*Chemistry of Heterocyclic Compounds, Vol. 46, No. 8, 2010*

# THEORETICAL INVESTIGATION OF THE REACTION OF UNSYMMETRICAL 3,6-DISUBSTITUTED *sym*-TETRAZINES WITH CERTAIN ENAMINES

**E. S. Afonkina[1]*, V. A. Potemkin[2], and M. A. Grishina[2]**

*A theoretical investigation has been carried out of the reaction of 6-(3,5-dimethylpyrazol-1-yl)-sym-tetrazin-3-ylhydrazones of ketones with enamines such as 1-morpholinocyclopentene and 1-piperidinocyclopentene. A [4+2] cycloaddition mechanism of unsymmetrical 3,6-disubstituted tetrazines with enamines is proposed (the Carboni–Lindsey reaction). As a result only one product is preferentially obtained, having a substituent in the ortho position relative to the dimethylpyrazolyl radical, however in the case of small steric problems under kinetic conditions, control of the process is possible and all possible stereoisomers are obtained.*

**Keywords**: *sym*-tetrazine, quantum-chemical semiempirical PM3 method, molecular orbitals, Carboni-Lindsey reaction, HOMO, LUMO, stereoisomer.

The urgency of investigating reactions of nitrogen-containing heterocyclic compounds is determined by the broad practical value of these substances. Derivatives of tetrazine are used widely for constructing medicinal agents and also are used as dyestuffs, herbicides, desensitizers of photographic emulsions, inhibitors, antioxidants, and stabilizers of hydrocarbon polymers and unsaturated oils. Among other processes of interest is the [4+2] cycloaddition (Carboni–Lindsey reaction), characteristic of 3,6-disubstituted tetrazines with unsaturated hydrocarbons, as a result of which the corresponding 3,6-disubstituted pyridazines are formed [1-3]. Unlike the classical [4+2] cycloaddition of the Diels–Alder reaction the Carboni–Lindsey reaction is electron-inverse (reaction with inverted electron requirements). For the classical Diels–Alder reaction interaction of the HOMO of the diene and the LUMO of the dienophile is characteristic, while in the Carboni–Lindsey reaction the LUMO of the diene and the HOMO of the dienophile participate.

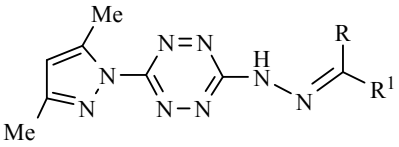
In the present work a theoretical analysis has been carried out of the conformational tautomeric states of the initial derivatives of *sym*-tetrazine and of the reaction products, which are pyridazine derivatives. Investigation of the tautomeric state of tetrazine derivatives **1a-i** within the framework of the semiempirical PM3 method [4] showed that the total energy of the tautomeric form **A** is 4.3-5.3 kcal/mol less than the energy of form **B** (Table 1).

* To whom correspondence should be addressed, e-mail: elena.chelyabinsk@hotmail.com.

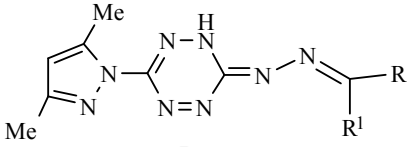
[1]Chelyabinsk State University, Chelyabinsk 454021, Russia.
[2]Chelyabinsk State Medical Academy, Chelyabinsk 454092, Russia.

Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 8, pp. 1217-1221, August, 2010. Original article submitted November 27, 2009.



**A**

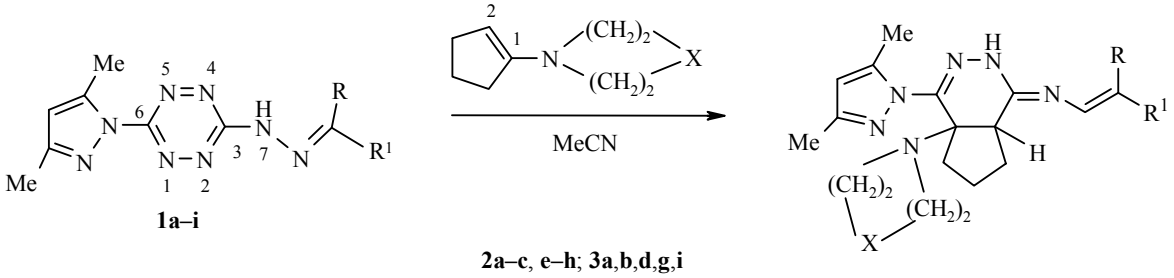


**B**

TABLE 1. Total Energy of the Tautomeric Forms **A** and **B** of *sym*-Tetrazine Derivatives

| Compound | Total energy of tautomeric forms, kcal/mol | |
|---|---|---|
| | **A** | **B** |
| **1a** | -71766.6 | -71762.3 |
| **1b** | -68319.1 | -68314.9 |
| **1c** | -89905.3 | -89900.1 |
| **1d** | -84030.9 | -89900.1 |
| **1e** | -62137.9 | -62133.4 |
| **1f** | -76490.5 | -76485.7 |
| **1g** | -86704.3 | -86699.4 |
| **1h** | -83441.3 | -83436.3 |
| **1i** | -84285.7 | -84280.7 |

From the total energy and enthalpy of formation of these compounds it may be proposed that in the Carboni–Lindsey reaction the tetrazine derivative reacts with the enamine in the form given in this Scheme.



**1a–i**

MeCN

**2a–c**, **e–h**; **3a**,**b**,**d**,**g**,**i**

**1–3 a** R + $R^1$ = $(CH_2)_5$, **b** R + $R^1$ = $(CH_2)_4$; **1c**, **2c** R = H, $R^1$ = 4-$NO_2C_6H_4$, **1d, 3d** R = H, $R^1$ = 4-$Me_2NC_6H_4$; **1, 2 e** R = $R^1$ = Me, **f** R = Me, $R^1$ = Ph; **1g–3g** R = Me, $R^1$ = 4-$MeOC_6H_4$; **1h, 2h** R = Me, $R^1$ = 4-$ClC_6H_4$; **1i, 3i** R = Me, $R^1$ = 4-$BrC_6H_4$; **2** X = O; **3** X = $CH_2$

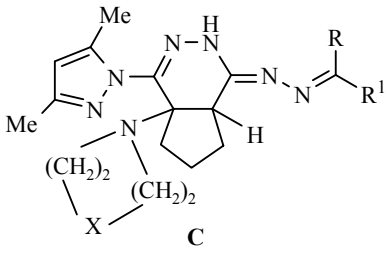
Investigation of the population of the LUMO and HOMO of tetrazine derivatives **1a-i** and enamine showed that the LUMO is distributed on the C(3) and C(6) atoms of tetrazine derivatives (Table 2), but the HOMO is distributed on the C(1) and C(2) atoms of the molecules of 1-morpholinocyclopentene and 1-piperidinocyclopentene. The C(3) atom possesses the greatest LUMO population in the tetrazine ring of reactants **1a-i** and the greatest HOMO population is observed at the C(2) atom in enamines.

Consequently, in the reaction being investigated orientation of the C(2) atom of the enamine beside the C(3) atom of the tetrazine derivative occurs initially. The morpholine and piperidine radicals of the enamines are therefore located near the pyrazole portion of the molecule of the second reactant. Addition of the carbon atoms at the double bond of the enamine molecule occurs to atom C(3) and C(6) of the tetrazine derivative. As a result products **2a-c**,**e-h** and **3a**,**b**,**d**,**g**,**i** are formed in which the substituents are in the *ortho* position relative to the dimethylpyrazole radical, which confirms the mechanism of electron-inverse cycloaddition. On the basis of the total energy and enthalpy of formation, calculated by the semiempirical PM3 method, it may be proposed that the product is the (*ss*)-isomer or its mirror-image the (*rr*)-isomer. In this way hydrogen is located at the first nitrogen atom in the pyridazine ring. The results obtained were confirmed by the experimental data given in [1, 5].

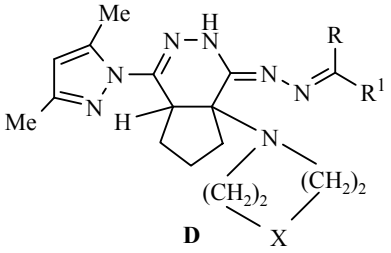
TABLE 2. Population of LUMO on C(3) and C(6) Atoms in Tetrazine Derivatives

| Compound | Population of LUMO on atom | |
|---|---|---|
| | C(3) | C(6) |
| **1a** | 0.2789 | 0.2608 |
| **1b** | 0.2848 | 0.2675 |
| **1c** | 0.2089 | 0.1993 |
| **1d** | 0.2804 | 0.2606 |
| **1e** | 0.2790 | 0.2633 |
| **1f** | 0.2826 | 0.2623 |
| **1g** | 0.2844 | 0.2617 |
| **1h** | 0.2789 | 0.2607 |
| **1i** | 0.2788 | 0.2609 |

The formation of a product of type **C** is thermodynamically more favorable, but there are kinetic reasons for the formation of product **D**. Thus, on interacting tetrazine derivatives **1e** and **1f** with 1-piperidinocyclopentene isomers **D** are formed, in which the piperidine radical is in the *meta* position.




**C**




**D**

In the present case a complex is formed with a 1-piperidinocyclopentene of a different character, as a result of which under kinetic conditions the *meta* isomer must be formed on rapid progress of the process, and under thermodynamic conditions the *ortho* isomer is formed. Compounds **3e** and **3f** have radicals R and $R^1$ with minimal volume, consequently the disposition of the piperidine radical in the *meta* position relative to the dimethylpyrazole radical is sterically more favorable.

The electron-inverse mechanism for the [4+2] cycloaddition reaction is confirmed in the present work. It has been shown that on interacting *sym*-tetrazine derivatives with enamines the C(2) atom of the enamine is oriented close to the C(3) atom of the tetrazine ring. It was established that the (*ss*)-product is thermodynamically more favored than its mirror antipode, the (*rr)*-isomer with a pyrimidine or morpholine substituent in the *ortho* position relative to the dimethylpyrazole radical. It was shown that one product, having the substituent in the *ortho* position, is preferentially obtained as a result of the reaction being considered. In the case of small R and $R^1$ substituents in the ketonic fragment of the 6-(3,5-dimethylpyrazol-1-yl)-*sym*-tetrazin-3-ylhydrazones, it is possible to obtain isomers with pyrimidyl or morpholino substituents in the *ortho* and *meta* positions under kinetic conditions of carrying out the reaction, and also two tautomeric forms of the initial compound, i.e. all the possible stereoisomers. It follows that conditions have been developed for conducting the process and it is possible to suggest new [4+2] cycloaddition reactions for tetrazine derivatives bearing other R and $R^1$ radicals.

## EXPERIMENTAL

Multiconformational analysis was carried out using the MultiGen algorithm [6-8]. The tautomeric state of tetrazine derivatives **1a-i** was investigated within the framework of the semiempirical quantum-chemical PM3 method [4]. The population of the LUMO and HOMO of the tetrazine derivatives and enamines were calculated with the program complex GAMESS [4] on the 6-31G basis.

## REFERENCES


1. G. L. Rusinov, R. I. Ishmetova, N. I. Latosh, N. I. Ganebnykh, O. N. Chupakhin, and V. A. Potemkin, *Izv. Akad. Nauk, Ser. Khim.*, 354 (2000).
2. E. S. Afonkina, V. A. Potemkin, and M. A. Grishina, in: *Abstr. X Young Peoples' Conference on Organic Chemistry* [in Russian], Reaktiv, Ufa (2007), p. 100.
3. A. R. Katritzky, C. W. Rees, and E. F. V. Scriven, in: *Comprehensive Heterocyclic Chemistry II. A Review of the Literature 1982-1995*, Vol. 6, Pergamon, New York (2000).
4. J. J. P. Stewart, *J. Comput-Aided Mol. Des.*, **4**, No. 1, 1 (1990).
5. G. L. Rusinov, R. I. Ishmetova, I. N. Ganebnykh, O. N. Chupakhin, G. G. Aleksandrov, and I. A. Litvinov, *Heterocycl. Commun.*, **19**, 39 (2003).
6. V. A. Potemkin, M. A. Grishina, O. V. Fedorova, G. L. Rusinov, I. G. Ovchinnikova, and R. I. Ishmetova, *Pharm. Chem. J.*, **37**, 468 (2003).
7. E. V. Bartashevich, M. A. Grishina, V. A. Potemkin, and A. V. Belik, *Zh. Struk. Khim.*, **43**, 1120 (2002).
8. M. A. Grishina, V. A. Potemkin, R. M. Arslambekov, and A. V. Belik, in: *Proceedings of the First National Conference "Information–Computer Technology in Solving Fundamental and Applied Scientific Problems of Chemistry, Biology, Pharmaceutics, and Medicine"* [in Russian], Moscow (2002), p. 22.