Tautomerization of thiourea dioxide in aqueous solution

S. V. Makarov and E. V. Kudrik*

Ivanovo University of Chemistry and Technology,
7 prosp. Engel'sa, 153460 Ivanovo, Russian Federation.
Fax: +7 (093 2) 41 7995. E-mail: makarov@icti.ivanovo.su

Tautomerization of thiourea dioxide (TD) in an aqueous solution was studied by the semiempirical AM1 method. A possible mechanism of the process involves stepwise intermolecular proton transfer in TD oligomers followed by their breakdown and the formation of solvated monomers of aminoiminomethanesulfinic acid.

Key words: thiourea dioxide; aminoiminomethanesulfinic acid; quantum-chemical calculations, AM1 method, proton transfer, tautomerization, aqueous solutions.

Many thioureas are highly toxic. It is believed that the toxicity of thioureas is determined by their oxidation[1,2] and by the ability of the oxides formed to undergo desulfuration[3] and that the higher this ability, the higher the toxicity. On the other hand, the results of our studies[4,5] contradict the above-mentioned conclsuions. The rates of desulfuration of the dioxides of *N*-methylthiourea and *N*-phenylthiourea were found to be lower than that of thiourea dioxide (TD), though *N*-methylthiourea and *N*-phenylthioureas are much stronger toxicants than thiourea. It seems likely, there are some other reasons responsible for the toxicity of thioureas.

Unfortunately, information on dioxides of most thioureas is unavailable. The only well-studied representative of this group of compounds is TD,[6] which is known[7] to exist in the crystalline state in the form $(NH_2)_2CSO_2$ (**1**), where the molecules are linked by a system of hydrogen bonds.

It is assumed[8,9] that dissolution of TD in water is followed by rearrangement of its molecules into aminoiminomethanesulfinic acid (AIMSA) $NH_2(NH)CSO_2H$ (**2**). This conclusion was based on the changes in the pH and ^1H NMR spectrum of aqueous TD solution with time. It should be noted that these changes are not due to the decomposition of TD. The results of semiempirical quantum-chemical AM1 calculations[10] confirmed that species **2** becomes more thermodynamically favorable in aqueous solutions.

Taking into account an important role of the proton transfer processes in biological systems, in this work we carried out a theoretical study of tautomeric transformations of TD in aqueous solutions using the method of critical points on the potential energy surface (PES).

Calculation Procedure

Calculations were carried out by the semiempirical AM1 method[11] using the MOPAC 6 program package. A TD dimer was used as the model structure. Solvent effects were taken into account in the reacting molecule approximation by performing calculations only for those water molecules which are involved in the hydrogen bonding with O and H atoms of TD molecules. Transition states were determined using the SADDLE procedure incorporated into the MOPAC 6 program package.

Results and Discussion

According to calculations, the activation barrier to proton transfer between different fragments of TD molecule exceeds 500 kJ mol^{-1}. This indicates the impossibility for proton transfer to occur in a TD monomer without involvement of a water molecule.

Scheme 1 of possible routes of the transformation of TD into AIMSA in an aqueous solution is presented below. Here, the atomic charges are not shown since the *ab initio* calculations[7] with the 6-31G* basis set showed that the structure of TD is described by a resonance between the structures $(H_2N)_2C^+—S^+O^-O^-$ and $(H_2N)_2C^+—S(=O)O^-$. According to the same calculations,[7] the atomic charges of C, S, and O are 0.4067, 1.1334, and −0.7718 e for a TD monomer and 0.4008, 1.2165, and −0.8088 e for a TD dimer.[7] Routes *1* and *3* imply proton transfer in solvated TD dimers, whereas route *2* implies that in solvated TD monomers.

Consider the possibility of transformation following route *1*. Assuming that proton transfer occurs stepwise, this route must involve a stage of the formation of mixed dimeric TD—AIMSA structures. However, our calculations showed that these structures are thermodynamically unstable. Optimization of their geometry leads to cleavage of the interfragment bonds to give the corresponding monomers. We believe that this confirms the low probability of proton transfer following route *1*.

Consider the routes *2* and *3* in more detail. The thermodynamic characteristics of the structures corresponding to the main critical points on the PES for route *2* (**7**, **8**, and transition state **9** (TS) between them)

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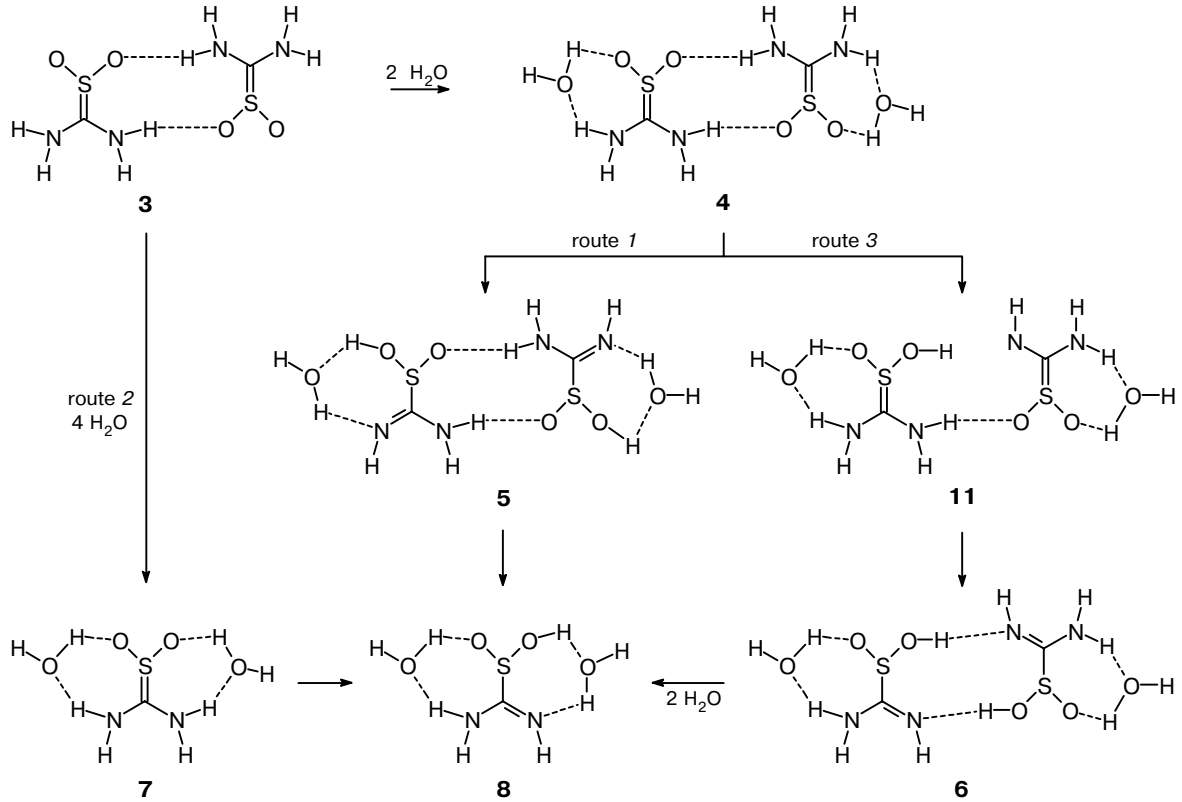
Scheme 1



and route *3* (**4**, **6**, **8**, TS **10** and **12**, and a local minimum **11**) are listed in Table 1.

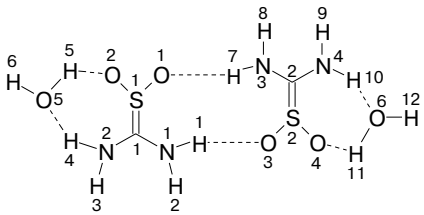
The data listed in Table 1 show that route *3* of proton transfer is the most preferable. This is indicated by the much lower height of the barrier to the rate-determining stage compared to route *2* (107.1 *vs.* 155.5 kJ mol^{-1}, respectively).

Two maxima corresponding to the TS **10** and **12** and a local minimum corresponding to the intermediate **11** formed after transfer of one proton were found on the PES when moving along the reaction pathway (route *3*). From the data listed in Table 1 it follows that the rate-determining stage of the reaction is transfer of the first proton (the activation barriers to the transfer of the first and second protons are 107.2 and 29.8 kJ mol^{-1}, respec-

Table 1. Thermodynamic characteristics of structures **4** and **6**—**12** corresponding to the main critical points for routes *2* and *3*

Compound	$\Delta_f H°_{298}$	$\Delta_f G°_{298}$	$S°_{298}$
	kJ mol^{-1}		/J mol^{-1} K^{-1}
4	−1169.5	−1350.0	605.8
6	−1142.1	−1329.0	627.3
7	−836.9	−973.3	457.5
8	−845.4	−987.8	477.7
9	−690.2	−817.8	428.6
10	−1064.1	−1242.8	599.9
11	−1096.3	−1277.9	609.4
12	−1074.5	−1248.1	582.5

Table 2. Interatomic distances (*d*) in transition states **10** and **12** and intermediate **11**



Bond	*d*/Å		
	10	**11**	**12**
C(1)—S(1)	1.89	1.84	1.83
C(2)—S(2)	1.90	1.82	1.83
C(1)—N(1)	1.32	1.33	1.30
C(1)—N(2)	1.37	1.35	1.40
C(2)—N(3)	1.33	1.30	1.32
C(2)—N(4)	1.35	1.41	1.34
S(1)—O(1)	1.60	1.70	1.60
S(1)—O(2)	1.52	1.45	1.50
S(2)—O(3)	1.60	1.60	1.68
S(2)—O(4)	1.46	1.50	1.45
O(1)—H(7)	2.21	2.08	1.33
O(3)—H(1)	1.34	1.33	0.96
N(1)—H(1)	1.20	2.47	—
N(3)—H(7)	1.01	1.01	1.21

tively). The interatomic distances in the TS **10** and **12** and in intermediate **11** are listed in Table 2. The first stage of tautomeric transformation involves transfer of the proton H(1) and is accompanied by shortening of the O(1)—H(7) bond, followed by transfer of the proton H(7). The energy characteristics of TS **10** and **12** are close to those of intermediate **11**. Based on the Hammond postulate,[12] these TS can be considered as the "late" transition state with respect to structure **4** (TS **10**) and the "early" transition state with respect to structure **11** (TS **12**).

The results obtained in this work allow an alternative interpretation of experimental data.

As was mentioned above, changes in the ^{1}H NMR spectrum (splitting of a singlet signal into a doublet) and a decrease in the pH of the solution with time were the main arguments in favor of the formation of the tautomeric form of TD (AIMSA) in aqueous solutions. The rate of splitting of the ^{1}H NMR signal was found to be much higher than the rate at which the steady-state pH value was established. The ratio of the transfer rates of the first and second protons suggests that the changes in the ^{1}H NMR spectrum of TD with time are not closely related to proton transfer and to the formation of AIMSA.

The following explanation seems to be more correct. Dissolution of TD in water is likely followed by the formation of solvated TD oligomers, which makes protons inequivalent due to the formation of different types of hydrogen bonds (a fraction of protons form H-bonds with water molecules while other protons interact with the other TD molecule). Thus, splitting of the ^{1}H NMR spectrum is due to the solvation of TD oligomers. The determining role of solvation is also indicated by the fact that analogous effect was observed[13] in DMSO, which is also known to be a strong solvent for TD. As such, proton transfer followed by the formation of AIMSA is responsible for the slow decrease in the pH of aqueous solutions of TD with time.

Thus, the most probable mechanism of tautomeric transformation of TD in aqueous solutions involves a stepwise intermolecular transfer of two protons in the TD oligomers followed by their breakdown to give solvated AIMSA monomers.

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References

1. S. M. Mitchell and G. B. Steventon, *Sulfur Reports*, 1994, **16**, 117.
2. K. Ziegler-Skylakakis, S. Nil, J. Pan, and U. Andrae, *Environ. Mol. Mutagen.*, 1998, **31**, 362.
3. A. E. Miller, J. J. Bischoff, and K. Pae, *Chem. Res. Toxicol.*, 1988, **1**, 169.
4. K. Lekhimena, S. V. Makarov, and V. V. Budanov, *Izv. Vus. Khim. Khim. Tekhnol.* [*Bull. High. Educ. Inst. Chem. Chem. Technol.*], 1991, **34**, 122 (in Russian).
5. S. A. Svarovsky, R. H. Simoyi, and S. V. Makarov, *J. Chem. Soc., Dalton Trans.*, 2000, 511.
6. V. V. Budanov and S. V. Makarov, *Khimiya serosoderzhashchikh vosstanovitelei* [*Chemistry of Sulfur-Containing Reducing Agents*], Khimiya, Moscow, 1994, 140 pp. (in Russian).
7. J. S. Song, E. H. Kim, S. K. Hang, S. S. Yun, I.-H. Suh, S. S. Choi, S. Lee, and W. P. Jensen, *Bull. Kor. Chem. Soc.*, 1996, **17**, 201.
8. V. Lepentsiotis, R. van Eldik, D. M. Stulov, and S. V. Makarov, *J. Chem. Soc., Dalton Trans.*, 1998, 2915.
9. S. M. Evdokimova, A. N. Aleksandrova, S. V. Makarov, and V. V. Budanov, *Izv. Vus. Khim. Khim. Tekhnol.* [*Bull. High. Educ. Inst. Chem. Chem. Technol.*], 1995, **38**, 27 (in Russian).
10. S. V. Makarov, E. V. Kudrik, A. V. Lyubimtsev, and D. M. Stulov, *Zh. Obshch. Khim.*, 2000, **70**, 1488 [*Russ. J. Gen. Chem.*, 2000, in press (Engl. Transl.)].
11. M. J. S. Dewar, E. G. Zoebisch, E. F. Healy, and J. J. P. Stewart, *J. Am. Chem. Soc.*, 1985, **107**, 3902.
12. J. S. Hammond, *J. Am. Chem. Soc.*, 1955, **77**, 334.
13. G. Gattow and W. Manz, *Z. Anorg. Allg. Chem.*, 1988, **561**, 66.

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