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The azido-tetrazole and diazo-1,2,3-triazole tautomerism in six-membered heteroaromatic rings and their relationships with aromaticity: Azines and perimidine

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Dedicated to Professor Geneviève Pfister-Guillouzo for her prominent contribution to photoelectron spectroscopy

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ABSTRACT

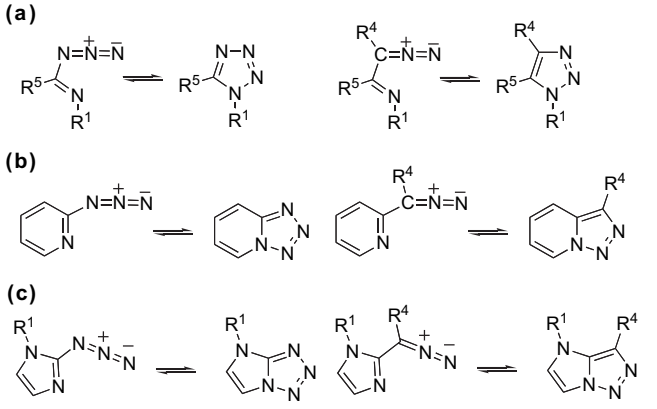
The properties of 28 molecules together with 12 transition states belonging to the series of azido-azines, tetrazolo-azines, diazo-azines, and 1,2,3-triazolo-azines have been studied at the B3LYP/6-31G(d), B3LYP/6-311++G(d,p) and, for 26 cases, at the G3B3 level. Energies, NICS and bond critical points were used to discuss the ring-chain tautomerism of these compounds in relation with the aromaticity of the azines (pyridine, pyrimidine, quinazoline, 1,3-diazapyrene, and perimidine) and the azoles (tetrazoles and 1,2,3-triazoles).

1. Introduction

The phenomenon known as ring-chain isomerism or tautomerism is one of the most curious aspects of organic chemistry.[1] The most studied cases are the azidoazomethine/tetrazole[2] and diazo-azomethine/1,2,3-triazole valence isomerism of tetrazoles and 1,2,3-triazoles (Scheme 1).[3] The imino C=N bond could be part of a heterocyclic ring, either a six-membered ring (azines, Scheme 1b) or a five-membered ring (azoles, Scheme 1c). In this first paper we will report our theoretical results concerning azines.

There is an abundant experimental literature concerning the equilibria reported in Scheme 1b (not only pyridines but all azines including benzo-fused derivatives),[4] but only a few theoretical studies:

– *C*-substituent effects on the equilibrium 2-azidopyridine (**1A*Z***)/tetrazolo[1,5-*a*]pyridine (**1Tet**) (Scheme 2) have been reported;



Scheme 1. Valence isomerism in the tetrazoles and 1,2,3-triazoles and in the azine and azole series. Always the open-chain compounds (azide and diazo) are the reactants and the ring compounds (tetrazole and 1,2,3-triazole) are the products.

when there is no substituent, at the MP2/6-31G(d,p) level, the tetrazole form is favored by 16.3 kJ mol^{-1} with a TS (that resembles the tetrazole) of 109.2 kJ mol^{-1}.[5] This work has been

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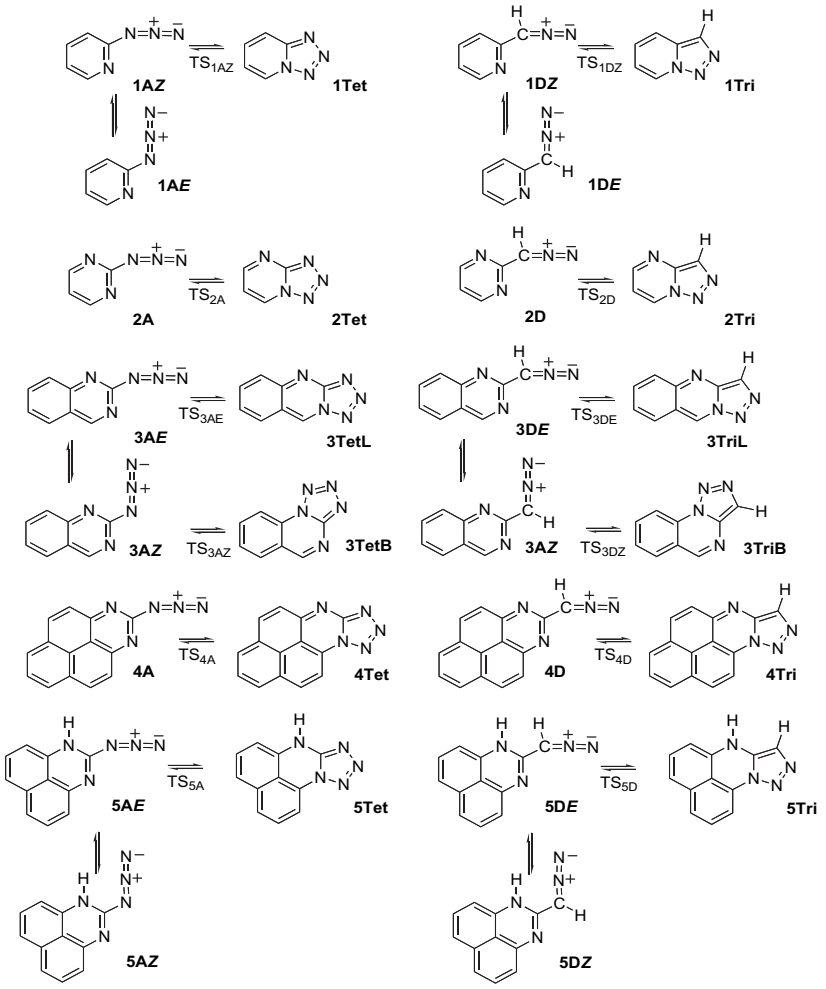

Scheme 2. Studied compounds. **A**: azido, **Tet**: tetrazolo, **D**: diazo, **Tri**: 1,2,3-triazolo, **L**: linear, **B**: bent. The conformation of the azido/diazo substituent is defined using the *E*/*Z* convention.

repeated at the B3LYP/6-31++G(d,p) but large errors in the published data (in hartree) prevents their consideration.[6] In the case of compounds bearing both a nitro group and another substituent, calculations have been carried out using Ahlrichs double-ζ basis sets (for 6-nitro and 8-nitro derivatives, the azide is more stable than the tetrazole by 24.7 and 11.6 kJ mol^{-1}).[7]

- Semiempirical calculations (AM1 and PM3) have been carried out on the azido/tetrazole tautomerism of tetrazolopyridazines; in all cases the azido tautomers are the most stables ones.[8]
- 'Pauling's last compound' (2-azido-5,8-dihydroxy-tri-*s*-triazine),[9] triazido-*s*-triazine and triazido-tri-*s*-triazine, were studied theoretically in relation with their explosive properties at the B3LYP/aug-ccpVDZ level of theory. In the last case, the triazido-tri-*s*-triazine tautomer is more stable than the tetrazolo one (only one ring) by 51.7 kJ mol^{-1}.[10]

2. Results and discussion

The compounds we have studied are gathered in Scheme 2. They have been selected to determine the effect of a second N atom (2-azidopyrimidine **2A**) as well as the fusion with benzene rings [2-azidoquinazoline **3A**, 2-azido-1,6-dihydrobenzo[*gh*]perimidine (2-azido-1,3-diazapyrene)[11] **4A**]. 2-Azido-1*H*-perimidine (**5A**) was chosen because although structurally close to **4A** it is very different where aromaticity is concerned. Remember that 1*H*-perimidine is an unusual heterocycle[12] that in some aspects is more similar to benzimidazole (a π-rich heteroaromatic substance) than to quinazoline (a π-deficient heterocycle).[13]

We have calculated the energies associated with the molecules of Scheme 2 including the transition states at three different levels (see Computational details): B3LYP/6-31G(d), B3LYP/6-311++G(d,p), and G3B3. The relative free energies at 298 K (ΔΔG in kJ mol^{-1}) are reported in Table 1 while the absolute values (in hartrees) can be found in the Supplementary data.

2.1. The case of 2-azidopyridine/tetrazolo[1,5-*a*]pyridine (1Tet/1A*Z*)

The problem to compare calculated free energies with experimental data is that the latter have been determined in solution (or worse, in the solid-state) and that solvent effects have a large influence on K_T.[1c,2c] Fortunately, the case of **1Tet**/**1AZ** (remember that the tetrazole is the product and the azide is the reactant) has been studied in the gas-phase at various temperatures (between 391 and 533 K).[14] Using photoelectron spectroscopy and assuming that the intensities of the first bands (8.9 and 9.25 eV) in the PE spectrum are proportional to the partial pressure of the corresponding tautomers, tetrazole **1Tet** and azide **1AZ**, it is possible to determine K_T=[**1Tet**]/[**1AZ**] (at each temperature and from these data, calculate $\Delta H = -(7.6 \pm 0.4)$ kJ mol^{-1} and $\Delta S = -(14.9 \pm 0.9)$ J K^{-1} mol^{-1} (Fig. 1)). These experiments do not distinguish between **1AZ** and **1AE**, but all the calculations favor the first one by about 15 kJ mol^{-1},

Table 1
Dipole moments (D) and relative free energies ($\Delta\Delta G$, kJ mol^{-1}) of the compounds of Scheme 2 (all minima and TS have C_s symmetry) calculated at the B3LYP/6-31G(d), B3LYP/6-311++G(d,p) and G3B3 levels. Number of imaginary frequencies: 0 for the minima and 1 for the TSs

Heterocycle	Dipole B3LYP/6-31G(d)	ΔΔG B3LYP /6-31G(d)	ΔΔG B3LYP /6-311++G (d,p)	ΔΔG G3B3
Azidopyridine (**1AZ**)	3.16	**0.0**	**0.0**	**0.0**
Azidopyridine (**1AE**)	3.42	14.8	16.5	15.4
Tetrazolo (**1Tet**)	6.47	2.8	15.8	−1.3
(TS_{1AZ})	4.26	78.6	86.2	82.2
Azidopyrimidine (**2A**)	3.52	**0.0**	**0.0**	**0.0**
Tetrazole (**2Tet**)	7.12	22.5	36.0	19.9
(TS_{2A})	5.23	95.3	103.5	99.8
Azidoquinazoline (**3AE**)	4.37	0.5	0.8	1.6
Tetrazole linear (**3TetL**)	8.32	44.0	57.1	44.8
(TS_{3AE})	6.46	105.2	113.7	112.7
Azidoquinazoline (**3AZ**)	4.28	**0.0**	**0.0**	**0.0**
Tetrazole bent (**3TetB**)	8.34	4.3	18.8	1.4
(TS_{3AZ})	5.99	87.9	96.1	90.8
Azido-1,3-diazapyrene (**4A**)	5.70	**0.0**	**0.0**	
Tetrazole (**4Tet**)	10.05	17.1	31.2	
(TS_{4A})	7.74	93.8	102.1	
Azidoperimidine (**5AE**)	2.43	**0.0**	**0.0**	
Azidoperimidine (**5AZ**)	2.75	24.9	27.1	
Tetrazole (**5Tet**)	6.13	−12.2	2.7	
(TS_{5A})	2.81	70.4	78.6	
Diazopyridine (**1DZ**)	3.05	**0.0**	**0.0**	**0.0**
Diazopyridine (**1DE**)	1.45	2.2	3.3	3.3
Triazole (**1Tri**)	5.06	−19.3	−8.6	−25.6
(TS_{1DZ})	3.28	51.7	57.8	58.1
Diazopyrimidine (**2D**)	1.91	**0.0**	**0.0**	**0.0**
Triazole (**2Tri**)	4.78	3.2	14.8	−2.1
(TS_{2D})	3.02	67.4	74.6	73.8
Diazoquinazoline (**3DE**)	2.49	−0.3	0.1	0.3
Triazole linear (**3TriL**)	5.78	26.8	38.2	24.4
(TS_{3DE})	4.20	78.0	85.8	86.8
Diazoquinazoline (**3DZ**)	2.37	**0.0**	**0.0**	**0.0**
Triazole bent (**3TriB**)	5.53	−14.7	−1.7	−20.6
(TS_{3DZ})	3.40	60.3	67.7	65.2
Diazo-1,3-diazapyrene (**4D**)	3.56	**0.0**	**0.0**	
Triazole (**4Tri**)	6.92	−0.6	11.9	
(TS_{4D})	5.08	66.8	74.1	
Diazoperimidine (**5DE**)	4.00	**0.0**	**0.0**	
Diazoperimidine (**5DZ**)	1.91	2.3	4.0	
Triazole (**5Tri**)	5.09	−25.7	−12.2	
(TS_{5D})	3.46	47.7	54.8	

which corresponds to the lone-pair/lone-pair repulsion of the second one.

The experimental equation predicts for 298 K (25 °C) ΔG=3.2 kJ mol^{-1}, which agrees both with the B3LYP/6-31G(d) (2.8 kJ mol^{-1}) and the G3B3 calculations (−1.3 kJ mol^{-1}) but not with the B3LYP/6-311++G(d,p) ones (15.8 kJ mol^{-1}). The tetrazole **1Tet** is more stable than the azide **1AZ**, but the entropy (high temperatures) favors the azide. In Figure 1 is represented the equation corresponding to the G3B3 calculations. Both lines cross at about 118 K, and taking into account the approximations used in the experimental determination, we can conclude that both B3LYP/6-31G(d) and G3B3 calculations reproduce fairly well the experimental reality in the case of **1**.

Concerning the minima, the B3LYP/6-311++G(d,p) calculations penalize the tetrazole/triazole rings by about 13.0 kJ mol^{-1} with regard to the B3LYP/6-31G(d) and by about 16.2 kJ mol^{-1} with regard to the G3B3 calculations [there is a small difference of about 3.6 kJ mol^{-1} between B3LYP/6-31G(d) and G3B3]. Therefore, in the following discussion we will use the less expensive B3LYP/6-31G(d) calculations.

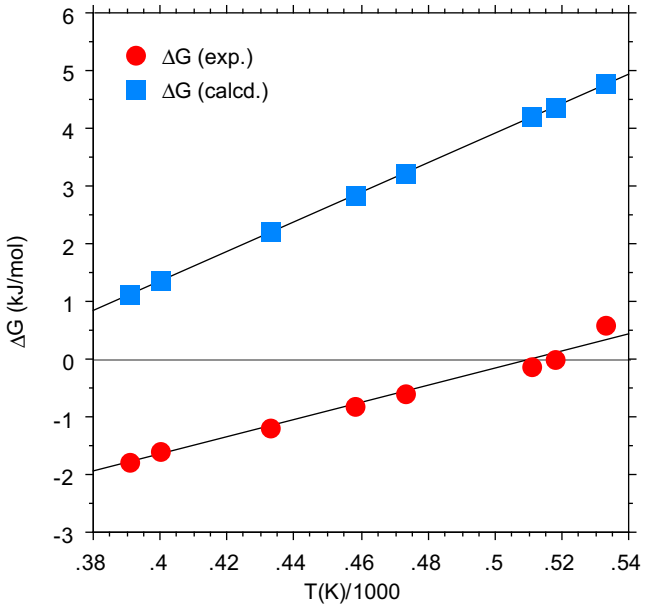

Figure 1. Equation of the trendlines: Experimental (red points) ΔG (kJ mol^{-1})=−(7.6±0.4)+(14.9±0.9) T(K)/1000; calculated at the G3B3 level (blue squares) ΔG (kJ mol^{-1})=−8.9+25.65 T(K)/1000.

2.2. The minima

The data of Table 1 calculated at the B3LYP/6-31G(d) level can be analyzed using a presence-absence matrix known in medicinal chemistry as a Free–Wilson model.[15] A multiple regression of the twelve ring compounds (**1Tet**, **2Tet**, **3TetL**, **3TetB**, **4Tet**, **5Tet**, **1Tri**, **2Tri**, **3TriL**, **3TriB**, **4Tri** and **5Tri**) free-energies leads to the following contributions (n=12, R^2=0.996): the 1,2,3-triazoles are more stable than the tetrazoles by (18.1±1.2) kJ mol^{-1}, the bent isomers are more stable than the linear isomers by (40.6±2.0) kJ mol^{-1}. The contributions of the azines are: pyridine −(17.3±1.5), pyrimidine (3.8±1.5), quinazoline −(14.3±1.5), diazapyrene −(0.8±1.5) and perimidine −(28.0±1.5) kJ mol^{-1}. These contributions are unrelated to any aromaticity criteria,[16] save the −28.0 value for the non-aromatic perimidine.[13,14]

Concerning the fact that the triazoles are relatively to the open compounds more stable than the tetrazoles by about 18 kJ mol^{-1}, it should be noted that the values are about 22 **1**, 19 **2**, 17 **3L**, 19 **3B**, 18 **4** and 14 **5** 18 kJ mol^{-1}. The highest value is for pyridine, which has no lone-pair/lone-pair interactions and the lowest one is for perimidine that has an attractive N–H/LP interaction. The four other values have an average value of 18.3 kJ mol^{-1}. The information about the comparative aromaticity of 1*H*-1,2,3-triazole and 1*H*-tetrazole is conflicting. Most authors consider that the aromaticity decreases with increasing aza-substitution, particularly in β-position.[17] Other authors, using delocalization indexes, deduced that tetrazole is more aromatic than triazole.[18] The 18 kJ mol^{-1} value we have determined is a new and energetic determination of the difference in aromaticity between both heterocycles.

The result that bent isomers (**3TetB** and **3TriB**) are considerably more stable than the linear ones (**3TetL** and **3TriL**) agrees with all known experimental data: only the bent isomers are known.[19] This is actually a more general result involving many heterocyclic isomers.[20]

2.3. The transition states

For the TS a similar analysis of the transition states (n=12, R^2=0.84) leads to the following effect. The TS lies on average

65±4 kJ mol^{-1} above the azide of minimum energy with the following effects: they are higher for tetrazoles than for triazoles (29±5 kJ mol^{-1}), and two heterocycles show non-additivity, with deviations of −(16±9 kJ mol^{-1}) for the diazapyrene **4** and −(21±7 kJ mol^{-1}) for the perimidine **5**.

Note that our TS for azidopyridine (TS_{1AZ}), about 80 kJ mol^{-1}, is lower in energy than that calculated at the MP2/6-31G(d,p) level (109.2 kJ mol^{-1}).[5] The differences between both basis sets in our B3LYP calculations amounts to 7.7 kJ mol^{-1} being lower with the small one (the B3G3 calculations are just in between). This difference corresponds to the fact that the rings (tetrazoles and triazoles) are calculated with too high energies with the larger basis set and that the TSs resembles the ring-closed structures, as previously commented for tetrazoles.[5]

An AIM analysis (see Computational details) of some TSs, Figure 2, shows clearly their tetrazole (left side)/triazole (right side) aspect. This is independent of which the open form (azido/diazo) or the cyclic one (tetrazole/triazole) is the most stable. Thus, the Hammond–Leffler postulate (the TS should resemble the most stable form) is not followed in several cases.[21]

The N···N distances (Å) calculated at the B3LYP/6-31G(d) computational level are: 2.045 (TS_{1AZ}), 1.994 (TS_{2A}), 1.948 (TS_{3AE}), 2.037 (TS_{3AZ}), 2.007 (TS_{4A}), 2.113 (TS_{5A}), 2.087 (TS_{1DZ}), 2.005 (TS_{2D}), 1.927 (TS_{3DE}), 2.067 (TS_{3DZ}), 2.016 (TS_{4D}), 2.168 (TS_{5D}). Those of diazo (D) and azide (A) are linearly related: $d_{NN}(D)=-(0.93\pm0.13)+(1.47\pm0.06)\,d_{NN}(A)$, $n=6$, $R^2=0.992$. The energies of the TSs (Table 1) are linearly related to these N···N distances: A/Tet, TS (kJ mol^{-1})=(531±50)−(219±25) d_{NN} (Å), $n=6$, $R^2=0.952$; D/Tri, TS (kJ mol^{-1})=(333±30)−(133±15) d_{NN} (Å), $n=6$, $R^2=0.953$.

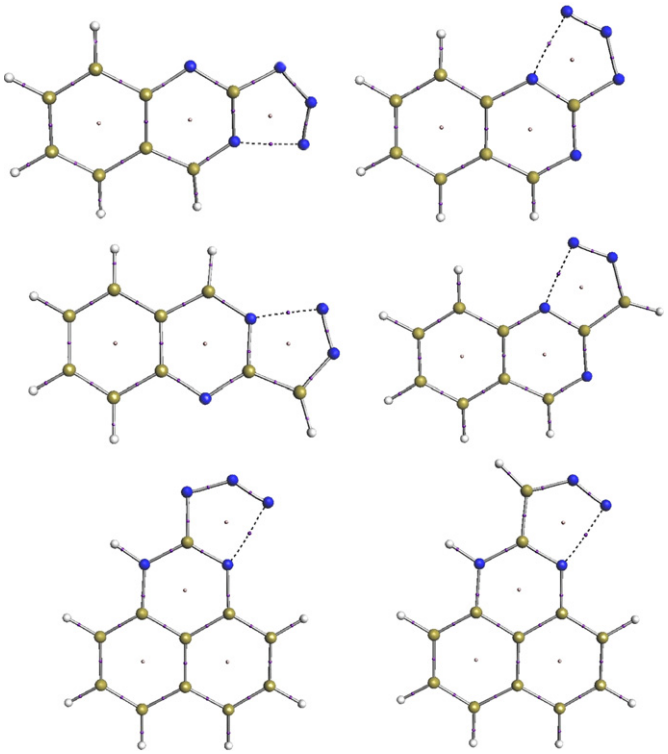

Figure 2. Molecular graphs of TS_{3AE}, TS_{3AZ}, TS_{3DE}, TS_{3DZ}, TS_{5A}, and TS_{5D} from top to bottom and right to left respectively, calculated at the B3LYP/6-31G(d) level. Bond critical points (bcp) and ring critical points (rcp) are shown as well as the bond paths.

2.4. The NICS(1) values

NICS(1) values [NICS(0) values will not be reported] calculated at the B3LYP/6-31G(d) level are reported in Table 2.

Table 2 deserves several comments:

(1) Excluding perimidine, the tetrazole and 1,2,3-triazole ring have averaged NICS(1) values of 15.29 and 15.71 ppm. In the case of perimidine derivatives, **5Tet** and **5Tri**, these values are 10.51 and 10.72 ppm, respectively. In both cases, there is a small increase of the NICS in agreement with 1,2,3-triazoles being more aromatic than tetrazoles in these bicyclic compounds. In the parent compounds, 1*H*-tetrazole (13.49 ppm) is more aromatic than 1*H*-1,2,3-triazole (12.73 ppm).[22] The near 5 ppm decrease observed for the perimidine derivatives is associated with their non-aromatic character (for instance, for 6*H*-pyrrolo[1,2-*e*][1,2,3-triazole, a non-aromatic pyrroline derivative, NICS(1)=11.79 ppm).[15c]

(2) Excluding perimidine, the six-membered rings both in open compounds (azides and diazo) and in ring compounds (tetrazolo and triazolo) have NICS(1) about 10 ppm: azides 10.0, diazo 9.2, tetrazolo 9.4, and triazolo 8.7. Although similar there is

Table 2
NICS(1) values in ppm for the minima and the TS (only for heterocycles)

Molecule	Azine	Azole	Molecule	Azine	Azole
Azidopyridine (**1AZ**)	10.02	—	Diazopyridine (**1DZ**)	9.25	—
Azidopyridine (**1AE**)	10.24	—	Diazopyridine (**1DE**)	9.46	—
Tetrazole (**1Tet**)	9.38	15.47	Tetrazole (**1Tri**)	8.72	15.66
(TS_{1AZ})	10.47	8.94	(TS_{1DZ})	9.80	8.25
Azidopyrimidine (**2A**)	9.42	—	Diazopyrimidine (**2D**)	8.51	—
Tetrazole (**2Tet**)	9.05	15.30	Triazole (**2Tri**)	8.41	15.60
(TS_{2A})	9.79	8.37	(TS_{2D})	8.87	8.13
Azidoquinazoline (**3AE**)	9.68	—	Diazoquinazoline (**3DE**)	8.76	—
Tetrazole linear (**3TetL**)	11.52	15.81	Triazole linear (**3TriL**)	11.09	16.54
(TS_{3AE})	10.92	8.06	(TS_{3DE})	9.99	8.30
Azidoquinazoline (**3AZ**)	9.64	—	Diazoquinazoline (**3AZ**)	8.88	—
Tetrazole bent (**3TetB**)	7.01	14.35	Triazole bent (**3TriB**)	6.31	14.54
(TS_{3AZ})	9.01	7.99	(TS_{3DZ})	8.20	7.61
Azido-1,3-diazapyrene (**4A**)	11.23	—	Diazo-1,3-diazapyrene (**4D**)	10.40	—
Tetrazole (**4Tet**)	9.84	15.53	Triazole (**4Tri**)	9.19	16.23
(TS_{4A})	11.08	7.87	(TS_{4D})	10.00	7.92
Azidoperimidine (**5AE**)	−2.53	—	Diazoperimidine (**5DE**)	−2.66	—
Azidoperimidine (**5AZ**)	−2.50	—	Diazoperimidine (**5DZ**)	−2.78	—
Tetrazole (**5Tet**)	−1.15	10.51	Triazole (**5Tri**)	−0.95	10.72
(TS_{5A})	−1.79	7.54	(TS_{5D})	−1.73	6.55

a decrease in magnetic aromaticity from azides to diazo and from tetrazolo to triazolo derivatives. Perimidines are clearly antiaromatic, being the open compounds (−2.6 ppm) more antiaromatic than the cyclic ones −1.0 ppm.

(3) The NICS(1) of the azines TS are intermediate between those of the open and ring structures (60% open, 40% ring by multiple regression), thus ressembling slightly more the azides/diazo than the tetrazoles/triazoles. The NICS(1) of the azoles TS are not correlated with those of the minima.

(4) Is there some trend when comparing the differences in energy [$\Delta\Delta G$ in kJ mol^{-1}, Table 1, B3LYP/6-31G(d)] and the NICS(1)? The best one is with NICS(1) of the six-membered ring in the tetrazole or the triazole derivative (in ppm, Table 2: see Fig. 3). It is clear that perimidine is different from other azines but even if perimidine is removed, the remaining azines (blue and red lines) show some tendency: when NICS(1) increases, $\Delta\Delta G$ increases.

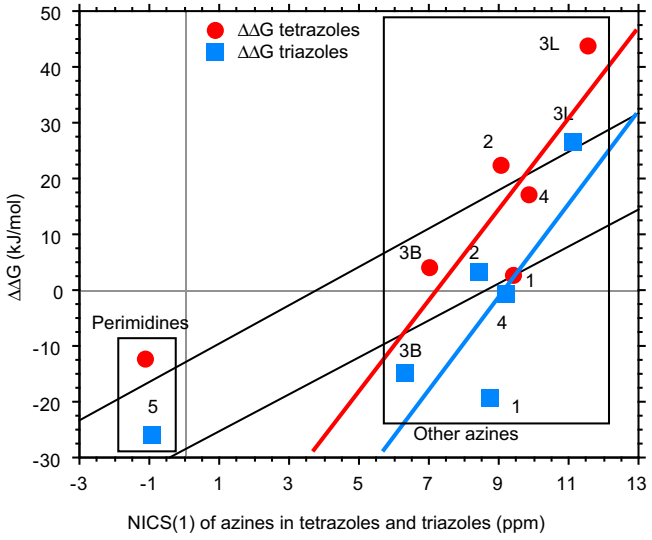

Figure 3. Representation of $\Delta\Delta G$ vs NICS(1).

2.5. AIM analysis

The AIM analysis of the calculated structures provides 84 N···N bond critical points (bcp) that cover between 1.13 and 2.17 Å in the interatomic N···N distances. The representation of the electron density and Laplacian at the bcp vs the interatomic distances (Figs. 4 and 5, respectively) shows in the first case a good exponential relationship while in the second case the relationship is more complex, in agreement with the described behavior of other bonding interactions.[23,24]

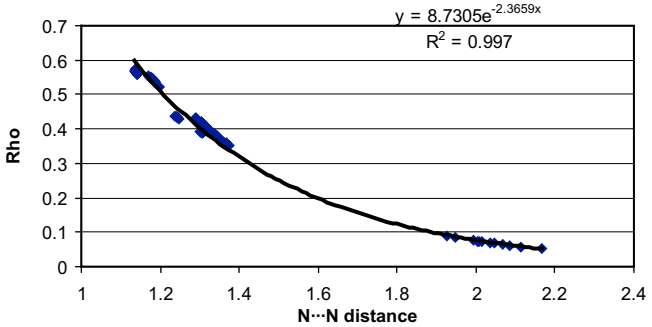

Figure 4. Plot of ρ (au) of the bcp vs the N···N distance (Å).

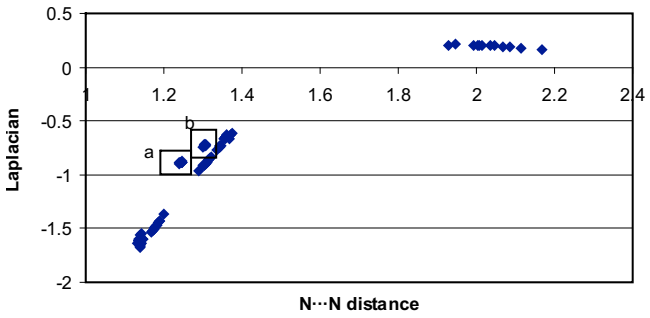

Figure 5. Plot of the Laplacian (au) of the bcp vs the N···N distance (Å). There are some points that clearly deviate: (a) Corresponds to the N1–N2 of C–N1–N2–N3 in the minima. (b) Corresponds to the N1–N2 in the TS.

The values of the Laplacian are negative for those N–N bonds that traditionally are considered as covalent while the N···N bond that are starting to be formed in the TS structures shows positive values. In addition it is worth mentioning that the values of the N1–N2 bonds show slightly different values to the rest of the N–N contacts, which can be associated to a different environment of this bond with respect to the others studied here.[25]

3. Conclusions

Theoretical calculations within the DFT approximation have allowed determining the properties of a series of minima and transitions states corresponding to a ring-chain tautomerism. All studied azines are aromatic save the antiaromatic or, at least, non-aromatic perimidine. The transition states are in the range 85 (azido/tetrazole) to 65 kJ mol^{-1} (diazo/triazole). NICS and energetic description of aromaticity are not consistent save the trivial case of perimidine.

4. Computational details

The optimization of the geometries of the structures were first carried out at the B3LYP/6-31G(d) and then reoptimized at the B3LYP/6-311++G(d,p) computational level,[26–31] within the Gaussian-03 package.[32] Frequency calculations at both levels were carried out to confirm that the obtained structures correspond to energy minima.[33] G3B3 calculations were carried out for 26 of the 40 cases (65%).[34] NICS(1) values[35,36] were calculated within the GIAO approximation on the B3LYP/6-31G(d) optimized geometries at the same computational level. The electron density of the molecules has been analyzed within the atoms in molecules (AIM) methodology[37] with the AIMPAC and MORPHY98 programs.[38–40] The electron density molecular graphs have been represented with the MORPHY3 program.[41]

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Supplementary data

Supplementary data associated with this article can be found in the online version doi:10.1016/j.tet.2010.02.035.

References and notes

1. For selected leading references on ring-chain tautomerism, see: (a) Elguero, J.; Marzin, C.; Katritzky, A. R.; Linda, P. *The Tautomerism of Heterocycles*; Academic: New York, NY, 1976; p 498; (b) Elguero, J.; Claramunt, R. M.; Summers, A. J. H. The chemistry of aromatic azapentalenes *Adv. Heterocycl. Chem.* **1978**, *22*, 183 (pp 258–261); (c) Minkin, V. I.; Garnovskii, A. D.; Elguero, J.; Katritzky, A. R.; Denisko, O. V. The tautomerism of heterocycles: five-membered rings with two or more heteroatoms *Adv. Heterocycl. Chem.* **2000**, *76*, 157 (pp 264–281); (d) Alkorta, I.; Elguero, J. How aromaticity affects the chemical and physicochemical properties of heterocycles: a computational approach *Top. Heterocycl. Chem.* **2009**, *19*, 155.
2. (a) Burke, L. A.; Elguero, J.; Leroy, G.; Sana, M. *J. Am. Chem. Soc.* **1976**, *98*, 1685; (b) Wong, M. W.; Leung-Toung, R.; Wentrup, C. *J. Am. Chem. Soc.* **1993**, *115*, 2465; (c) Cubero, E.; Orozco, M.; Luque, F. J. *J. Am. Chem. Soc.* **1998**, *120*, 4723; (d) Quapp, W.; Hirsch, M.; Imig, O.; Heidrich, D. J. *Comput. Chem.* **1998**, *19*, 1087; (e) Cubero, E.; Orozco, M.; Luque, F. J. *J. Org. Chem.* **1998**, *63*, 2354; (f) Abu-Eittah, R. H.; Taha, F.; Hamed, M. M.; El-Kelany, K. E. *J. Mol. Struct. Theochem* **2009**, *895*, 142.
3. (a) Burke, L. A.; Nguyen, M. T.; Sana, M. *J. Am. Chem. Soc.* **1978**, *100*, 3668; (b) L'abbé, G.; Godts, F.; Toppet, S. *J. Chem. Soc., Chem. Commun.* **1985**, 589; (c) Bakulev, V. A.; Gloriozov, I. P. *Khim. Geterotsikl. Soedin.* **1989**, 504; (d) L'abbé, G.; Luyten, I.; Toppet, S. *J. Heterocycl. Chem.* **1992**, *29*, 713; (e) Rees, C. W.; Yue, T.-Y. *J. Chem. Soc., Perkin Trans. 1* **2001**, 662; (f) Yoo, E. J.; Ahlquist, M.; Kim, S. H.; Bae, I.; Fokin, V. V.; Sharpless, K. B.; Chang, S. *Angew. Chem., Int. Ed.* **2007**, *46*, 1730; Related to this and the previous topic is the pentazene/pentazol ring-chain isomerism: Burke, L. A.; Fazen, P. J. *Int. J. Quantum Chem.* **2009**, *109*, 3613.
4. Only recent papers and reviews: (a) Butler, R. N. *Adv. Heterocycl. Chem.* **1977**, *21*, 323; (b) Hill, W. E.; Künstlinger, M.; Breitmaier, E. *Angew. Chem., Int. Ed. Engl.* **1980**, *19*, 924; (c) Messmer, A.; Hajós, G. *J. Org. Chem.* **1981**, *46*, 843; (d) von Philipsborn, W.; Müller, R. *Angew. Chem.* **1986**, *25*, 383; (e) Denisov, A. Y.; Krivopalov, V. P.; Mamatyuk, V. I.; Mamaev, V. P. *Magn. Reson. Chem.* **1988**, *26*, 42; (f) Steinschifter, W.; Stadlbauer, W. *J. Prakt. Chem.* **1994**, *336*, 311; (g) Krivopalov, V. P.; Mamatyuk, V. I.; Nikolaenkova, E. B. *Russ. Chem. Bull.* **1995**, *44*, 1435; (h) Huynh, M. H. V.; Hiskey, M. A.; Chavez, D. E.; Naud, D. L.; Gilardi, R. D. *J. Am. Chem. Soc.* **2005**, *127*, 12537; (i) Boga, C.; Del Vecchio, E.; Forlani, L.; Mazzanti, A.; Lario, C. M.; Todesco, P. E.; Tozzi, S. *J. Org. Chem.* **2009**, *74*, 5568.
5. Kanyalkar, M.; Coutinho, E. C. *Tetrahedron* **2000**, *56*, 8775.
6. Monajjemi, M.; Honarparvar, B.; Monajemi, H. *J. Mex. Chem. Soc.* **2006**, *50*, 143.
7. Cmoch, P.; Wiench, J. W.; Stefaniak, L.; Webb, G. A. *J. Mol. Struct.* **1999**, *510*, 165.
8. Katrusiak, A.; Skierska, U.; Katrusiak, A. *J. Mol. Struct.* **2005**, *751*, 65.
9. (a) *Chem. Eng. News* **2000**, *Aug 7*, 62; (b) Alkorta, I.; Jagerovic, N.; Elguero, J. *ARKIVOC* **2004**, *iv*, 130.
10. Zheng, W.; Wong, N.-B.; Liang, X.; Long, X.; Tian, A. *J. Phys. Chem. A* **2004**, *108*, 840.
11. Borovlev, I. V.; Demidov, O. P. *Chem. Heterocycl. Comp.* **2008**, *44*, 1131.
12. For reviews of perimidine chemistry see: (a) Pozharskii, A. F.; Dalnikovskaya, V. V. *Russ. Chem. Rev.* **1981**, *50*, 816; (b) Claramunt, R. M.; Dotor, J.; Elguero, J. *An. Quím.* **1995**, *91*, 151; (c) Undheim, K.; Benneche, T. In *Comprehensive Heterocyclic Chemistry II*; Katritzky, A. R., Rees, C. W., Scriven, E. F. V., Eds.; Pergamon: Oxford, 1996; Vol. 6, Chapter 2.
13. (a) Claramunt, R. M.; Elguero, J. *Chem. Lett.* **1977**, 1441; (b) Konstantinchenko, A. A.; Lyashenko, P. I.; Pozharskii, A. F. *Khim. Geterotsikl. Soedin.* **1981**, 1114; (c) Pozharskii, A. F.; Vinogradova, O. V.; Kuz'menko, V. V. *Khim. Geterotsikl. Soedin.* **1995**, 421.
14. Guimon, C.; Khayar, S.; Pfister-Guillouzo, G.; Claramunt, R. M.; Elguero, J. *Spectrosc. Lett.* **1981**, *14*, 747.
15. (a) Free, S. M. J.; Wilson, J. W. *J. Med. Chem.* **1964**, *7*, 395; (b) Kubinyi, H. In *QSAR: Hansch Analysis and Related Approaches. Methods and Principles in Medicinal Chemistry*; Mannhold, R., Krogsgaard-Larsen, P., Timmerman, H., Eds.; VCH: Weinheim, 1993; Vol. 1; (c) Alkorta, I.; Blanco, F.; Elguero, J. *Tetrahedron* **2008**, *64*, 3826.
16. Bird, C. W. *Tetrahedron* **1996**, *52*, 9945.
17. (a) Kassimi, N. E.-B.; Doerksen, R. J.; Thakkar, A. J. *J. Phys. Chem.* **1995**, *99*, 12790; (b) Kotelevskii, S. I.; Prezhdo, O. V. *Tetrahedron* **2001**, *57*, 5715; (c) Doerksen, R. J.; Steeves, V. J.; Thakkar, A. J. *J. Comput. Meth. Sci. Eng.* **2004**, *4*, 427; (d) Raczynska, E. D.; Kosinska, W.; Osmialowski, B.; Gawinecki, R. *Chem. Rev.* **2005**, *105*, 3561.
18. Mandado, M.; Otero, N.; Mosquera, R. A. *Tetrahedron* **2006**, *62*, 12204.
19. (a) Wentrup, C. *Helv. Chim. Acta* **1978**, *61*, 1755; (b) Hooper, D. L.; Manning, H. W.; LeFrance, R. J.; Vaughan, K. *Can. J. Chem.* **1986**, *64*, 250; (c) Krivopalov, V. P.; Baram, S. G.; Denisov, A. Y.; Mamatyuk, V. I. *Izv. Akad. Nauk SSSR* **1989**, 2002; (d) Bencteux, E.; Houssin, R.; Hénichart, J.-P. *J. Heterocycl. Chem.* **1997**, *34*, 1375; (e) Bertelli, L.; Biagi, G.; Giorgi, I.; Livi, O.; Manera, C.; Scartoni, V.; Lucacchini, A.; Giannaccini, G.; Barili, P. L. *Eur. J. Med. Chem.* **2000**, *35*, 333; (f) Jones, P.; Chambers, M. *Tetrahedron* **2002**, *58*, 9973; (g) Angibaud, P.; Bourdrez, X.; End, D. W.; Freyne, E.; Janicot, M.; Lezouret, P.; Ligny, Y.; Mannens, G.; Damsch, S.; Mevellec, L.; Meyer, C.; Muller, P.; Pilatte, I.; Poncelet, V.; Roux, B.; Smets, G.; Van Dun, J.; Van Remoortere, P.; Veneta, M.; Wouters, W. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 4365; (h) Kvaskoff, D.; Bednarek, P.; George, L.; Waich, K.; Wentrup, C. *J. Org. Chem.* **2006**, *71*, 4049.
20. (a) Barbe, J.; Boyer, G.; Carignano, I.; Elguero, J.; Galy, J.-P.; Morel, S.; Oughedani, R. *Tetrahedron Lett.* **1991**, *32*, 6709; (b) Galy, J.-P.; Morel, S.; Boyer, G.; Elguero, J. *J. Heterocycl. Chem.* **1996**, *33*, 1551.
21. (a) Jencks, W. P. *Catalysis in Chemistry and Enzymology*; McGraw Hill: New York, NY, 1969; p 195; (b) Smith, M. B.; March, J. *March's Advanced Organic Chemistry*, 6th ed.; Wiley-Interscience: Hoboken, New Jersey, 2007; p 308.
22. Chen, Z.; Wannere, C. S.; Corminboeuf, C.; Puchta, R.; Schleyer, P. v. R. *Chem. Rev.* **2005**, *105*, 3842 (see p 3875).
23. Espinosa, E.; Alkorta, I.; Elguero, J.; Molins, E. *J. Chem. Phys.* **2002**, *117*, 5529.
24. Picazo, O.; Alkorta, I.; Elguero, J. *J. Org. Chem.* **2003**, *68*, 7485.
25. Mata, I.; Molins, E.; Alkorta, I.; Espinosa, E. *J. Chem. Phys.* **2009**, *130*, 044104.
26. Becke, A. D. *Phys. Rev. A* **1988**, *38*, 3098.
27. Becke, A. D. *J. Chem. Phys.* **1993**, *98*, 5648.
28. Lee, C.; Yang, W.; Parr, R. G. *Phys. Rev. B* **1988**, *37*, 785.
29. Hariharan, P. A.; Pople, J. A. *Theor. Chim. Acta* **1973**, *28*, 213.
30. Ditchfield, R.; Hehre, W. J.; Pople, J. A. *J. Chem. Phys.* **1971**, *54*, 724.
31. Frisch, M. J.; Pople, J. A.; Krishnam, R.; Binkley, J. S. *J. Chem. Phys.* **1984**, *80*, 3265.
32. Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Montgomery, J. A., Jr.; Vreven, T.; Kudin, K. N.; Burant, J. C.; Millam, J. M.; Iyengar, S. S.; Tomasi, J.; Barone, V.; Mennucci, B.; Cossi, M.; Scalmani, G.; Rega, N.; Petersson, G. A.; Nakatsuji, H.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Klene, M.; Li, X.; Knox, J. E.; Hratchian, H. P.; Cross, J. B.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Ayala, P. Y.; Morokuma, K.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Zakrzewski, V. G.; Dapprich, S.; Daniels, A. D.; Strain, M. C.; Farkas, O.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Ortiz, J. V.; Cui, Q.; Baboul, A. G.; Clifford, S.; Cioslowski, J.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Challacombe, M.; Gill, P. M. W.; Johnson, B.; Chen, W.; Wong, M. W.; Gonzalez, C.; Pople, J. A. *Gaussian 03*; Gaussian: Pittsburgh, PA, 2003.
33. McIver, J. W.; Komornicki, A. K. *J. Am. Chem. Soc.* **1972**, *94*, 2625.
34. Curtiss, L. A.; Raghavachari, K.; Redfern, P. C.; Rassolov, V.; Pople, J. A. *J. Chem. Phys.* **1998**, *109*, 7764; Baboul, A. G.; Curtiss, L. A.; Redfern, P. C.; Raghavachari, K. *J. Chem. Phys.* **1999**, *110*, 7650; Anantharaman, B.; Melius, C. F. *J. Phys. Chem. A* **2005**, *109*, 1734.
35. (a) Ditchfield, R. *Mol. Phys.* **1974**, *27*, 789; (b) London, F. *J. Phys. Radium* **1937**, *8*, 397.
36. (a) Schleyer, P. v. R.; Maerker, C.; Dransfeld, A.; Jiao, H.; Hommes, N. J. R. v. *J. Am. Chem. Soc.* **1996**, *118*, 6317; (b) Schleyer, P. v. R.; Manoharan, M.; Wang, Z. X.; Kiran, B.; Jiao, H.; Puchta, R.; Eikema Hommes, N. J. R. v. *Org. Lett.* **2001**, *3*, 2465.
37. Bader, R. F. W. *Atoms in Molecules: A Quantum Theory*; Clarendon: Oxford, 1990.
38. Biegler-König, F. W.; Bader, R. F. W.; Tang, T. H. *J. Comput. Chem.* **1982**, *3*, 317.
39. Popelier, P.L.A., with a contribution from R.G.A. Bone (UMIST, Engl, EU) MORPHY98, a topological analysis program, 1999.
40. Popelier, P. L. A. *Chem. Phys. Lett.* **1994**, *228*, 160.
41. Rafat, M.; Popelier, P. L. A. *J. Comput. Chem.* **2007**, *28*, 2602.