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Quantum-chemical study of the mechanism of aminomethylation of tetrazoles according to the elimination–addition scheme without preliminary formation of N-protonated azolium salts

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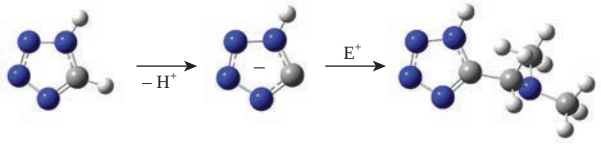
Based on analysis of quantum chemical DFT/B3LYP/6-31G(d) calculations results, thermodynamic characteristics of electrophilic dimethylaminomethylation of 1*H*-tetrazole and 1-methyltetrazole according to addition–elimination and elimination–addition schemes were correlated. The possibility of the dimethylaminomethylation without the preliminary formation of N-protonated azolium salts was demonstrated.



Specific features and restrictions of electrophilic reactions of azoles proceeding according to three alternative mechanisms have been recently reviewed.[1] These mechanisms comprise (1) addition–elimination through cationic σ-complex, (2) elimination–addition *via* ylide-carbene arised from the deprotonation of the preliminary formed N-protonated azolium ion, and (3) elimination–addition *via* ylide-carbene formed by deprotonation without preliminary generation of N-protonated azolium ion. Quantum chemical calculations performed with a DFT/B3LYP/6-31G(d,p) method and available experimental data showed that 1,2-azoles and 2-substituted 1,3-azoles (the structure of the latter does not permit formation of stable ylide-carbene) react with electrophiles according to the traditional addition-elimination mechanism, whereas 2-unsubstituted 1,3-azoles react *via* ylide mechanism. Note that the product structure formed from 1,3-azoles is in relation with the reaction mechanism, namely, 5-subsitution occurs according to the traditional mechanism, and 2-substitution takes place in case of the ylide one.

As for azoles with three and four heteroatoms, the realization of mechanisms (1) and (2) is less likely. The increase in the number of nitrogen atoms in azole molecule should significantly decrease its ability to react *via* electrophile addition and, therefore, significantly hinder the electrophilic substitution according to the addition–elimination mechanism due to the deactivating effect of 'pyridine-like' N atoms. This effect is close to the deactivation effect of nitro group in benzene ring. Respective experimental data were obtained by Katritzky as partial rate factors (log k_{ArH}/k_{PhH}) for isotope exchange in hetarenes and benzene (pD 0, 100 °C)[2–4] and as standardized nitration constants (lg k_{20}) for some heteroaromatic and aromatic compounds (HNO_3–H_2SO_4, H_0 –6.6, 25 °C).[5–8]

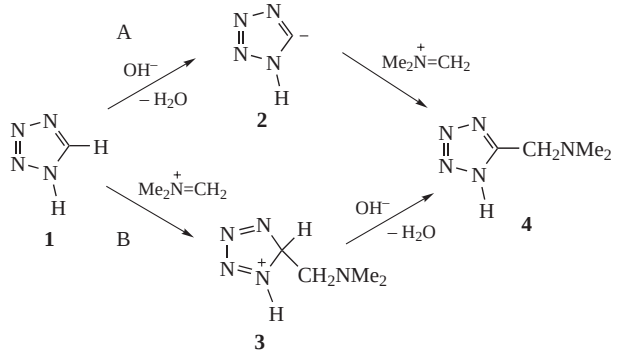
Thus, one can see some similarity between triazole/dinitropyrrole and tetrazole/trinitropyrrole pairs in regard to susceptibility towards traditional-scheme electrophilic substitution. However, the generation of ylide should be preceded by the stage of azolium ion formation, and the ability of azoles with different number of heteroatoms to undergo this transformation varies significantly, *i.e.*, while 1,2,4-triazole (pK_a = 2.45) is a base of medium strength like thiazole, tetrazole (pK_a = –2.68) is a very weak base which nevertheless would readily undergo electrophilic substitution under very mild conditions.[1,9–11]

The novel mechanism of electrophilic substitution in azoles with three or four heteroatoms was formulated and substantiated *via* quantum chemical DFT/B3LYP/6-31G(d,p) calculations.[12] This mechanism (3) does not implement preliminary N-protonation of azole molecule and is realized owing to high electron-withdrawing activity of several 'pyridine-like' nitrogen atoms. The key step of the mechanism includes CH-deprotonation followed by electrophile addition to the generated carbanion. This mechanism was compared with the traditional ones (Schemes 1–3).

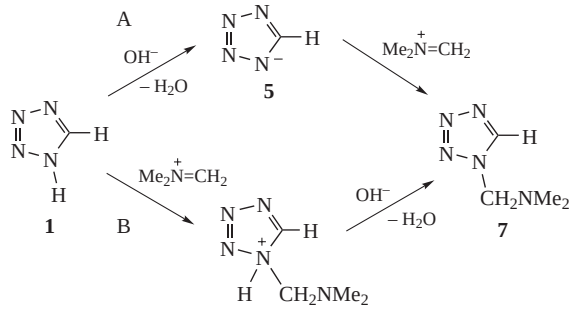
The effects of diverse factors on calculated values of thermodynamic characteristics were studied in subsequent works. Thus, negligible effect of the basis set increasing from DFT/B3LYP/6-31G(dp) to DFT/B3LYP/6-31G(2df,p)[13] and significant solvent effect[14] were observed. The features of behavior of *N*(1)-methyl- and *N*(2)-methyl-substituted tetrazoles were considered.[15,16]

Note that electrophilic substitution was experimentally studied for 1-methyltetrazole when the substitution occurred at C(5) atom, while in the cases of unsubstituted tetrazole electrophile is directed to N(1) or N(2) positions.[11,17] Therefore, results of the Mannich reaction of N-unsubstituted tetrazoles giving 5-aminomethylation products[18] have been absolutely unexpected. Yet, considering the experimental part of the work,[18] it should be noted that aminomethylation conditions for 1*H*- and 1-methyltetrazole are different. The reactions of the latter as well as of 1-ethyltetrazole proceed under rather mild conditions: a mixture of 1-alkyltetrazole and dimethylamine hydrochloride (0.05 mol each) and formaldehyde (37% aq., 10 ml) was boiled for 5 h in water (30 ml), and after usual workup 1-alkyl-5-(dimethylaminomethyl)tetrazoles were isolated in 60–80% yields. In the case of N-unsubstituted tetrazole, the reaction was carried out with paraformaldehyde and catalytic amounts of concentrated hydrochloric acid in boiling benzene–nitrobenzene mixture with azeotropic removal of water, however, the yield of the 5-dimethylaminomethylation product was not indicated.[18]

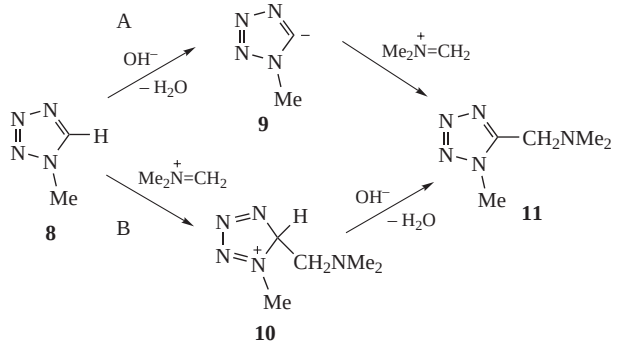
Karavai and Gaponik[18] accepted our supposition on the ylide mechanism in the electrophilic substitution of tetrazole. The same idea was briefly mentioned in review,[9] while that time



Scheme 1



Scheme 2



Scheme 3

experimental data on aminomethylation of tetrazole were absent. Later the idea of the ylide mechanism was discussed in refs. 10 and 19. Strong objections against this mechanism in the case of tetrazole proposed in ref. 17 stimulated us to study the problem of the mechanism of electrophilic substitution in tetrazole series in detail.

In this study, quantum chemical calculations were carried out within the framework of the density functional theory (DFT) using the B3LYP functional and the 6-31G(d) basis set with full geometry optimization of structures **1**–**11** (see Schemes 1–3) and *N*,*N*-dimethyl-*N*-methylidenammonium $Me_2N^+=CH_2$ (Y^+). The solvation effects were included in the overlapping sphere (IEF-PCM) approximation[20] using water as solvent. The localization of stable states of molecules on the potential energy surface (PES) was controlled by the absence of negative values of Hesse matrix. Thermodynamic characteristics (total energies ΔE_{tot}, enthalpies ΔH, Gibbs energies ΔG, entropies ΔS) of electrophilic substitution reactions of tetrazoles were calculated for standard conditions (T = 298 K, p = 1 atm) using the Gaussian 09 program.[20]

Reactions of tetrazole **1** (interactions at C and N atoms) and 1-methyltetrazole **8** as models (see Schemes 1–3) were carried out for two routes: elimination–addition (A) and addition–elimination (B). Hydroxide anion was used as model nucleophile and $Me_2N^+=CH_2$ (Y^+) cation as an electrophile. Scheme 1 describes reactions at C atom, Scheme 2 at N(1) atom, and Scheme 3 describes reaction of *N*-methyltetrazole (naturally, at C atom only).

The main results of calculations are given in Table 1. The changes in total energy, enthalpy, and Gibbs energy show that the first step of the process A, deprotonation of tetrazole molecules, is exothermic while the first step of the process B, addition of iminium species $Me_2N^+=CH_2$ to the same tetrazolium molecules, is endothermic. At the same time, the proton elimination from nitrogen atom is more advantageous, however, both reactions of 1*H*- and 1-methyltetrazoles with electrophile at carbon atoms do occur because molecules of compounds **7** and **11** have comparable stabilities. Taking into account that addition of electrophile occurs with a greater endothermal effect, one may conclude that aminomethylation of 1*H*-tetrazole and 1-methyltetrazole can proceed by the route A, that is, through deprotonation followed by addition of electrophile. The

Table 1 Thermodynamic characteristics of reactions calculated by B3LYP/6-31+G(d) method under standard conditions (T = 298 K, P = 1 atm) in gas phase and in aqueous solution using IEF-PCM approximation.

Reaction	Gas phase				Solution			
	ΔE_{tot}/kcal mol^{-1}	ΔH/kcal mol^{-1}	ΔG/kcal mol^{-1}	$\sim K_r$	ΔE_{tot}/kcal mol^{-1}	ΔH/kcal mol^{-1}	ΔG/kcal mol^{-1}	$\sim K_r$
1*H*-Tetrazole reactions at carbon atom								
1 + OH^- → **2**$^-$ + H_2O	–22.83	–22.55	–23.67	10^{17}	2.88	3.16	2.04	10^{-2}
2$^-$ + Y^+ → **4**	–154.22	–154.78	–142.55	10^{104}	–49.02	–49.69	–36.61	10^{26}
1 + Y^+ → **3**$^+$	52.4	50.31	66.29	10^{-49}	60.66	58.39	75.29	10^{-56}
3$^+$ + OH^- → **4** + H_2O	–229.45	–227.64	–232.51	10^{170}	–106.8	–104.92	–109.86	10^{80}
1*H*-Tetrazole reactions at nitrogen atom								
1 + OH^- → **5**$^-$ + H_2O	–59.26	–59.1	–60.04	10^{44}	–30.99	–30.8	–31.79	10^{23}
5$^-$ + Y^+ → **7**	–118.1	–118.6	–106.2	10^{77}	–12.95	–13.52	–0.68	10^{0}
1 + Y^+ → **6**$^+$	55.02	52.78	69.12	10^{-51}	61.8	59.44	76.48	10^{-57}
6$^+$ + OH^- → **7** + H_2O	–232.39	–230.48	–325.37	10^{172}	–105.74	–103.76	–108.95	10^{79}
N-Methyltetrazole reactions at carbon atom								
8 + OH^- → **9**$^-$ + H_2O	–20.44	–19.7	–21.89	10^{16}	4.74	5.47	3.29	10^{-3}
9$^-$ + Y^+ → **11**	–155.52	–156.01	–143.65	10^{105}	–49.94	–50.62	–36.95	10^{27}
8 + Y^+ → **10**$^+$	44.47	42.44	58.56	10^{-43}	55.33	53.18	69.99	10^{-52}
10$^+$ + OH^- → **11** + H_2O	–220.43	–218.15	–224.11	10^{164}	–100.53	–98.34	–103.65	10^{76}

equilibrium constants K_r for reactions (see Table 1) were evaluated using the equation $\ln K_r = -\Delta G/RT$, where ΔG is the change in Gibbs energy, R is the universal gas constant, T is absolute temperature.

It should be emphasized that the possibility of the transformation of σ-complex **6** into a less energetically preferred product **7** is caused by the existence of >N–CH_2–NMe_2 grouping in the cation, owing to which this cation may be regarded as an efficient dimethylaminomethylation agent [similar to the well-recognized $CH_2(NMe_2)_2$ one]. The reaction mechanisms of analogous Mannich-type reagents, *gem*-disubstituted methanes such as $ClCH_2OH$, $ClCH_2OR$, $RSCH_2Y$, $HSCH_2Y$ or $RSeCH_2Y$, $HSeCH_2Y$ (Y = OH, Cl), were studied in detail using quantum chemical calculations.[21]

It is of note that Karavai and Gaponik[18] considered the attack at the N atom (see Scheme 2, transformation **1**→**6** in our case) to be a reversible reaction. Despite the energetic disadvantage of **6**→**7** transfer, it can in principle occur under more drastic conditions owing to irreversibility of the C-aminomethylation. Similarly, halogenation of 1*H*-tetrazole is not impossible[22] (to this, numerous *N*-halogen-substituted compounds known as halogenating agents are comprehensively reviewed[23–25]). Finally, easy transformation of mercury derivatives with Hg–N bond (*e.g.*, generated from *o*- or *p*-aminobenzoic esters and mercury acetate) into Hg–C ones in alcohol solution on addition of acetic acid is reported.[26–28]

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This article is dedicated to the bright memory of brilliant experts in quantum chemistry, ideal co-authors, honest and great men Nikolai D. Chuvylkin and Alexander N. Subbotin.

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