Computational Studies on Intramolecular Cycloadditions of Azidoenynes and Azidobutenenitriles to Give 6*H*-Pyrrolo[1,2-*c*][1,2,3]triazoles and 5*H*-Pyrrolo[1,2-*d*]tetrazoles

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Energetics of intramolecular cycloadditions of azidoenynes and azidobutenenitriles to give 6*H*-pyrrolo[1,2-*c*][1,2,3]triazoles and 5*H*-pyrrolo[1,2-*d*]tetrazoles have been calculated at the B3LYP/6.311 + + G(3df,3pd) level of theory in ideal gas and in H_2O as solvent. Stabilities of the corresponding anions, tautomers, and isomers are discussed. Transition states of the cyclization of parent compounds are determined at the same level of theory.

Introduction. – The heterocyclic compounds 1,2,3-triazoles (*v*-triazoles) and 1,2,3,4-tetrazoles have been known for more than 100 years. In the last decades, the chemistry of these heterocycles has gained in importance due to the discovery of their various biological activities [1].

The *Huisgen* 1,3-dipolar cycloaddition reaction of azides and alkynes has drawn great attention because of its efficiency and versatility to provide fast access to an enormous variety of medicinally interesting triazoles [2]. Moreover, the Cu^I-catalyzed azide-alkyne cycloaddition (CuAAC) is versatile for numerous applications [3] and does well meet the criteria of a 'click' reaction: fast reaction rate, high yields, and outstanding orthogonal reactivity [4]. For example, the click approach was a suitable procedure for the preparation of peptide–steroid conjugates [5] or protein conjugation with chitosan [6]. Moreover, spectacular 3D alkyne-azide cycloadditions with highly spatiotemporal control have been described [7].

The tetrazole ring is an isostere of carboxylic acid[1]), and quite a number of studies dealing with the synthesis of new tetrazole derivatives exhibiting diverse biological activities are published annually [9]. The most common approach to synthesize 5-substituted tetrazoles is the *Huisgen* addition of N_3^- to a nitrile in the presence of an acid catalyst [1b][10].

The bimolecular 1,3-cycloaddition of various organic azides to alkynes led mainly to 1,4-disubstituted-1,2,3-triazoles, especially in the presence of a Cu catalyst[2]) (*Scheme 1*) [11].

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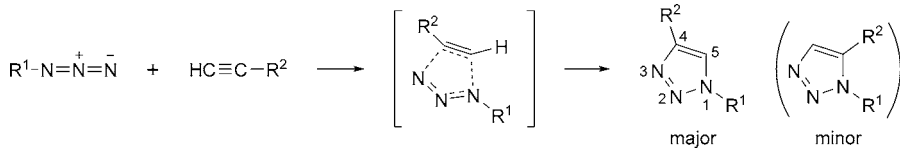
[1]) According to *Burger*, isosteres are 'compounds or groups that possess near-equal molecular shapes and volumes, approximately the same distribution of electrons, and which exhibit similar physical properties' [8].

[2]) For computational studies concerning uncatalyzed and Cu-catalyzed cycloadditions, see [12].

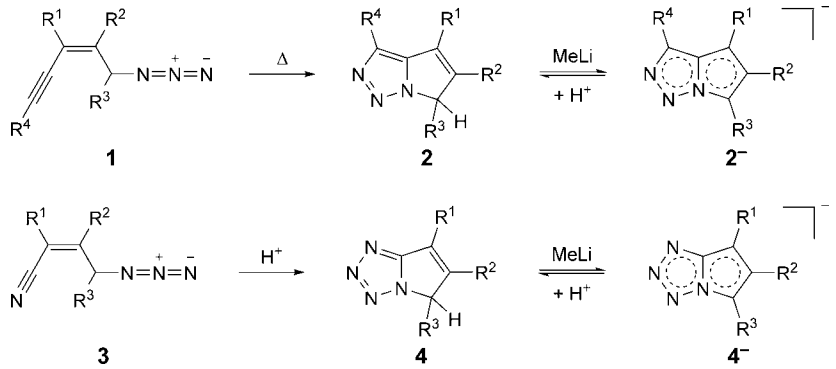
Scheme 1. *Thermal Cycloaddition of an Alkylazide and an Alkyne*



The synthesis of 6*H*-pyrrolo[1,2-*c*][1,2,3]triazoles **2** by the uncatalyzed intramolecular 1,3-dipolar cycloaddition reaction of 1-azidopent-2-en-4-ynes **1** has been previously reported by us [13]. Azidoenynes **1** were obtained by the treatment of 1-chloropent-2-en-4-ynes [14] with NaN_3. Moreover, the cyclization of 4-azidobut-2-enenitriles **3** in acidic medium led to 5*H*-pyrrolo[1,2-*d*]tetrazoles **4** [15]. The alkylation and the acylation of the corresponding ten-π-electron monoanions $\mathbf{2}^-$ and $\mathbf{4}^-$ also have been described (*Scheme 2*) [15][16].

Herein, we aim to provide a better understanding of these reactions by the thorough report of calculated thermodynamic and kinetic data concerning various steps.

Scheme 2. *Previously Investigated Intramolecular Cyclizations and Formation of Monoanions*



Results and Discussion. – *Energetics of the Cyclization Reactions.* First, we calculated the variations of energies ΔE or *Gibbs* energies ΔG for the thermal cyclization of azidoenynes **1a**–**1g** to bicyclic triazoles **2a**–**2g**. The reaction was strongly exergonic by *ca.* 44 to *ca.* 50 kcal mol^{-1} (*Table 1* and Table SI 1 in the *Supporting Information* (SI)[3]). We noted that the presence of Me groups moderately increased the exergonicity. In contrast, the presence of the disubstituted acetylenic moiety of **1g** was unfavorable. In H_2O as solvent, the reaction was more exergonic, implying that there is a build-up of partial charges in the rate-limiting transition state.

The thermal cyclization of 4-azidobut-2-enenitriles **3a**–**3f** to **4a**–**4f** was weakly exergonic and explained the lack of experimental observation in neutral medium (*Table 2* and Table SI 2). Nevertheless, the use of H_2O as solvent facilitated this thermal cyclization.

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[3]) Supporting material available upon request from the authors.

Table 1. *Energetics of the Thermal Cycloaddition of 1-Azidopent-2-en-4-ynes* **1a**–**1g** *to 6*H-*Pyrrolo-[1,2-*c*][1,2,3]triazoles* **2a**–**2g** (see *Scheme 2* and Table SI 1)

	R	$\Delta E = E^2 - E^1$ [kcal mol^{-1}][a])	$\Delta G = G^2 - G^1$ [kcal mol^{-1}][a])	$\Delta E = E^2 - E^1$ [kcal mol^{-1}][b])	$\Delta G = G^2 - G^1$ [kcal mol^{-1}][b])
1a → **2a**	$R^1 = R^2 = R^3 = R^4 = H$	– 51.22	– 44.82	– 55.26	– 48.64
1b → **2b**	$R^1 = Me$, $R^2 = R^3 = R^4 = H$	– 52.77	– 46.49	– 56.81	– 50.36
1c → **2c**	$R^1 = R^3 = R^4 = H$, $R^2 = Me$	– 52.12	– 45.94	– 56.55	– 50.09
1d → **2d**	$R^1 = R^2 = Me$, $R^3 = R^4 = H$	– 54.45	– 47.78	– 58.92	– 52.13
1e → **2e**	$R^1 = R^4 = H$, $R^2 = R^3 = Me$	– 53.04	– 46.58	– 57.20	– 50.55
1f → **2f**	$R^1 = R^2 = R^3 = Me$, $R^4 = H$	– 56.43	– 50.18	– 60.67	– 54.13
1g → **2g**	$R^1 = R^4 = Me$, $R^2 = R^3 = H$	– 49.07	– 43.07	– 56.52	– 46.63

[a]) Calculated in ideal gas. [b]) Calculated using H_2O as solvent.

Table 2. *Energetics of the Thermal Cycloaddition of 4-Azidobut-2-enenitriles* **3a**–**3f** *to 5*H-*Pyrrolo[1,2-*d*]tetrazoles* **4a**–**4f** (see *Scheme 2* and Table SI 2)

	R	$\Delta E = E^4 - E^3$ [kcal mol^{-1}][a])	$\Delta G = G^4 - G^3$ [kcal mol^{-1}][a])	$\Delta E = E^4 - E^3$ [kcal mol^{-1}][b])	$\Delta G = G^4 - G^3$ [kcal mol^{-1}][b])
3a → **4a**	$R^1 = R^2 = R^3 = H$	– 9.66	– 4.37	– 13.02	– 7.54
3b → **4b**	$R^1 = Me$, $R^2 = R^3 = H$	– 11.40	– 6.28	– 14.55	– 9.34
3c → **4c**	$R^1 = R^3 = H$, $R^2 = Me$	– 8.87	– 3.58	– 12.60	– 7.27
3d → **4d**	$R^1 = R^2 = Me$, $R^3 = H$	– 12.69	– 7.17	– 16.22	– 10.06
3e → **4e**	$R^1 = H$, $R^2 = R^3 = Me$	– 11.07	– 5.86	– 14.61	– 9.35
3f → **4f**	$R^1 = R^2 = R^3 = Me$	– 14.48	– 9.41	– 17.81	– 12.43

[a]) Calculated in ideal gas. [b]) Calculated using H_2O as solvent.

To further facilitate the cyclization, the reaction was conducted in HSO_3Cl as solvent[4]) [15]. As one might expect, pure (*E*) isomers **3** were reluctant to cyclization, which suggested that for this system, little alkene isomerization occurred. One could expect that the protonation occurred at the N-atom of the CN group to give **3(H$^+$)** or at the terminal N-atom of the N_3 group yielding **3(H$^+$N$_3$)**.

Calculations showed that the N-atom of the CN group was most basic, as **3(H$^+$)** was more stable than **3(H$^+$N$_3$)** (*Scheme 3* and *Table 3*).

The cyclization of the H-bearing azidobutenynes **3a(H$^+$)**–**3f(H$^+$)** to the H-bearing tetrazoles **4a(H$^+$)**–**4f(H$^+$)** was exergonic. We noted the stabilization of **4b(H$^+$)**, **4d(H$^+$)**, and **4f(H$^+$)**, induced by the presence of Me group R^1 at C(6). The exergonicity was slightly reduced in H_2O as solvent (*Table 4* and Table SI 4).

In contrast, the cyclization of **3a(H$^+$N$_3$)**–**3f(H$^+$N$_3$)** with a H-bearing N_3 group was strongly exergonic and led to a N(3)-protonated tetrazole (*Table 5*).

Various Tautomerizations and Isomerizations. First, we studied the possibility for **2** to give rise to the tautomeric 1*H*-pyrrolo[1,2-*c*][1,2,3]triazoles **Iso2a**/**Iso2d** with an

[4]) Intramolecular cyclization of CN and N_3 groups was also observed in the presence of 2 equiv. of BF_3 [17].

Scheme 3. *Intramolecular Cyclization of H-Bearing Azidobutenynes* **3a**–**3f**

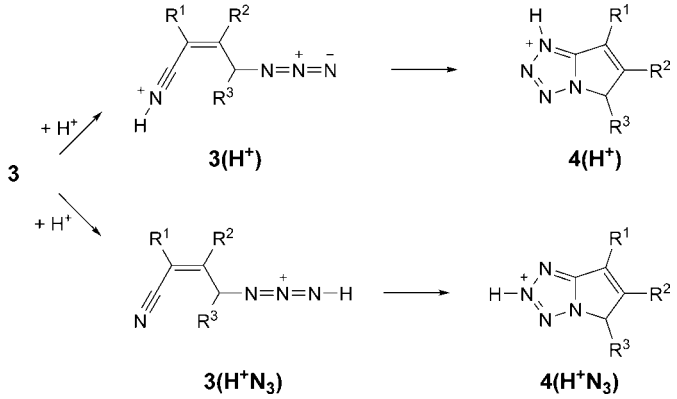


Table 3. *Relative Stabilities of the H-Bearing 4-Azidobut-2-enenitriles* **3a**–**3f** (see *Scheme 3* and Table SI 3)

Compound	R	$\Delta E = E^{3(H^+)} - E^{3(H^+N_3)}$	$\Delta G = G^{3(H^+)} - G^{3(H^+N_3)}$
		[kcal mol^{-1}]	[kcal mol^{-1}]
3a	$R^1 = R^2 = R^3 = H$	15.96[a]); 13.59[b])	11.67[a]); 13.88[b])
3b	R^1 = Me, $R^2 = R^3 = H$	14.17[a]); 12.67[b])	15.31[a]); 12.80[b])
3c	$R^1 = R^3 = H$, R^2 = Me	26.26[a]); 14.93[b])	20.50[a]); 16.11[b])
3d	$R^1 = R^2$ = Me, $R^3 = H$	17.46[a]); 14.61[b])	19.23[a]); 14.99[b])
3e	$R^1 = H$, $R^2 = R^3$ = Me	20.82[a]); 14.25[b])	21.95[a]); 15.53[b])
3f	$R^1 = R^2 = R^3$ = Me	10.97[a]); 13.41[b])	7.90[a]); 14.63[b])

[a]) Calculated in ideal gas. [b]) Calculated using H_2O as solvent.

Table 4. *Energetics of the Acid-Catalyzed Cycloaddition of H-Bearing 4-Azidobut-2-enenitriles* **3a(H$^+$)**–**3f(H$^+$)** *to Protonated 5*H*-Pyrrolo[1,2-*d*]tetrazoles* **4a(H$^+$)**–**4f(H$^+$)** *after Protonation of the CN Group* (see *Scheme 3* and Table SI 4)

	R	$\Delta E = E^{4(H^+)} - E^{3(H^+)}$	$\Delta G = G^{4(H^+)} - G^{3(H^+)}$	$\Delta E = E^{4(H^+)} - E^{3(H^+)}$	$\Delta G = G^{4(H^+)} - G^{3(H^+)}$
		[kcal mol^{-1}][a])	[kcal mol^{-1}][a])	[kcal mol^{-1}][b])	[kcal mol^{-1}][b])
3a(H$^+$) → **4a(H$^+$)**	$R^1 = R^2 = R^3 = H$	– 36.83	– 29.43	– 34.78	– 27.66
3b(H$^+$) → **4b(H$^+$)**	R^1 = Me, $R^2 = R^3 = H$	– 38.42	– 31.04	– 36.41	– 29.45
3c(H$^+$) → **4c(H$^+$)**	$R^1 = R^3 = H$, R^2 = Me	– 36.52	– 29.01	– 35.33	– 27.78
3d(H$^+$) → **4d(H$^+$)**	$R^1 = R^2$ = Me, $R^3 = H$	– 38.92	– 31.56	– 38.06	– 30.73
3e(H$^+$) → **4e(H$^+$)**	$R^1 = H$, $R^2 = R^3$ = Me	– 21.18	– 15.27	– 22.90	– 16.37
3f(H$^+$) → **4f(H$^+$)**	$R^1 = R^2 = R^3$ = Me	– 40.21	– 32.43	– 39.09	– 31.61

[a]) Calculated in ideal gas. [b]) Calculated using H_2O as solvent.

Table 5. *Energetics of the Acid-Catalyzed Cycloaddition of Protonated 4-Azidobut-2-enenitriles* **3a(H^+N_3) – 3f(H^+N_3)** *to H-Bearing 5*H*-Pyrrolo[1,2-*d*]tetrazoles* **4a(H^+N_3) – 4f(H^+N_3)** *after Protonation of the N_3 Group* (see *Scheme 3* and Table SI 5)

	R	$\Delta E = E^{4(H^+N_3)} - E^{3(H^+N_3)}$	$\Delta G = G^{4(H^+N_3)} - G^{3(H^+N_3)}$
		[kcal mol^{-1}]	[kcal mol^{-1}]
3a(H^+N_3) → **4a(H^+N_3)**	$R^1 = R^2 = R^3 = H$	– 51.82[a]); 44.77[b])	– 45.00[a]); 37.48[b])
3b(H^+N_3) → **4b(H^+N_3)**	R^1 = Me, $R^2 = R^3 = H$	– 51.86[a]); 45.51[b])	– 45.07[a]); 38.30[b])
3c(H^+N_3) → **4c(H^+N_3)**	$R^1 = R^3 = H$, R^2 = Me	– 53.52[a]); 46.14[b])	– 46.36[a]); 39.28[b])
3d(H^+N_3) → **4d(H^+N_3)**	$R^1 = R^2$ = Me, $R^3 = H$	– 54.93[a]); 47.82[b])	– 48.67[a]); 40.17[b])
3e(H^+N_3) → **4e(H^+N_3)**	$R^1 = H$, $R^2 = R^3$ = Me	– 56.60[a]); 46.11[b])	– 49.75[a]); 39.44[b])
3f(H^+N_3) → **4f(H^+N_3)**	$R^1 = R^2 = R^3$ = Me	– 49.68[a]); 48.53[b])	– 38.25[a]); 41.65[b])

[a]) Calculated in ideal gas. [b]) Calculated using H_2O as solvent.

aromatic character with ten π-electrons (*Scheme 4*) [18]. But, according to the experimental observations, **Iso2a**/**Iso2d** was less stable than **2a**/**2d**. In fact, the presence of two adjacent heteroatoms, each contributing by a *doublet* to the π-system as for **Iso2a**/**Iso2d**, was more unfavorable than the mutual repulsion of the two unshared electron pairs in **2a**/**2d** (note that the tautomeric H-atom of **Iso2a**/**Iso2d** is not in the plane of the rings).

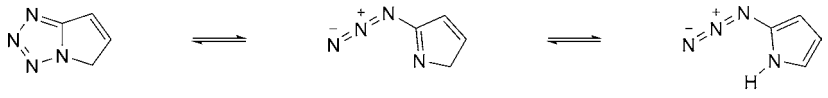
In the case of pyrrolotetrazoles **4**, a tetrazole-azidoisopyrrole isomerization is possible (*Scheme 5*) [19]. Calculations showed that **4a** was slightly more stable than the corresponding open-chain valence tautomer azidoisopyrrole **5a**. In contrast, the aromatic tautomeric azidopyrrole **6a** was, as expected, more stable.

The aromatic tautomer **Iso4a**/**Iso4d** with a ten-π-electron structure was less stable than **4a**/**4d**. This result was surprising, because, in addition of the aromaticity of **Iso4a**/**Iso4d**, for **4a**/**4d**, two mutual repulsions of the unshared electron pairs occurred, whereas only one occurred for **Iso4a**/**Iso4d**, as seen in *Scheme 6* [20].

Scheme 4. *Tautomerism of* **2a** *and* **2d** (see Table SI 11)

a $R^1 = R^2 = H$, ΔE = 8.17 kcal mol^{-1}, ΔG = 8.37 kcal mol^{-1}
d $R^1 = R^2$ = Me, ΔE = 11.22 kcal mol^{-1}, ΔG = 10.62 kcal mol^{-1}

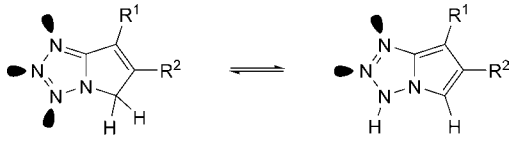
Scheme 5. *Isomerizations of* **4a**



ΔE = 1.20 kcal mol^{-1}
ΔG = 1.23 kcal mol^{-1}

ΔE = –7.04 kcal mol^{-1}
ΔG = –6.86 kcal mol^{-1}

Scheme 6. *Mutual Repulsion of Unshared Electron Pairs in the Tautomers* **4a**/**4d** *and* **Iso4a**/**Iso4d** (see Table SI 12)



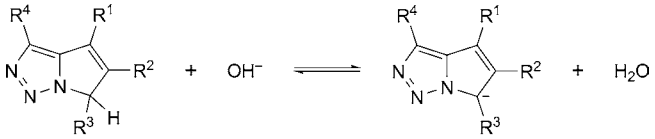
a $R^1 = R^2 = H$, ΔE = 14.5 kcal mol^{-1}, ΔG = 14.3 kcal mol^{-1}
d $R^1 = R^2 = Me$, ΔE = 19.8 kcal mol^{-1}, ΔG = 17.0 kcal mol^{-1}

Formation of the Monoanions. From **2a**–**2g** or **4a**–**4f**, the formation of the ten-π-electron monoanions occurred after treatment with MeLi. Interestingly, **2a**–**2g** or **4a**–**4f** were recovered by protonation of the corresponding monoanion (*Scheme 2*) [15]. Calculations showed that **2a**–**2g** or **4a**–**4f** were strongly more acidic than H_2O, as the H-atom exchange reactions were exergonic by *ca.* 40 to *ca.* 55 kcal mol^{-1} in ideal gas and by *ca.* 8 to *ca.* 16 kcal mol^{-1} using H_2O as solvent (*Tables 6* and *7*).

Triazole anions and tetrazole anions are isoelectronic, and for the parent compounds **2a**$^-$ and **4a**$^-$, the HOMOs were very similar, but that of tetrazole was more stable (*Figs. 1* and *2*).

Computational Transition States. As model for the cyclization of 1-azidopent-2-en-4-ynes **1**, we studied the cyclization of **1a** to triazole **2a**; for the cyclization of 4-azidobut-2-enenitriles **3** to tetrazoles **4**, we explored the cyclization of **3a** [21].

Table 6. *Energetics of the Formation of the Ten-π-Electron Monoanions* **2a**$^-$–**2g**$^-$ *from* 6H-*Pyrrolo[1,2-c][1,2,3]triazoles* **2a**–**2g** (see Table SI 6)



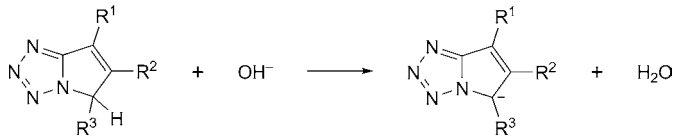
$\Delta E = \{[E^{2-} + E^{H_2O}] - [E^{2} + E^{OH^-}]\} \cdot 627.5095$ [kcal mol^{-1}]

$\Delta G = \{[G^{2-} + G^{H_2O}] - [G^{2} + G^{OH^-}]\} \cdot 627.5095$ [kcal mol^{-1}]

	R	ΔE [kcal mol^{-1}][a])	ΔG [kcal mol^{-1}][a])	ΔE [kcal mol^{-1}][b])	ΔG [kcal mol^{-1}][b])
2a⇌**2a**$^-$	$R^1 = R^2 = R^3 = R^4 = H$	– 46.40	– 48.06	– 14.53	– 16.16
2b⇌**2b**$^-$	R^1 = Me, $R^2 = R^3 = R^4 = H$	– 42.78	– 45.01	– 10.22	– 12.34
2c⇌**2c**$^-$	$R^1 = R^3 = R^4 = H$, R^2 = Me	– 43.59	– 45.86	– 11.32	– 13.18
2d⇌**2d**$^-$	$R^1 = R^2$ = Me, $R^3 = R^4 = H$	– 41.66	– 44.65	– 8.34	– 10.35
2e⇌**2e**$^-$	$R^1 = R^4 = H$, $R^2 = R^3$ = Me	– 43.43	– 46.44	– 10.74	– 13.77
2f⇌**2f**$^-$	$R^1 = R^2 = R^3$ = Me, $R^4 = H$	– 40.30	– 42.97	– 5.58	– 8.25
2g⇌**2g**$^-$	$R^1 = R^4$ = Me, $R^2 = R^3 = H$	– 2.78	– 4.51	– 8.75	– 10.58

[a]) Calculated in ideal gas. [b]) Calculated using H_2O as solvent.

Table 7. *Energetics of the Formation of the Ten-π-Electron Monoanions* **4a**$^-$ – **4f**$^-$ *from* 5H-*Pyrrolo[1,2-d]tetrazoles* **4a** – **4f** (see Table SI 7)



4a – 4f **4a$^-$ – 4f$^-$**

$\Delta E = \{[E^{4-} + E^{H_2O}] - [E^{4} + E^{OH^-}]\} \cdot 627.5095$ [kcal mol^{-1}]

$\Delta G = \{[G^{4-} + G^{H_2O}] - [G^{4} + G^{OH^-}]\} \cdot 627.5095$ [kcal mol^{-1}]

	R	ΔE	ΔG	ΔE	ΔG
		[kcal mol^{-1}][a])	[kcal mol^{-1}][a])	[kcal mol^{-1}][b])	[kcal mol^{-1}][b])
4a → **4a**$^-$	$R^1 = R^2 = R^3 = H$	– 55.08	– 56.36	– 21.01	– 22.40
4b → **4b**$^-$	R^1 = Me, $R^2 = R^3 = H$	– 50.74	– 52.67	– 16.59	– 18.44
4c → **4c**$^-$	$R^1 = R^3 = H$, R^2 = Me	– 52.85	– 54.25	– 18.16	– 19.60
4d → **4d**$^-$	$R^1 = R^2$ = Me, $R^3 = H$	– 49.14	– 50.68	– 29.80	– 24.89
4e → **4e**$^-$	$R^1 = H$, $R^2 = R^3$ = Me	– 51.29	– 53.95	– 16.90	– 18.68
4f → **4f**$^-$	$R^1 = R^2 = R^3$ = Me	– 47.52	– 49.70	– 12.96	– 14.94

[a]) Calculated in ideal gas. [b]) Calculated using H_2O as solvent.

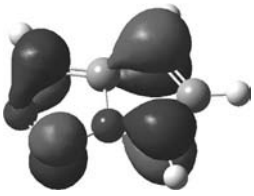


Fig. 1. *Structure of the HOMO* (28th MO, $E = -0.15693$ a.u. using H_2O as solvent, $E = -0.00311$ a.u. in ideal gas) *of triazole* **2a**$^-$ *at the B3LYP/6.311++G(3df,3pd) level of theory.* This figure is available in color in the SI.

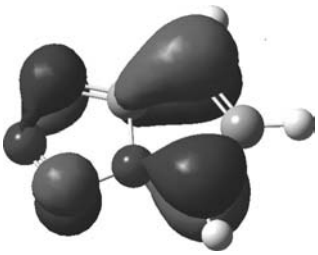


Fig. 2. *Structure of the HOMO* (28th MO, $E = -0.17555$ a.u. using H_2O as solvent, $E = -0.02306$ a.u. in ideal gas) *of tetrazole* **4a**$^-$ *at the B3LYP/6.311++G(3df,3pd) level of theory.* This figure is available in color in the SI.

According to the experimental results, the cyclization of **1a** was easier than that of **3a**. This was indicated by a strong difference of 6.2 kcal mol^{-1} between the transition state energies (*Fig. 3*).

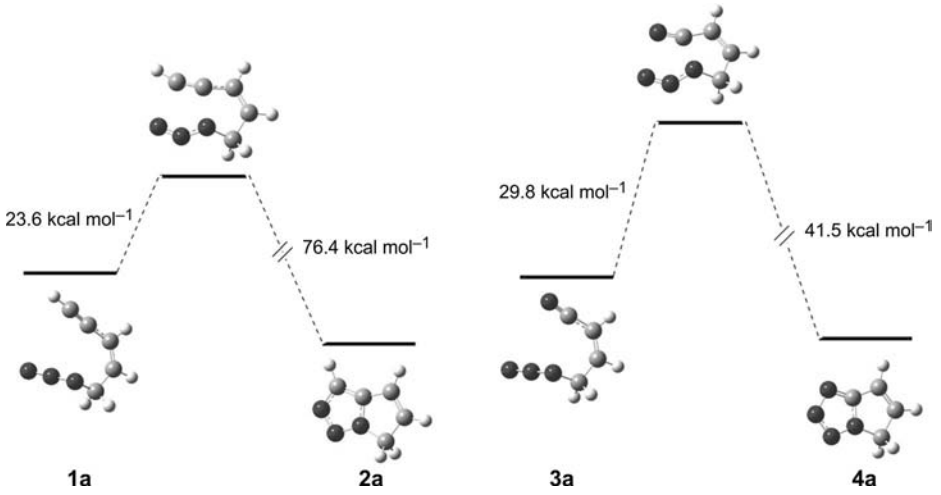


Fig. 3. *Transition states of the cyclization of* **1a** *to* **2a** (left) *and* **3a** *to* **4a** (right). This figure is available in color in the SI.

Computational Details. – All calculations were performed with the GAUSSIAN 09, revision D.01, suites of program [22]. The gas-phase geometries of all compounds were optimized without any constraint by the density functional theory method B3LYP [23] with the 6.311++G(3df,3pd) basis set. A vibrational analysis was performed at the same level of theory in order to determine the zero-point vibrational energy (ZPE), the absolute *Gibbs* energy, and to characterize each stationary point as a minimum. The absolute total energies, *E*, were evaluated at 0 K and the absolute *Gibbs* energies, *G*, at 298.15 K.

All transition-state geometries were confirmed by intrinsic reaction coordinates (IRC) calculations. In order to enhance the accuracy of the calculations, single point energies were calculated at the B3LYP/6-311++G(3df,3pd) level of theory. Zero-point energies and thermodynamic data were calculated using the specified scaling factor (0.960) [24].

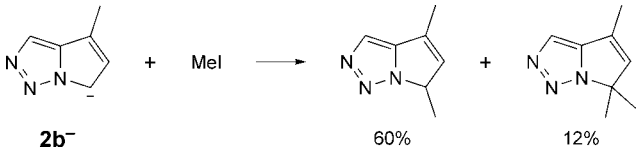
Conclusions. – The strong affinity of the N_3 group for the acetylenic linkage allowed the strained intramolecular cyclization of 1-azidopent-2-en-4-ynes **1** to 6*H*-pyrrolo[1,2-*c*][1,2,3]triazoles **2**. Calculations confirmed that this reaction is exothermic and occurs with a low activation barrier of 23.6 kcal mol^{-1} for the parent compounds.

The cyclization of 4-azidobut-2-enenitriles **3** to 5*H*-pyrrolo[1,2-*d*]tetrazoles **4** is more difficult and occurs only from the H-bearing form.

Surprisingly, the non-aromatic structure of **2** or **4** is more stable than that of tautomer 1*H*-pyrrolo[1,2-*c*][1,2,3]triazoles **Iso2** or **Iso4**, respectively, having an aromatic character with ten π-electrons. In fact, vicinal *doublet*s in the π-system are more unfavorable than the mutual repulsion of two unshared electron pairs.

In contrast, ten-π-electron monoanions were easily obtained and alkylation of these anions with MeI occurs exclusively at C(6) (*Scheme 7*) [15].

Scheme 7. *Alkylation of the Anion* **2b**$^-$



The transition state for the cyclization of **1a** and **3a** showed a small amount of asynchrony (see the *Computational Transition States* section in the SI).

This work has been financially supported by the *CNRS* and the Aix-Marseille Université.

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Received January 6, 2015