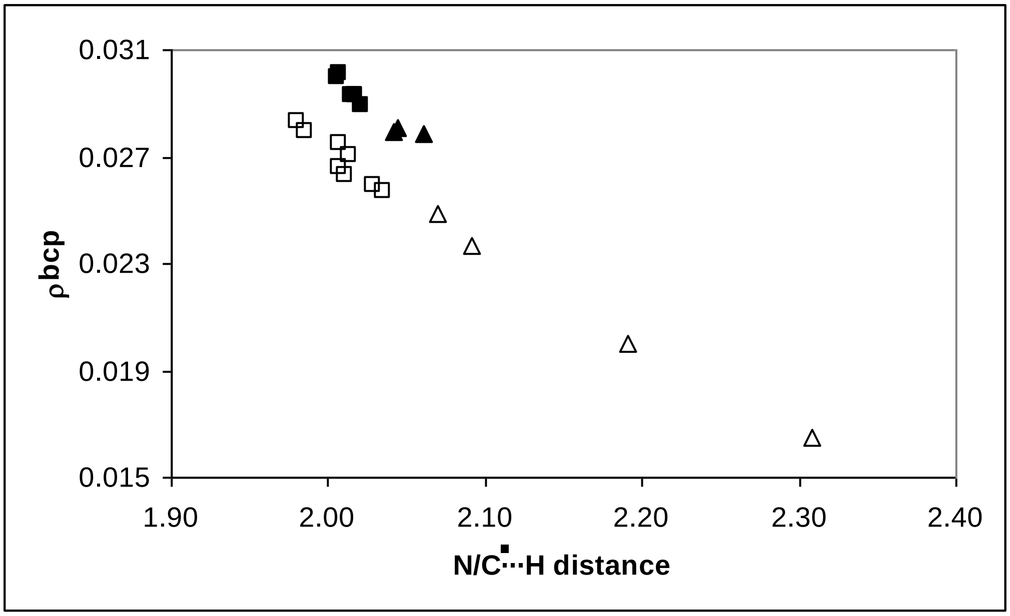


Figure 9. Electron density at the bcp *vs*. the interatomic distances. The black symbols correspond to compounds **1-9** while the white ones to **10-21**. The squares indicate the N···H interactions while the triangles the C$^\bullet$···H ones.

In conclusion, the present work on pyridinium-*N*-(heteroaryl)aminides provides a rationale for the design of new conjugated heterocyclic-*N*-aminides. The conformational preferences of the radicals and the different transition states have been calculated and some relationships between them found. The molecular electrostatic potential analysis can be used to explain the modification of the reactivity between closed-shell and open-shell structures. The topological analysis of the electron density of the N···H and C$^\bullet$···H hydrogen bonds shows that both are similar.

The analysis developed here (B3LYP/6-31G*) goes much farther (MEP, electron density) than the previous work carried out at the AM1 level and should be considered more reliable. Depending on the property that is desired to optimize, further experimental work should explore other six- or five-membered rings.

Computational Details

Calculations were carried out at the B3LYP/6-31G* level[22,23] (unrestricted for radicals) using the Gaussian 03 programs.[24]Frequency calculations at the same level were carried out to verify that the structures correspond to energy minima (no imaginary frequencies) or to TS (only one imaginary frequency).

The analysis of the electron density of the systems has been carried out using the Morphy98 program,[25] and Morphy3 graphic interface[26] within the Atoms in Molecules (AIM) framework.[27]

Acknowledgements

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