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A theoretical study of the effect of copper(I) chloride on the azido/tetrazole isomerism

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Dedicated to our friend and colleague, Professor Zvonimir B. Maksic, who untimely passed away in March 2011

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ABSTRACT

B3LYP/6-31G(d), B3LYP/6-311++G(d,p), and CBS-QB3 calculations on the effect of CuCl on the azido/tetrazole isomerism have been performed. The cases of 2-azidopyridine and 2-azido-1*H*-imidazole have been selected as examples of heteroaromatic six- and five-membered rings. All minima and transition states have been characterized.

1. Introduction

Click chemistry, although an extension of Huisgen 1,3-dipolar cycloadditions,[1] has constituted a revolution in synthetic organic chemistry.[2] In its most usual form it involved the 1,3-dipolar cycloaddition of an organic azide on a terminal alkyne catalyzed by Cu(I) [generated in situ by reduction of a Cu(II) compound] to afford regioselectively 1,2,3-triazoles (represented schematically in Fig. 1). DFT studies on this reaction have been reported both for the catalyzed[3,4] and the uncatalyzed varieties.[5]

Less frequent but obviously related is the reaction of organic azides with nitriles to afford tetrazoles. Also initiated by Sharpless,[6,7] it was used subsequently with great success.[8–10] The main difference with the synthesis of triazoles is that only activated azides react. Both [2+3] cycloadditions and their click modification can occur intramolecularly, generally a flexible link connects both moieties;[11–14] the intramolecular cycloaddition of azides to nitriles has been studied theoretically at the B3LYP/6-311G(d,p) level.[15]

There are two publications that deserve a separate comment. The existence of the azido/tetrazole tautomerism allows tetrazoles to react like azides in the presence of a Cu-catalyst (Fig. 2).[16]

A related reaction involving various pyrido-, quinolino-, pyrazino-, and quinoxalino-tetrazoles to yield *N*-heterocyclic derivatives of 1,2,3-triazoles in a Cu-catalyzed click reaction has been reported (Fig. 3).[17]

Recently we have devoted two papers to the azido/tetrazole equilibrium in the azine and the azole series,[18,19] that are conceptually very close to 1,3-dipolar cycloadditions, to the point of being christened by Reimlinger as '1,5-dipolar cycloadditions'.[20] In these papers we examined several equilibria including the two showed in Fig. 4.

2-Azidopyridine (**1A**) existing in two conformations, ***E*** and ***Z***, is in equilibrium with tetrazolo[1,5-*a*]pyridine (**1T**) while the two conformations of 2-azido-1*H*-imidazole (**2A*E*** and **2A*Z***) are in equilibrium with 4*H*-imidazo[1,5-*a*]tetrazole (**2T**).[18,19]

We decided to study the effect of click chemistry catalyst, CuCl [copper(I) chloride], on the equilibria represented in Fig. 4 and on the corresponding transitions states (TS).

Particularly relevant for our purpose is a paper of 1978 where the isomerization **1AZ** to **1T** is due to coordination with different metals, for instance Cu(II) (Fig. 5).[21] The authors do not determine the coordination site of the tetrazole but we have assumed (see later on), that is, N4.

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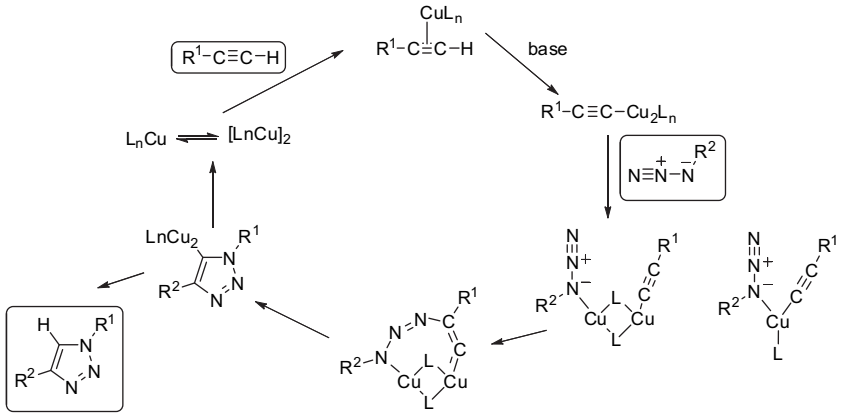


Fig. 1. Schematic representation of the classical click reaction. On the right side of the Cu_2L_2–azide–acetylide complex we have represented the simplified structure used by Himo et al.[3] for their calculations.

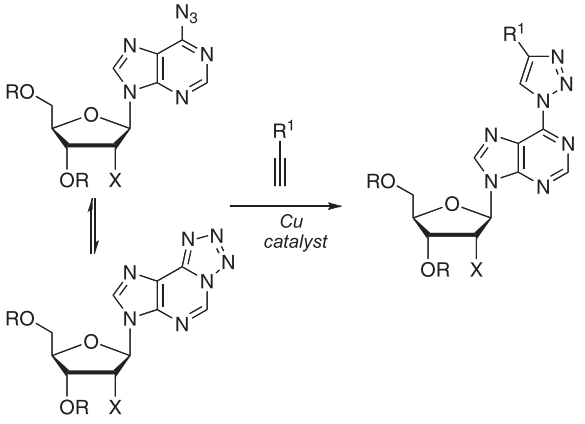


Fig. 2. Azide-tetrazole equilibrium of C-6 azidopurine nucleosides and their ligation reactions with alkynes.

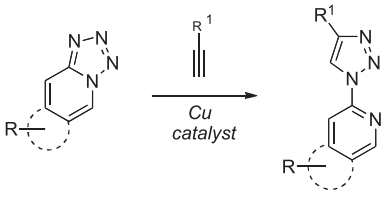


Fig. 3. Fused tetrazoles as azide surrogates in click reactions.

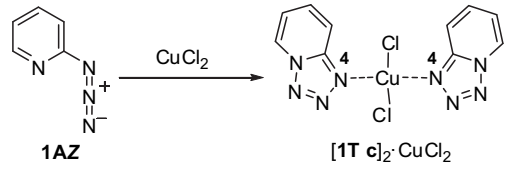


Fig. 5. A/T isomerization induced by coordination with a metal (see Fig. 7 for labels).

systems studied. As expected, the major concentration of negative potential occurs in those regions occupied by the nitrogen lone pairs (LP_N). Based on MEP regions and MEP minima values a series A/T:CuCl dimers have been optimized for pyridine (**1**) and imidazole (**2**) derivatives at three different computational levels [B3LYP/6-31G(d), B3LYP/6-311++G(d,p), and CBS-QB3] (Figs. 7 and 8). Explored geometries covers all the spectra of complexes formed through the most favorable $LP_N\cdots Cu$ interactions both for the azido as the tetrazole isomers. The possible dimers interacting by the π-aromatic region above and below the pyridine and imidazole rings were dismissed to simplify the study (after checking that MEP values corresponding to these areas were the lowest ones in almost all the cases).

Tables 1 and 2 report the dipole moments and relative energies for monomers and dimers and the interaction energies for dimers. The correlation coefficients obtained for the interaction energies of the dimers (Table 2) with the methods employed using only the 17 points common to the three methods, i.e., excluding **1AZ a1**, **1AZ a2**,

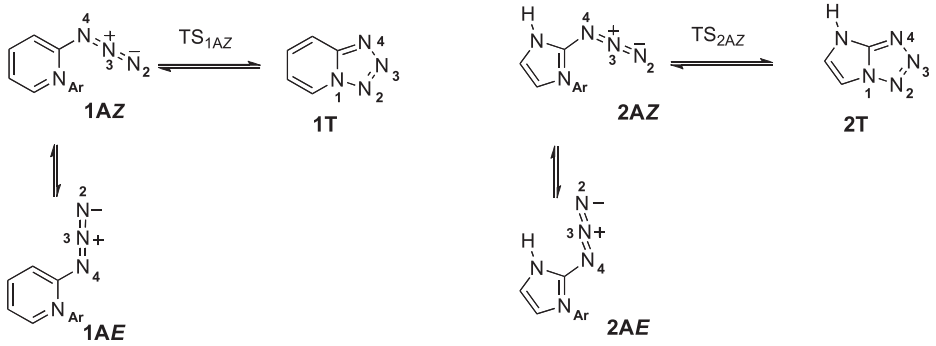


Fig. 4. The A/T equilibria involved in pyridine and imidazole.

2. Results and discussion

Fig. 6 shows the distribution of the molecular electrostatic potential (MEP) of the different isomers corresponding to the two **1AZ a3**, and **2AZ a1**, is good between B3LYP/6-31G(d) and B3LYP/6-311++G(d,p) (R^2=0.96) as well as between B3LYP/6-311++G(d,p) and CBS-QB3 (Eq. 1, R^2=0.91) but not so good between B3LYP/6-31G(d) and CBS-QB3 (R^2=0.79).

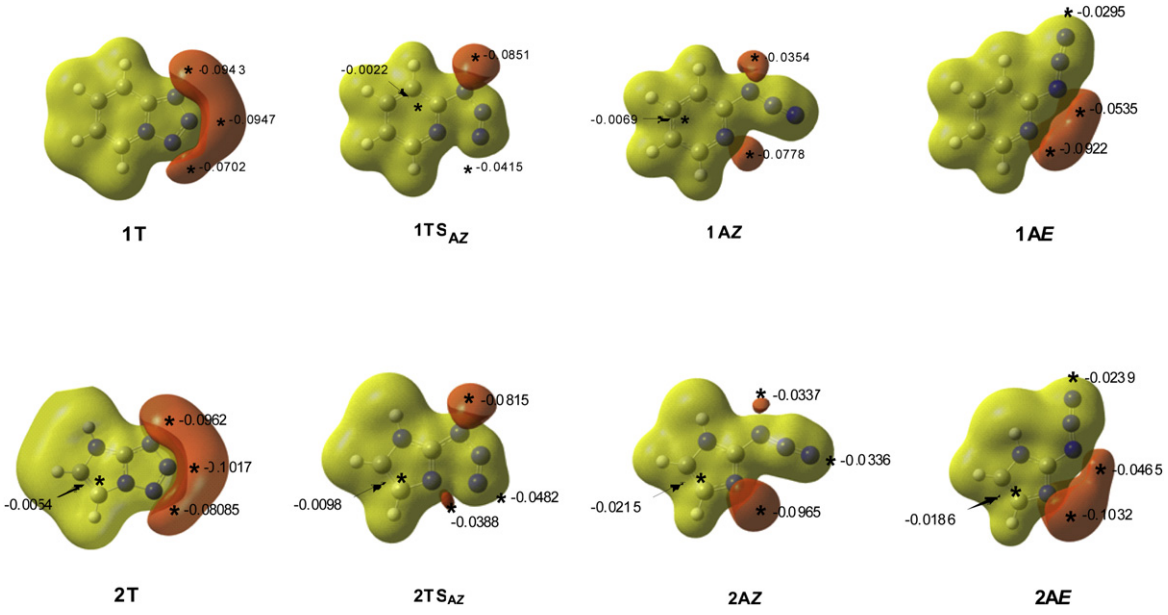


Fig. 6. MEP isosurfaces at ±0.04 a.u. (orange=negative region; yellow=positive region), the calculated values of MEP minima are indicated.

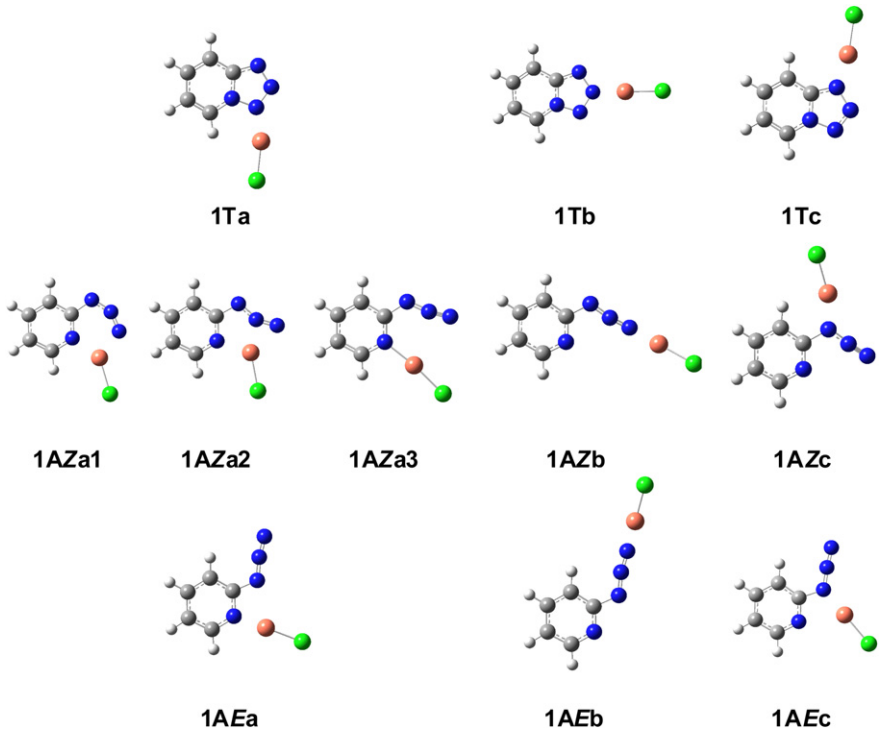


Fig. 7. Optimized geometries of A/T:CuCl dimers of pyridine derivatives (**1**).

$$E_{\text{int}}\,[\text{B3LYP}/6-311++\text{G}(\text{d},\text{p})] = -(7.6\pm7.0)+(0.79\pm0.06)\,E_{\text{int}}\,(\text{CBS}-\text{QB3}) \quad (1)$$

If the intercept was assumed to be 0, then Eq. 2 was obtained:

$$E_{\text{int}}[\text{B3LYP}/6-311++\text{G}(\text{d},\text{p})] = (0.86\pm0.02)\,E_{\text{int}}\,(\text{CBS}-\text{QB3}),\ R^2 = 0.995 \quad (2)$$

Note that only the two highest level methods [B3LYP/6-311++G(d,p) and CBS-QB3] match on the localization of the global minimum for each series of dimers (Table 2). Therefore the discussion of the results (geometries, energies, and transition states) will focus on the B3LYP/6-311++G(d,p) results.

2.1. The minima

The equilibria studied in this work (Fig. 4) involves five stationary points: three minima (**1**/**2T**, **1**/**2AZ**, and **1**/**2AE**) and two transitions states, one corresponding to the azido/tetrazole ring-chain isomerism (**1**/**2T**>>**1**/**2AZ**) and other, less important, corresponding to the rotation between the two azido forms (**1**/**2AZ**>>**1**/**2AE**). The relative energies of the monomers (Table 1) reveal the higher stabilization of the azido forms **1AZ** or **2AZ** with regarding to the tetrazole ones (**1T** and **2T**) with a significant energy difference, especially in the case of the imidazole derivatives (15.8 and 55.7 kJ mol^{-1} for **1** and **2**, respectively). **1**/**2AZ** forms are also favored compared to the respective azido rotamers **1**/**2AE** (16.5 and

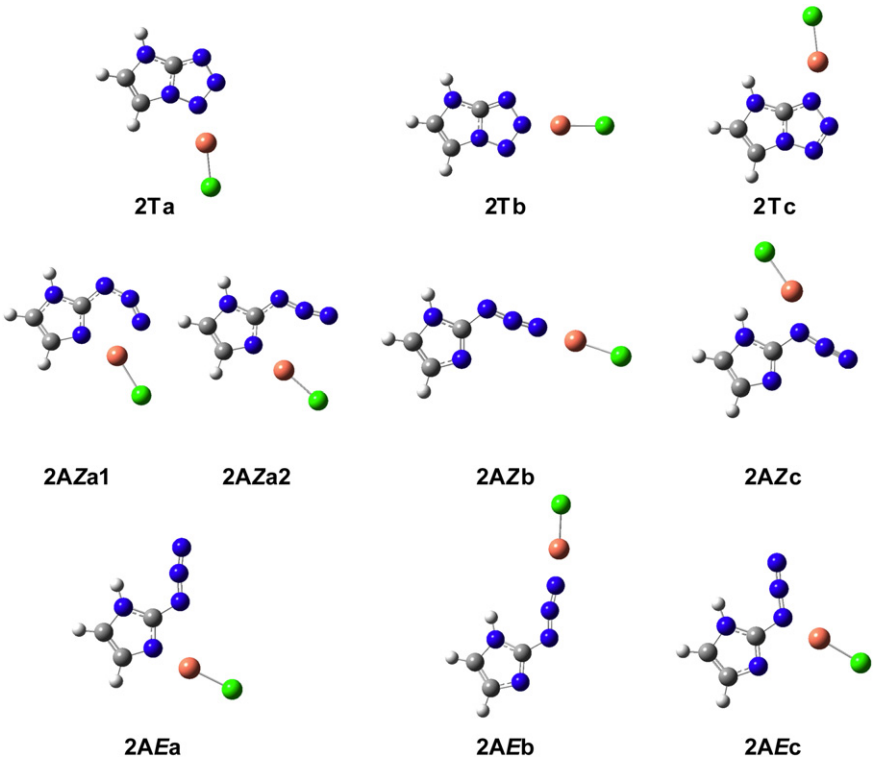


Fig. 8. Optimized geometries of A/T:CuCl dimers of imidazole derivatives (**2**).

Table 1
Relative energies of monomers [B3LYP/6-31G(d), B3LYP/6-311++G(d,p), and CBS-QB3]

Comp.	ImFreqs	Dipole B3LYP/ 6-31G(d)	ΔΔG B3LYP/ 6-31G(d)	ΔΔG B3LYP/ 6-311++G(d,p)	ΔΔG CBS-QB3
CuCl	0	4.69	—	—	—
1T	0	6.22	2.8	15.8	*−8.3*[a]
1AZ	0	3.07	**0.0**	**0.0**	**0.0**
1AE	0	3.27	14.8	16.5	15.4
2T	0	7.14	41.7	55.7	33.7
2AZ	0	3.75	**0.0**	**0.0**	**0.0**
2AE	0	3.83	18.5	20.1	19.1

In bold the 0.0 kJ mol^{-1} values for the same structure and in italics the absolute minimum.
[a] Absolute minimum at CBS-QB3 level.

20.1 kJ mol^{-1} for **1** and **2**, respectively at B3LYP/6-311++G(d,p) level). Now we will describe the changes observed under CuCl complexation.

Figs. 7 and 8 report the geometry of the A/T:CuCl complexes. Eleven different minima have been found for pyridine derivatives (**1**) and ten for imidazole ones (**2**). The geometry of the minima is almost the same in both series, but there are significant differences in the energy of the complexes. For the sake of clarity, we decided to use for the nitrogen atoms of the azide group, the same numbering inherited from the tetrazole ring (Fig. 4). As shown, there is a clear pattern of A/T:CuCl interactions depending on the isomeric state of the heteroaromatic system:

Table 2
Relative and interaction energies of A/T:CuCl dimers of pyridine (**1**) and imidazole (**2**) derivatives [B3LYP/6-31G(d), B3LYP/6-311++G(d,p), and CBS-QB3]

	Dipole B3LYP/ 6-31G(d)	ΔΔG B3LYP/ 6-31G(d)	ΔΔG B3LYP/ 6-311++G(d,p)	ΔΔG CBS-QB3	E_{int} B3LYP/ 6-31G(d)	E_{int} B3LYP/ 6-311++G(d,p)	E_{int} CBS-QB3
1T a	9.13	8.5	17.7	18.3	−215.9	−98.3	−115.0
1T b	13.14	1.3	7.5	13.1	−223.1	−108.5	−120.2
1T c	11.19	**0.0**	**0.0**	**0.0**	−224.4	−115.9	−133.3
1AZ a1	7.62	*−21.8*[a]	—[b]	59.9	−243.4	—[b]	−81.7
1AZ a2	7.99	*−14.5*[a]	—[b]	68.7	−236.1	—[b]	−72.8
1AZ a3	—[b]	—[b]	8.6	—[b]	—[b]	−91.5	—
1AZ b	9.06	32.4	30.6	68.5	−189.1	−69.6	−73.1
1AZ c	6.81	35.7	26.5	43.3	−185.8	−73.6	−98.3
1AE a	10.04	4.5	4.2	24.9	−231.8	−112.4	−132.1
1AE b	7.59	50.1	48.2	85.1	−186.3	−68.4	−71.9
1AE c	10.13	52.4	42.6	60.8	−183.9	−74.1	−96.2
2T a	11.82	52.7	68.3	54.0	−213.6	−102.6	−118.8
2T b	14.30	40.2	58.2	47.0	−226.2	−112.7	−125.8
2T c	10.08	40.0	52.1	35.7	−226.3	−118.8	−137.1
2AZ a1	8.98	*−29.6*[a]	—[b]	45.1	−254.3[b]	—[b]	−94.0
2AZ a2	10.55	**0.0**	**0.0**	**0.0**	−224.6	−115.2	−139.1
2AZ b	9.52	37.3	48.4	71.6	−187.4	−66.8	−67.5
2AZ c	3.48	44.3	46.6	45.7	−180.3	−68.6	−93.4
2AE a	11.45	14.2	13.4	16.2	−228.9	−121.9	−142.0
2AE b	5.77	57.3	68.8	96.7	−185.8	−66.5	−61.5
2AE c	10.62	73.4	71.9	75.5	−169.7	−63.4	−82.7

In bold the 0.0 kJ mol^{-1} values for the same structure and in italics the absolute minimum.
[a] Absolute minimum at B3LYP/6-31G(d) level.
[b] Minimum not found.

- **1**/**2T** isomers: three different minima located corresponding to the interaction of CuCl with the lone pairs of N2 [complex **a**], N3 [complex **b**], and N4 [complex **c**], respectively.
- **1**/**2*AZ*** isomers: five different minima located for pyridine derivatives (**1**) and four for imidazole (**2**) ones corresponding to the interaction of CuCl with the lone pairs of the aromatic nitrogen (N_{Ar}) [complexes **a1**, **a2** or **a3**], N2 [complex **b**], and N4 [complex **c**], respectively.
- **1**/**2*AE*** isomers: three different minima located corresponding to the interaction of CuCl with the lone pairs of the nitrogen aromatic (N_{Ar}) [complex **a**], N2 [complex **b**], and N4 [complex **c**], respectively.

It is worth noting the variability obtained for the **1**/**2*AZ* a** dimers. Initially, we were exploring the simple N···Cu interaction through the aromatic nitrogen (N_{Ar}) both in pyridine (**1**) and imidazole (**2**) rings (**1*AZ* a3** and **2*AZ* a2** complexes), however, the geometry of the systems favoring the establishment of secondary interactions with the nitrogen atoms N2 and N3, provided other three additional minima (**1*AZ* a1**, **1*AZ* a2**, and **2*AZ* a1** complexes).

The basicity and coordination ability of 1*H*-tetrazoles is N4>N3>>N2 (Fig. 5).[22–25] This is the order found for tetrazolo-pyridine: **1T c**>**1T b**>>**1T a** (Table 2) and for imidazo-tetrazole: **2T c**>**2T b**>>**2T a** (Table 2). A search in the CSD reveals several structures of tetrazoles coordinated by N4 to different metals (IRULAI, BOVSOV, NIXQIV, YOTBUF).[26]

Concerning azides the most basic and most coordinating nitrogen atoms are N2 and N4, the order depends on the *N*-substituent.[27,28] Table 2 results favor N2 (**b** series) over N4 (**c** series): **1AZ b**>**1AZ c**; **1AE b**>**1AE c**; **2AZ b**>**2AZ c**, save in the pair **2AE c**>**2AE b**.

2.1.1. Energy analysis B3LYP/6-311++G(d,p) results

1. The expected general trend should be that the more stable the complex (lower relative energy) the better interaction energies. This pattern is followed in the pyridine complexes where the highest interaction energy corresponds to the absolute minima (**1T c**), but less so in the imidazole ones.
2. More clear is the relation of the interaction energies with the most reactive regions of the aromatic rings, showing a good correlation between the interaction energies and the value of MEP minima (Fig. 9).
3. With regard to the precursor monomers, the complexation with CuCl in the pyridine system produces a displacement of the absolute minimum from the azido form (**1AZ**) to one of the tetrazole ones (**1Tc**), but in a narrow energy margin (<10 kJ mol^{-1}).

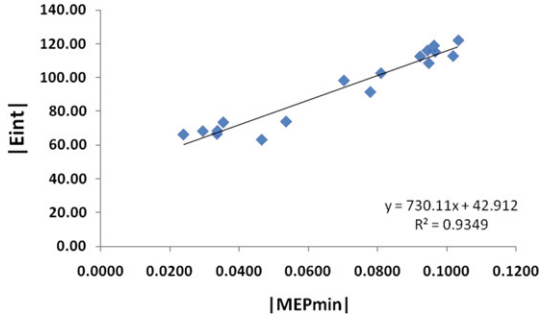


Fig. 9. Interaction energies versus MEP minima in absolute values [B3LYP/6-311++G(d,p)].

However, in imidazole derivatives this does not occur, being, as in the corresponding monomers, one of the azido geometries (**2*AZ* a2**) the most stable isomer. Moreover, focusing in the best geometries for each one of the isomers (**2T c**, **2*AZ* a2**, and **2*AE* a**), the energy ranges does not suffer significant modifications from the monomers to the dimers (55.7/52.1 and 18.5/13.4 kJ mol^{-1} for **2T**/**2T c** and **2*AE***/**2*AE* a**, respectively).

4. With regard to the azido isomers, the complexes formed by the interaction of the Cu atom with the aromatic nitrogen is always the most stable (**1*AZ* a3** and **1*AE* a** for pyridine series and **2*AZ* a2** and **2*AE* a** for imidazole ones), which is coherent with the values of the electrostatic potential, as it was mentioned above. This relation is also reflected in terms of interaction energies.

2.1.2. NBO charges. An NBO analysis (Table 3) has been done in order to describe the nature of the interaction. The second order perturbation analysis (E2) shows an important change transfer between the lone pair of the nitrogen atoms and the empty lone pair of the Cu atom for most of the complexes studied. The overall result of such interactions is the increment of the charge in the CuCl molecule as reflected by the last column of Table 3 (ΔCh CuCl).

Table 3
NBO Analysis [B3LYP/6-311++G(d,p)]

Compd	Orbital interaction	E2 (kJ mol^{-1})	ΔCh CuCl
1T a	LP N_2>>LP*Cu	304.0	−0.1087
1T b	LP N_3>>LP*Cu	284.5	−0.0871
1T c	LP N_4>>LP*Cu	292.6	−0.1179
1*AZ* a3	LP N_{Ar}>>LP*Cu	288.7	−0.1288
1*AZ* b	LP N_2>>LP*Cu	392.5	−0.0486
1*AZ* c	LP N_4>>LP*Cu	292.5	−0.0986
1*AE* a	LP N_{Ar}>>LP*Cu	274.9	−0.1115
1*AE* b	LP N_2>>LP*Cu	403.8	−0.0478
1*AE* c	LP N_4>>LP*Cu	260.6	−0.0926
2T a	LP N_2>>LP*Cu	163.8	−0.1118
2T b	LP N_3>>LP*Cu	157.8	−0.0991
2T c	LP N_4>>LP*Cu	162.0	−0.1253
2*AZ* a2	LP N_{Ar}>>LP*Cu	220.5	−0.1390
2*AZ* b	LP N_2>>LP*Cu	307.6	−0.0411
2*AZ* c	LP N_4>>LP*Cu	—[a]	−0.0996
2*AE* a	LP N_{Ar}>>LP*Cu	159.1	−0.1235
2*AE* b	LP N_2>>LP*Cu	311.4	−0.0430
2*AE* c	LP N_4>>LP*Cu	—[a]	−0.0783

[a] Orbital interaction not observed.

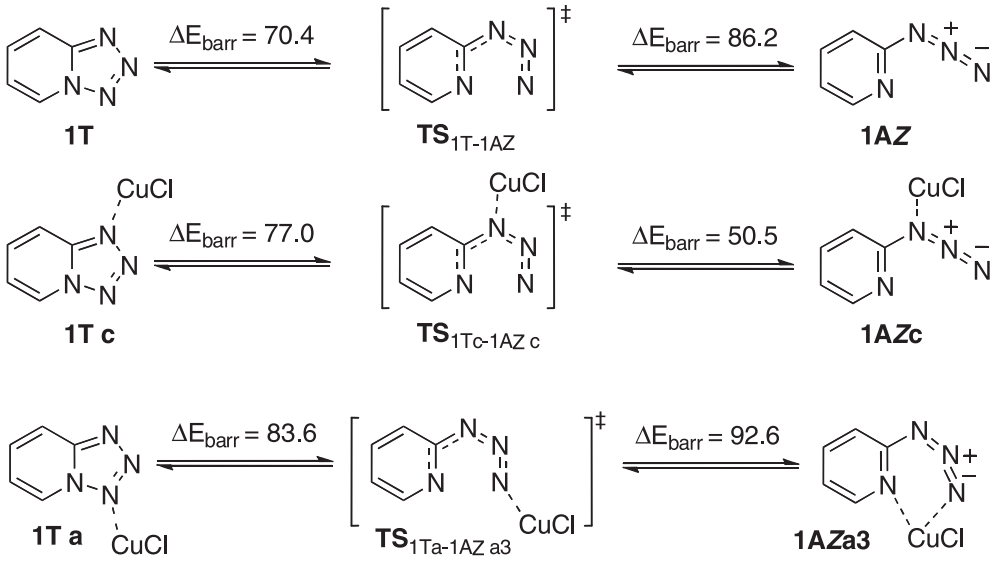
2.2. Transition states

The results concerning the transition states are reported in Schemes 1 and 2.

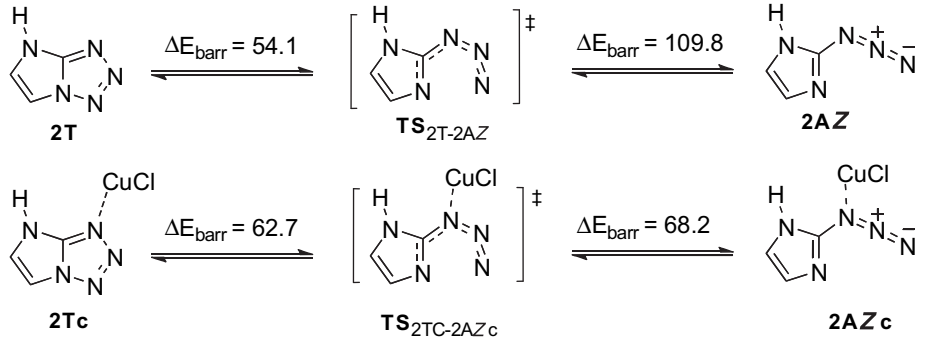
Effect of CuCl on A/T stabilities and on the energy barriers [B3LYP/6-311++G(d,p)].

The differences in energy can be discussed in a sort of adiabatic comparison, that is, between an azide and a tetrazole not connected by a TS (the CuCl molecule is on different N atoms), then the results are: pyridine, the azide (**1*AZ***) is 15.8 kJ mol^{-1} more stable that the tetrazole (**1T**), 1*H*-imidazole, the azide (**2*AZ***) is 55.7 kJ mol^{-1} more stable that the tetrazole (**2T**). In the pyridine series, coordination with CuCl transforms these values into the tetrazole (**1T c**) being 4.2 kJ mol^{-1} more stable that the azide (**1*AE* a**) (global effect: 20.0 kJ mol^{-1} of tetrazole stabilization); in the imidazole ones, the azide (**2*AZ* a2**) is more stable than the tetrazole (**2T c**) by 52.1 kJ mol^{-1} (global effect: 3.6 kJ mol^{-1} of tetrazole stabilization).

If the azide and the tetrazole are connected through TS, a kind of vertical comparison, the results are represented graphically in Fig. 10.



Scheme 1. Study of transition barrier on the catalyzed azido/tetrazole equilibrium of pyridine derivatives (**1**) [B3LYP/6-311++G(d,p)]. All values in kJ mol^{-1}.



Scheme 2. Study of transition barrier on the catalyzed azido/tetrazole equilibrium of imidazole derivatives (**2**) [B3LYP/6-311++G(d,p)]. All values in kJ mol^{-1}.

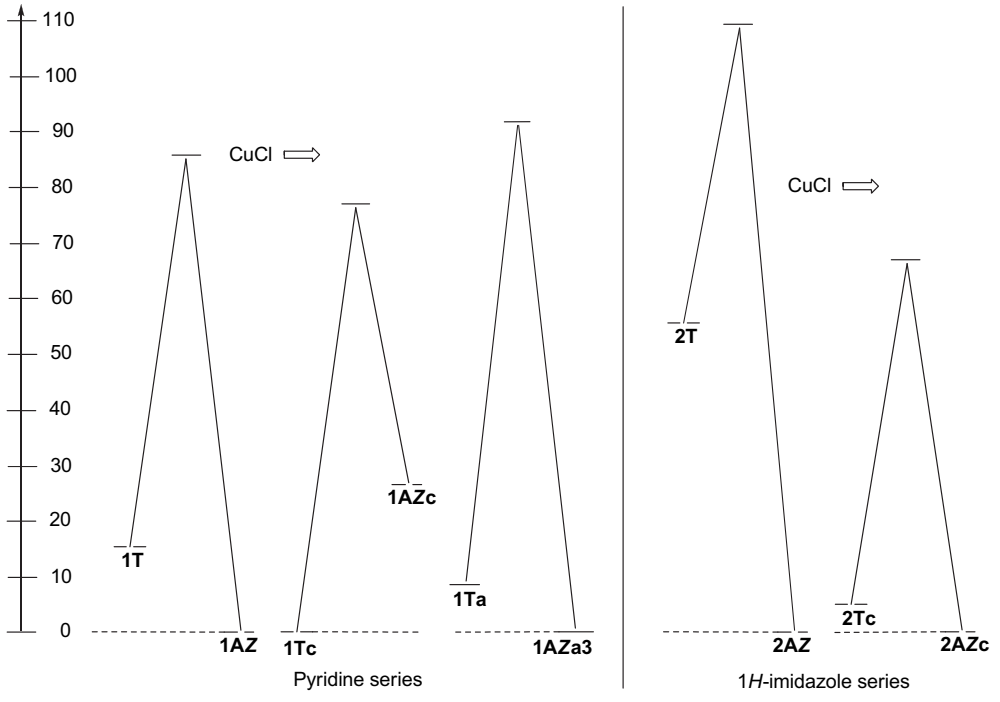


Fig. 10. Energetic profiles; for each pair, the most stable structures are represented at ΔΔG=0.0 kJ mol^{-1}.

It is clear that the effect of CuCl is more pronounced in the imidazole than in the pyridine series and this is probably related with the lower aromaticity of imidazole compared with pyridine.[29]

3. Conclusions

Although our main purpose was to study the effect of coordination with copper(I) chloride on the azido/tetrazole isomerism in the case of pyridine and imidazole, we feel that our results also shed light on the click reaction catalyzed by CuCl. The structure obtained when azides coordinate with the copper acetylide (Fig. 1) is very similar to our **1AZ c** (Fig. 7) and **2AZ c** (Fig. 8) complexes. The reactions depicted in Schemes 1 and 2 correspond to the profiles of Fig. 10. Note that both the position of the equilibrium and the barriers are modified.

Several experimental observations are related to the present calculations: (i) the existence of the azido/tetrazole tautomerism allows tetrazoles to react like azides in the presence of a Cu-catalyst (Figs. 2 and 3); (ii) the observed isomerization of **1AZ** to **1T c** (Fig. 5) correspond to the conversion of the free minimum (**1AZ**, Table 1) to the coordinated minimum (**1T c**, Table 2).

The MEP isosurfaces (Fig. 6) and the NBO charges (Table 3) complete the understanding of the interactions involved in the free molecules and the corresponding complexes.

4. Computational details

The optimization of the geometries of the structures was carried out at the B3LYP/6-31G(d), the B3LYP/6-311++G(d,p) level,[30–34] and the Complete Basis Set including Zero-point-corrected energy (CBS-QB3) method[35]within the Gaussian-09 package.[36] Frequency calculations at B3LYP levels were carried out to confirm that the obtained structures correspond to energy minima or to TSs (number of imaginary frequencies 0 for the minima and 1 for the TSs).[37] The Natural Bond Order analysis (NBO 3.0)[38] as implemented in the G09 has been used to analyze the orbital interaction and the atomic charges of the systems.

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Supplementary data

These data include absolute energies of the complexes and Cartesian coordinates of the optimized geometries at three calculated levels. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tet.2011.09.027.

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