THE STRUCTURE OF *N*-ACETYLAZOLES (AZOLIDES): A SEMIEMPIRICAL (AM1) COMPUTATIONAL STUDY

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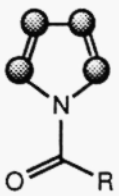
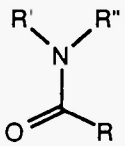
Abstract : Simple, inexpensive, AM1 calculations of a series of fourteen *N*-acetylazoles provide interesting relative information about geometry, E/Z conformational isomerism, rotational barriers, dipole moments and ν(C=O) stretching vibrations. Several additive models have been tried which provided good correlation coefficients.

Introduction

Azolides **A** are an important class of compounds (1) which show characteristic features intermediate between those of amides **B** and ketones **C**.



A



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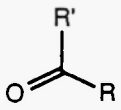
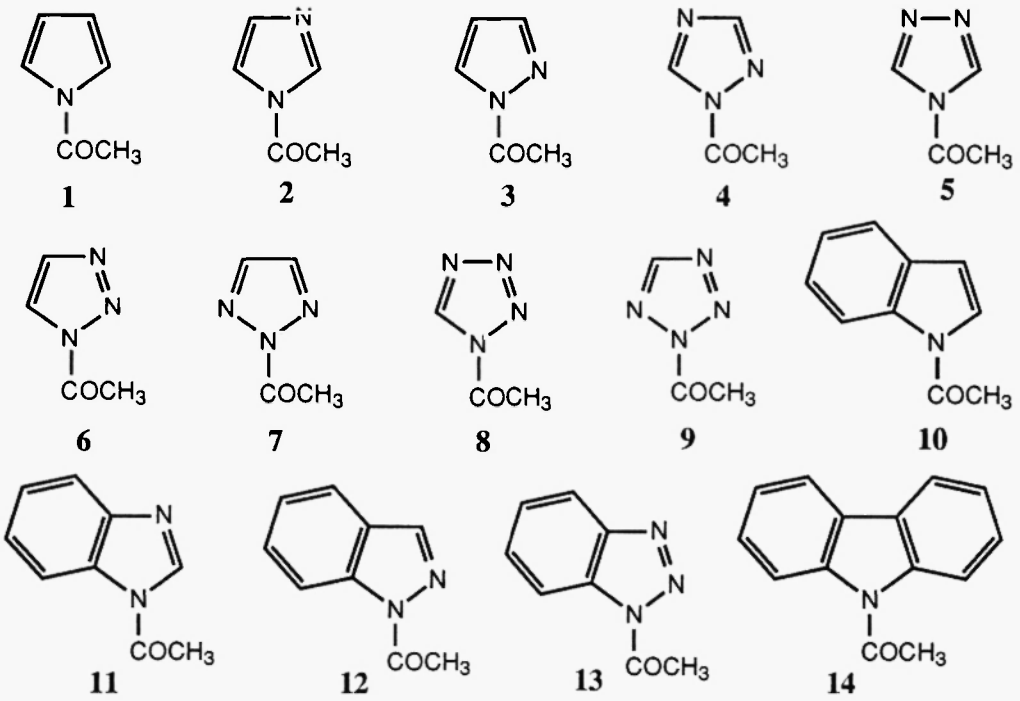


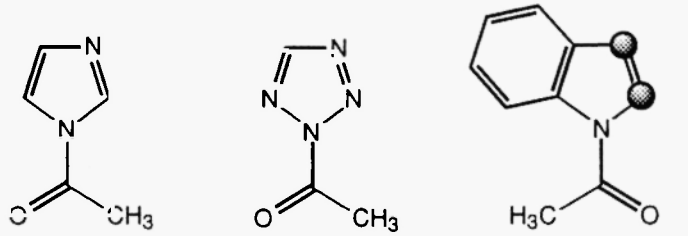
C

Collectively, they have been studied theoretically only two times (2,3) but with simple methods: EHT (2,3) and PCILO (2). Here, we would like to report AM1 calculations (4) of the following fourteen azolides **1-14** with complete optimization of the geometries. The azolides selected correspond to all possible cases save the *iso* isomers (isoindole, 2*H*-indazole and 2*H*-benzotriazole) which are much less common. The aims of this study are: i) to discuss the geometries of azolides (NCO moiety); ii) to determine the most stable rotamers; iii) to calculate the rotational barriers; and iv) to compare some calculated properties (C=O bond length, dipole moment) with experimental data when available.



Results and Discussion

Geometry.- The results of the calculations (N-C and C=O bond lengths in Å and NCO bond angle in °) are summarized in Table 1. The torsion angle τ is defined as follows: for 'symmetrical' azoles **1**, **5**, **7**, **14** there is no ambiguity (τ = 0° identical to τ = 180°); for other monocyclic azoles with one nitrogen atom in the α position **3**, **4**, **6**, **8** the τ = 180° corresponds to the *E* conformation (the O and N atoms on opposite sides of the CN bond), for monocyclic azoles having none or two nitrogen atoms in the α position **2**, **9** the conformations are depicted below; finally, for benzazoles **10**, **11**, **12**, **13** the τ = 0° conformation has the C=O group opposite to the fused benzene ring. The conformation of minimum energy (either 0 or 180°) and the other planar conformation (either 180 or 0°) are minima and have been found without any geometrical constraint; the orthogonal conformation, which can be assimilated to a transition state, has been fully optimized except the torsion angle τ which has been imposed to be 90°.



2, τ = 0° **9**, τ = 0° **10-13**, τ = 0°

Table 1. Calculated geometries of the CNO fragment of azolides **1-14** (Å, °) and corresponding heats of formation (kcal mol^{-1})

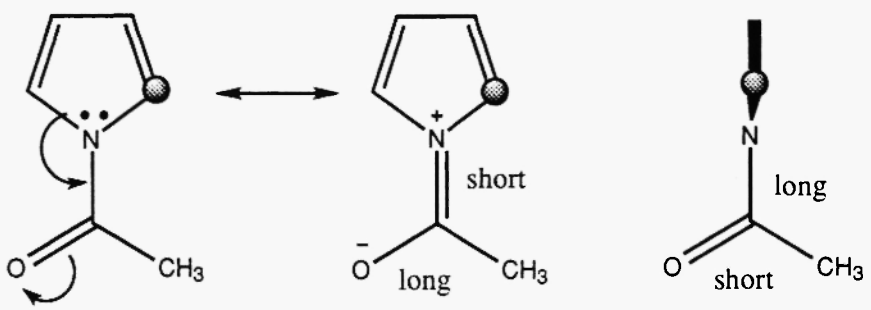
Azole	τ	N-C	C=O	NCO	ΔH_f
Pyrrole **1**	0.0	1.406	1.240	119.6	8.30
	90.0	1.432	1.233	120.6	15.97
Imidazole **2**	0.0	1.408	1.238	119.6	20.06
	90.0	1.431	1.232	120.2	26.97
	180.0	1.407	1.239	119.3	19.82
Pyrazole **3**	0.0	1.420	1.234	121.3	38.18
	90.0	1.453	1.229	119.7	41.87
	180.0	1.425	1.239	117.4	35.24
1*H*-1,2,4-Triazole **4**	0.0	1.506	1.232	121.1	49.92
	90.0	1.498	1.228	119.3	53.27
	180.0	1.499	1.236	117.5	46.00
4*H*-1,2,4-Triazole **5**	0.0	1.503	1.237	119.1	42.92
	90.0	1.502	1.231	119.7	49.23
1*H*-1,2,3-Triazole **6**	0.0	1.505	1.232	120.7	59.09
	90.0	1.499	1.228	119.2	62.34
	180.0	1.499	1.236	117.9	55.45
2*H*-1,2,3-Triazole **7**	0.0	1.501	1.230	119.6	64.88
	90.0	1.495	1.224	118.7	68.47
1*H*-Tetrazole **8**	0.0	1.504	1.230	120.4	82.96
	90.0	1.497	1.227	118.8	85.75
	180.0	1.498	1.234	117.4	79.23
2*H*-Tetrazole **9**	0.0	1.500	1.229	119.4	85.61
	90.0	1.494	1.223	118.2	88.96
	180.0	1.500	1.229	118.9	85.58
Indole **10**	0.0	1.403	1.243	118.4	24.02
	90.0	1.434	1.234	121.5	31.56
	180.0	1.401	1.241	120.5	23.28
Benzimidazole **11**	0.0	1.402	1.242	118.2	36.00
	90.0	1.430	1.233	120.9	43.74
	180.0	1.401	1.240	120.3	36.11
1*H*-Indazole **12**	0.0	1.504	1.236	120.5	55.74
	90.0	1.499	1.230	120.6	58.78
	180.0	1.502	1.239	118.7	50.88
1*H*-Benzotriazole **13**	0.0	1.503	1.235	120.2	76.52
	90.0	1.499	1.229	119.7	80.04
	180.0	1.501	1.237	118.5	72.41
9*H*-Carbazole **14**	0.0	1.402	1.244	119.6	37.67
	90.0	1.436	1.234	121.4	44.10

No X-ray structures of simple *N*-acetylazoles have been determined. The only relevant result is the structure of 1-acetyl-4-bromopyrazole (CSD [5] refcode: ABPZOL10) (6-8): N-C = 1.416 Å, C=O = 1.213 Å, NCO = 118.2°, τ = 176.7 ° which compares acceptably well with AM1 calculations: N-C = 1.425 Å, C=O = 1.239 Å, NCO = 117.4°, τ_1 = 180.0 ° for **3** (assuming that the effect of the 4-bromo substituent is negligeable).

A representation of N-C vs C=O bond lengths shows that there are three families according to the N-C distances: about 1.4 Å (**1**, **2**, **10**, **11**, **14**), about 1.45 Å (**3**) and about 1.5 Å (**4**, **5**, **6**, **7**, **8**, **9**, **12**, **13**); in the families that have more than one representative, the C=O bond length increases in the order (for $\tau = 0°$): **2** < **1** < **11** < **10** < **14** and **9** < **7**,**8** < **4**,**6** < **13** < **12** < **5**. Thus, it is essentially the number and position of the nitrogen atoms that are determinant in these classifications. A quantitative treatment leads to the equations summarized in Table 2 (the standard deviations have been omitted, but all the coefficients are significant).

Table 2. Linear equations relating geometrical properties to structure

CNO fragment	Intercept	Nα	Nβ	Bz(α,β)	n	r^2	Eq.
N-C (0,180°)	1.404	0.048	0.034	------	28	0.71	[1]
N-C (90°)	1.435	0.031	0.020	------	14	0.68	[2]
C=O (0,180°)	1.240	-0.0048	-0.0016	0.0019	28	0.91	[3]
C=O (90°)	1.233	-0.0044	-0.0016	0.0009	14	0.99	[4]
NCO (0,180°)	No correlation						
NCO (90°)	120.7	-0.98	-0.50	0.51	14	0.97	[5]
CNO fragment	Intercept	ΔNα	ΔNβ	ΔBz(α,β)	n	r^2	Eq.
NCO (0°)	119.4	1.59	-----	-0.87	14	0.91	[6]
NCO (180°)	119.4	-1.79	-----	1.06	14	0.96	[7]



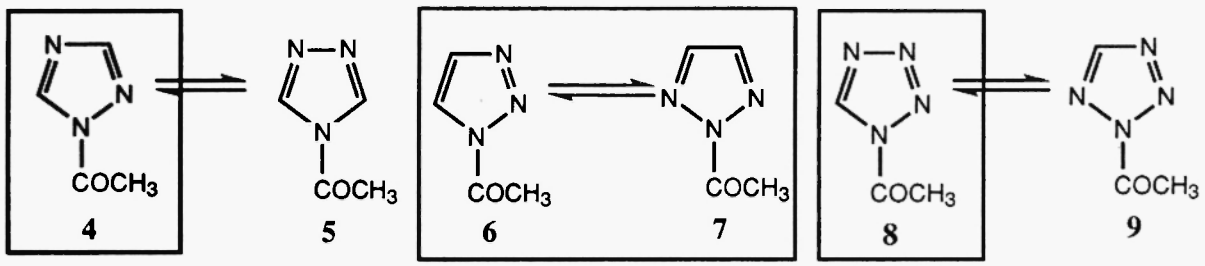
The results of Table 2 deserve some comments:

i) The 0 → 90° twist increases the N-C (+0.031 Å) and decreases the C=O (-0.007 Å) lengths as expected from the intuitive model represented above. The effect is more pronounced in the single bond than in the double bond which corresponds to the increasing difficulty of stretching double vs single bonds. For the same reason, the coefficients of Nα and Nβ are ten times or more larger for the N-C than for the C=O bond.

ii) The NCO angle for planar situations has values between 117.4° (**3**, $\tau = 180°$) and 121.3° (**14**, $\tau = 0$ or 180°). These angles do not depend on Nα, Nβ and Bz(α,β) or any combination of them. On the other hand NCO (90°) is linearly related to these parameters (Eq. [5]).

iii) For the NCO angle ($\tau = 0$ and $\tau = 180°$) instead of the number of nitrogen atoms and fused benzene rings, the differences should be considered, for instance, the difference in the number of nitrogen atoms at the α position (ΔNα) is 0 for pyrrole, imidazole and 2*H*-1,2,3-triazole and 1 for pyrazole and 1*H*-1,2,3-triazole. Using these new descriptors, equations [6] and [7] are found which reflect the opening of the NCO angle produced by the proximity of Nα or Bz(α,β).

Positional Isomerism, E/Z Conformational Isomerism and Rotational Barriers.- In Table 3 we have reported the calculated values corresponding to these properties. There is abundant information about three cases of isomerism, *N*-acetyl-1,2,4-triazole, only isomer **4** is observed (9-11), *N*-acetyl-1,2,3-triazole, both isomers are in equilibrium although **7** is predominant (10,12), and *N*-acetyltetrazole, isomer **8** is generally observed (13,14):



The results reported in Table 1 are mainly in contradiction with these findings: **5** is calculated (3.1 kcal mol^{-1}) more stable than **4**, **6** is calculated (9.4 kcal mol^{-1}) more stable than **7**, and only in the case of tetrazole the calculations agree, **8** being more stable (6.4 kcal mol^{-1}) than **9**. The same problems were found using the EHT method (2). It appears that the heat of formation (ΔH_f) of one isomer (or, may be, of both) is not well reproduced by the AM1 calculations. Probably, the calculated values have to be transformed using an equation like 'Corrected values' = -3.7 - 0.42 ΔH_f (Eq. [8]) to obtain something approaching the experimental findings: 1,2,4-triazole, -5 kcal mol^{-1} (only **4**), 1,2,3-triazole, + 0.2 kcal mol^{-1} (slight predominance of **7**) and tetrazole, -1.0 kcal mol^{-1} (**8** more stable).

Table 3. Preferred conformer, calculated and experimental barriers (kcal mol^{-1})

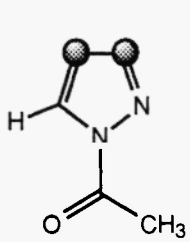
Compound	E(0)-E(180)	E(90)-E(0)	E(90)-E(180)	Experimental	Reference
1	0.00	7.66	7.66	12.0	(15)
2	0.25	6.91	7.16	10.5	(16)
3	2.94	3.69	6.63	*6.7*	
4	3.92	3.35	7.27	*7.0*	
5	0.00	6.31	6.31	*9.1*	
6	3.64	3.25	6.90	*6.5*	
7	0.00	3.59	3.59	*3.3*	

8	3.73	2.79	6.52	*5.6*	
9	0.03	3.35	3.35	*2.9*	
10	0.74	7.54	8.28	*12.5*	
11	-0.11	7.74	7.63	*12.0*	
12	4.86	3.04	7.90	*7.3*	
13	4.11	3.52	7.63	*7.5*	
14	0.00	6.43	6.43	9.4	(17

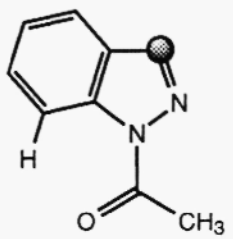
Concerning the conformation of azolides [E(0)-E(180)] (Table 3) three cases have to be considered:

i) 'Symmetrical' compounds: [E(0)-E(180)] = 0 kcal mol^{-1}, **1**, **5**, **7**, **14**.

ii) Compounds presenting in the α positions a N atom and a CH or a fused benzene ring: [E(0)-E(180)] = 3-5 kcal mol^{-1}, **3**, **4**, **6**, **8**, **12**, **13**. These compounds exist in the *E* conformation, in agreement with all existing evidence: X-ray, NMR and dipole moments (18).

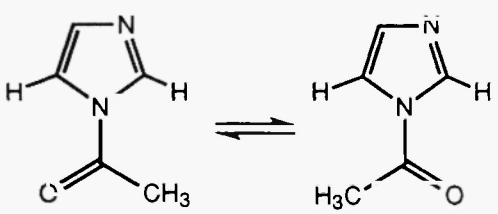


3, 4, 6, 8

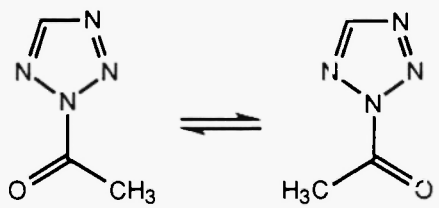


12, 13

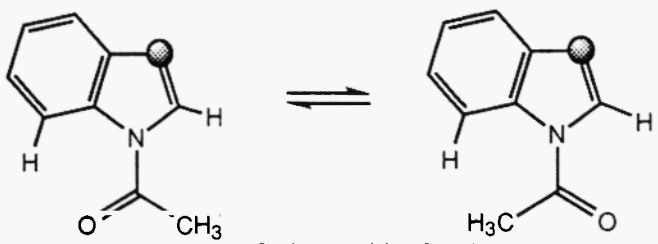
iii) Compounds having in the α positions two CH, two N atoms or a CH and a fused benzene ring: [E(0)-E(180)] < 1 kcal mol^{-1}, **2**, **9**, **10**, **11**. These compounds exist as mixtures of *E* and *Z* conformers. This result also agrees with NMR experiments (18).



2 (0.25)



9 (0.03)



10 (0.74), **11** (-0.11)

These conclusions can be expressed in a quantitative way:

$$[E(0)-E(180)] = (3.68\pm0.16) \times \Delta N(\alpha) + (0.56 \pm 0.20)\ \Delta Bz\ (\alpha,\beta),\ n = 14,\ r^2 = 0.983 \qquad [9]$$

The first term, the most important, shows the influence of the difference in N atoms at the α position (1 or 0) and the second term, the difference in fused benzene rings in α,β positions (1 or 0). The difference in number of N atoms at the β positions has a negligible effect.

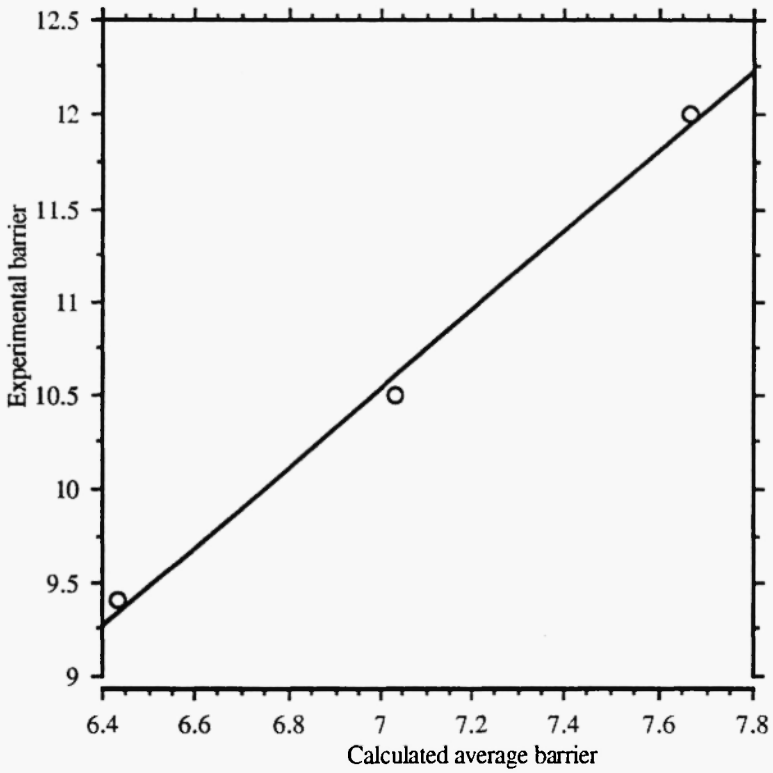


Figure 1

The barriers about the C-N bond in azolides are very characteristic of their somewhat diminished amidic character. The calculated barriers are too low compared with the experimental ones, but at least, they are proportional (Figure 1). This allows to predict the barriers (average values for the $E \rightarrow Z$ and $Z \rightarrow E$ processes) for the remaining compounds (in italics in Table 3). The best candidates for experimental determinations are compounds **5**, **10** and **11**, with barriers between 9 and 12 kcal mol^{-1} and with comparable *E/Z* populations.

These barriers can be described by the following equation:

$$\text{Barrier (kcal mol}^{-1}) = (11.4\pm0.4) - (4.0\pm0.4)\ N(\alpha) - (0.7\pm0.4)\ N(\beta),\ n = 14,\ r^2 = 0.92 \qquad [10]$$

Eq. [10] shows that as the number of nitrogen atoms increases the barrier lowered and that the effect is much more important in α than in β position.

Dipole moments.- The calculated and experimental values of the azolides are reported in Table 4.

Table 4. Calculated and experimental dipole moments (μ in D, in dioxane at 25°C) and C=O stretching vibration (cm^{-1}), Values from ref. (20) in parentheses.

Comp.	τ = 0	τ = 180	τ = 90	Exp.	Ref.	ν(C=O)	Ref.
1	2.65	2.71	2.65	2.54	(19)	1730	(21)
2	4.01	2.40	3.77	2.81 (2.96)	(19,20)	1745	(21)
3	4.48	1.06	2.85	1.55 (1.85)	(19,20)	1742	(21)
4	3.74	2.14	3.38	(2.09)	(20)	1759	(22)
5	4.74	5.36	4.74			------	---
6	5.87	1.22	4.40			1762	(10)
7	3.01	2.46	3.01			1780	(10)
8	6.10	3.52	5.50			1783	(22)
9	1.56	4.00	3.32			------	---
10	2.90	2.37	2.45	2.97	(19)	1711	(23)
11	2.02	3.70	3.22	2.54	(19)	1729	(22)
12	1.65	4.55	2.00			1720	(24)
13	0.77	5.94	3.88			1735	(23)
14	2.61	2.08	2.61			1692	(22)

The comparison between experimental and calculated dipole moments allows to estimate the *E/Z* equilibrium in solution. They are as follows: imidazolide **2**, 20-25% of *E* (τ = 0°)/75-80% of *Z* (τ = 180°); pyrazolide **3**, only *E* (τ = 180°), triazolide **4** only *E* (τ = 180°), indolide **10** only the τ = 0° conformer and benzimidazolide **11** 70-75% of the τ = 0° conformer.

C=O Stretching Frequencies.- The ν(C=O) bands of several azolides have been measured (Table 4). The corresponding frequencies are roughly related to the C=O bond distance by the following linear equation:

$$\nu_{C=O}\ (cm^{-1}) = (10135 \pm 1090) + (6780 \pm 880)\ d_{C=O}\ (Å),\ n = 12,\ r^2 = 0.86 \qquad [11]$$

Conclusions

It is of importance today to determine within which boundaries the rapid, inexpensive, user-friendly AM1 method can be reliable (25). This method, limited to comparison of a series of compounds as azolides, yields satisfactory results for geometries, *E/Z* isomerism, dipole moments and C=O stretchings and even for rotational barriers, although these are greatly underestimated. On the other hand, it fails completely for relative stabilities between isomers. This is not a surprise since i) the relative energies of prototropic tautomers (N-H) and isomers (N-CH_3, N-$COCH_3$, N-$SiMe_3$)

are the same (26) and ii) AM1 calculations provide the same unsatisfactory answer for the tautomerism of triazoles and tetrazoles (27). Therefore, *ab initio* calculations should be necessary to describe correctly the isomerism between azolides since they provide a correct answer for the annular tautomerism of NH-triazoles and tetrazoles (28-30).

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(27) ΔH_f values (in kcal mol^{-1}): **4** (76.97), **5** (72.91), **6** (86.36), **7** (92.34), **8** (109.65) and **9** (113.29). According to AM1 calculations 4-*H*-1,2,4-triazole (**5**) is more stable than 1-*H*-1,2,4-triazole (**4**) by 4.1 kcal mol^{-1}; 1-*H*-1,2,3-triazole (**6**) is more stable than 2-*H*-1,2,3-triazole (**7**) by 9.4 kcal mol^{-1}; 1-*H*-tetrazole (**8**) is more stable than 2-*H*-tetrazole (**9**) by 4.1 kcal mol-1;

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