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Thio- versus oxo-derivatives of DNA bases: theoretical study on possible mutagenic effect of sulfur atom

Al'ona Furmanchuk[a]; Jerzy Leszczynski[a]
[a] Department of Chemistry, Computational Center for Molecular Structure and Interactions, Jackson State University, Jackson, MS, USA

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Thio- versus oxo-derivatives of DNA bases: theoretical study on possible mutagenic effect of sulfur atom

Al'ona Furmanchuk and Jerzy Leszczynski*

Department of Chemistry, Computational Center for Molecular Structure and Interactions, Jackson State University, Jackson, MS, USA

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The molecular structures, energetics and mechanisms of proton transfer in 9-methyl-2*N*-substituted guanines and thioguanines have been studied at the gas phase (QCISD/cc-pVDZ//B3lyp/6-31G(d,p)) and polar solvent (IEFPCM//B3LYP/6-31G(d,p)) environments. Calculations predict the height of the proton transfer barrier for the thione → thiol reactions to be approximately 2–3 times lower than that for the keto → enol process. Similarly, presence of sufficiently long 2*N* substituent with the terminal OH group reduces the barrier. The polar media (water) significantly stabilizes thione and keto forms. Tautomeric concentration ratio and rate constants have also been calculated for all the considered processes.

Keywords: *ab initio*; 9-methyl-2*N*-substituted thioguanines; 9-methyl-2*N*-substituted guanines; tautomeric equilibrium

1. Introduction

Compounds that incorporate modified DNA base in their structures are widely used in modern hybridization-based technologies and drug design (*1*). 2*N*-Carbamoyldeoxyguanosine or its derivatives recently synthesized and incorporated into oligodeoxynucleotides are examples of such species (*2*). These analogs are useful for the development of functional oligodeoxynucleotides capable of a precise base recognition. In addition, 2*N* analogs become heavily exploited, since N2 atom of guanine is known to be susceptible to modifications by various potential carcinogens (*3*, *4*). Consequently, 2*N*-alkyl-guanines become known as potential anti-inflammatory drugs, A2a receptor agonists, and important intermediates in synthesis of adenosine (*5*, *6*).

The search for new drugs demands a detailed knowledge of the effects of each modification on the chemical properties of the novel compounds as well as their interactions with the environment. By selection of right substituent one can achieve desired biological activities. For instance, substitution of oxygen atoms by sulfur in oxopurines may induce the ability to stabilize the DNA (*7*, *8*). However at the same time, thio-group may change relative stability of tautomeric forms and enhance mutations in the DNA (*9*). Over the recent years, computational studies on DNA

*Corresponding author. Email: jerzy@ccmsi.us

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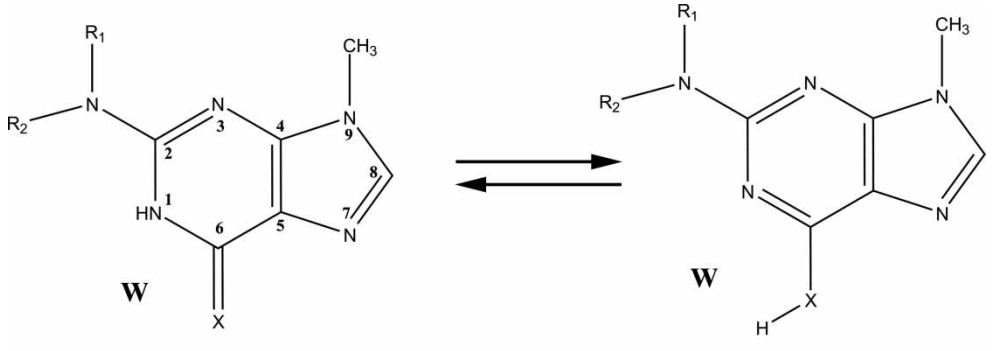
bases and their thio-derivatives reveal the importance of the thio-substitutions on the alteration of properties of such modified species, including their molecular structures, tautomeric stabilities, and proton transfer (*10–16*).

Two major types of mechanism of the prototropic tautomerization in investigated heterocycles are based on intermolecular or intramolecular proton transfer. An example of intermolecular mechanism can be illustrated by a recent study (*17*) of the dimerization of tautomeric forms followed by double proton transfer. However, self association (formation of dimers) in this case is due to the influence of nonpolar medium. Contrary to nonpolar media, tautomers in polar media are able to form bonds with solvent molecules. Hence, solvent-induced double proton transfer is also possible in polar environment (*18–21*). Intramolecular proton transfer mechanism is based on the idea that two moieties of the same molecule are acting as donor and acceptor simultaneously. Intramolecular mechanism could be related to a single (*20, 22, 23*) or double proton transfer.

Both, intramolecular and intermolecular mechanisms will be discussed in the present paper. In particular, 9-methyl-2*N*-substituted guanines will be examined for thione ↔ thiol and keto ↔ enol types of tautomerization (Figure 1).

The intermolecular dimerization has been excluded from the proposed mechanisms because of steric hindrance of the 2*N* substituent. Tautomeric equilibrium of selected thio-derivatives and their parent oxopurine compounds will be characterized by the estimation of equilibrium constants, tautomeric concentration ratio, and rate constants.

The aim of the present work is to study (i) the influence of the structural modifications on tautomeric equilibrium and mechanism of tautomerization, and (ii) the role of the polar medium (water) in the proton-transfer process. To gain a systematic understand of solvent effects, we will discuss prototropic tautomerism (a) in the gas phase, (b) in a microhydrated environment with one explicit water molecule, and (c) in a solvent by adopting the hybrid model, where the explicit solvent and continuum model are combined.



R_1	R_2	X	Abbreviations used	
			Gas phase	Solution
$-CH_3$	-OH	O	$I_{keto} \rightleftharpoons I_{enol}$	$Iw_{keto} \rightleftharpoons Iw_{enol}$
	$-(CH_2)_4OH$		$II_{keto} \rightleftharpoons II_{enol}$	$IIw_{keto} \rightleftharpoons IIw_{enol}$
$-CH_3$	-OH	S	$I_{thione} \rightleftharpoons I_{thiol}$	$Iw_{thione} \rightleftharpoons Iw_{thiol}$
	$-(CH_2)_4OH$		$II_{thione} \rightleftharpoons II_{thiol}$	$IIw_{thione} \rightleftharpoons IIw_{thiol}$
	$-(CH_2)_4SH$		$III_{thione} \rightleftharpoons III_{thiol}$	$IIIw_{thione} \rightleftharpoons IIIw_{thiol}$

Figure 1. Systems studied. W indicates the location where the proton transfer takes place. In the IEF–PCM calculations it also represents the position of one explicit water molecule.

2. Computational details

The tautomeric equilibrium for 9-methyl-2*N*-substituted guanines is predicted for the gas phase and polar solution (water). All the calculations were carried out using the Gaussian 03 code (*24*).

2.1. *Common setup*

The standard 6-31G (d,p) basis set was used for geometry optimization. All geometries of minima and transition states (TS) structures were optimized without symmetry restrictions (C_1 symmetry was assumed) at the DFT (B3LYP) level of theory (*25–27*). The characteristics of minima and TS were verified by establishing that the Hessians matrices of the energy second derivatives have all real or one imaginary eigenvalues, respectively. The detailed nature of TS structures has been determined by analyzing the motion described by the eigenvector associated with the imaginary frequency. Only the lowest energy tautomers were considered for minima structures.

The Free energy has been calculated by standard formula

$$\Delta G = \Delta H - T\Delta S. \tag{1}$$

To estimate the ΔH values, thermal correction to the enthalpies calculated at B3LYP/6-31G(d,p) level were added to the calculated energies. Entropy value and thermal correction to the ΔH term were calculated using the rigid rotor-harmonic oscillator approximation (*28*). Unless otherwise noted, the electronic energy was calculated at the same level of theory.

The tautomeric equilibrium constants (K_T) have been calculated from the following equation:

$$K_T = \exp\left(\frac{-\Delta G_T}{RT}\right). \tag{2}$$

The ΔG_T represents the Gibbs free energy difference between thiol and thione (or enol and keto) tautomers calculated at temperature T (298.15 K).

2.2. *Gas phase calculations*

For the gas phase study, the isolated species were considered. In addition to 'common setup' calculations, the electronic energies were refined by single-point calculations at the QCISD/cc-pVDZ level of theory (*29*).

2.3. *Microhydrated environment model*

The strong solute–solvent interactions are accounted in the microhydrated environment model (MEM) by explicit incorporation of water molecule in the first solvation shell. There are several polar sites that are capable of forming a hydrogen bond with water. However, only few of them are responsible for the tautomerization in given compounds. Thus, we initially located water molecule at the vicinity of the proton transfer region W (Figure 1) and then fully optimized the molecular structures of such species. All calculations for monohydrated tautomers and their TS are listed in the Section 2.1.

2.4. *Hybrid model*

Hybrid model is the combination of the MEM and continuum approach. In this work, the integral-equation-formalism polarizable continuum approach (IEF–PCM) (*30*) was employed for the

continuum model-based calculations. Such hybrid approach allows us to investigate the combined effect of specific and non-specific solute–solvent interactions.

Geometries of monohydrated structures from MEM were used for single-point calculations with IEF–PCM method at the B3LYP/6-31G (d,p) level of theory.

2.5. *Methodology justification*

Density Functional Theory (DFT) has proven to be a reliable and fast tool for optimization of medium-sized organic molecules. Consequently, all geometrical parameters in this study were optimized at the B3LYP level. However, sometimes DFT fails to reproduce correctly the experimentally measured difference of energies of tautomers. According to the Piacenza and Grimme (*31*) and our experiences (*32*), the Quadratic Configuration Interaction method with Single and Double excitations method is reliable for prediction of energetics of systems similar to those studied in the present work. Therefore, to refine the relative energies of the tautomers, we also performed single-point QCISD gas phase calculations. Unfortunately, high computational demand of the QCISD method does not allow us to use the same level of theory for the solvent calculations.

3. Results and discussion

3.1. *Proton transfer and mechanism of tautomerization*

As was stated before, location where proton transfer takes place is denoted by W. To gain insight into the process at W vicinity, we modeled it in different environments.

3.1.1. *Isolated systems*

We found out that both R_2 and X substituents play an important role in the proton transfer. Short R_2 group is able to participate in hydrogen bonding only in the case when there is no hydrogen bound to N_1 atom (Figure 2). This means that only I_{enol} tautomer is stabilized by the hydrogen bonding with short R_2 (R_2=OH). The long R_2 substituent (R_2=$(CH_2)_4OH$ and $(CH_2)_4SH$) allows OH terminal group to form two hydrogen bonds with the ring of each (II_{enol} and II_{keto}) tautomer.

A slight elongation of N_1-H_1 and C_6-O_6 bonds as well as a decrease in the value of $\angle N_1-C_6-O_6$ can be seen as a result of such double bonding in II_{keto} tautomer. On the other hand, long R_2 chain decreases structural tension at the W vicinity of the enol tautomer. Consequently, the values of $\angle N_2-C_2-N_1$ and $\angle N_1-C_6-O_6$ for II_{enol} are bigger than the corresponding values for I_{enol}. A correlation between the length of R_2 substituent and the number of protons transferred at W region has been also revealed. Whereas, short R_2 substituent plays only a stabilization role in the enol form, the OH terminal group of longer R_2 substituent is involved in the double proton transfer. Such features lead to a difference in the type of proton transfer mechanism and the structures of TS.

The influence of X substituent can be revealed by comparing the structures of $N_{keto(enol)}$ (Figure 2) and $N_{thione(thiol)}$ (Figure 3), where (N = I, II, and III).

The difference in nature between sulfur and oxygen leads to the formation of much longer C_6=S_6 and S_6=H_6 bonds than the corresponding C_6=O_6 and O_6-H_6 ones. An analysis of $N_{keto(enol)}$ and $N_{thione(thiol)}$ structures reveals also an influence of X substituent on the length of H-bonds between a long R_2 and the ring. Substitution of oxygen by the more bulky sulfur atom reduces the hydrogen bond interaction between tautomers and water. The lengths of two H-bonds increase from 1.865 and 2.02 Å in II_{keto} to 1.861 and 2.427 Å in II_{thione}. Double substitution by sulfur in III_{thione} yields even larger bond distances (2.69 and 3.67 Å). Similar pattern is observed

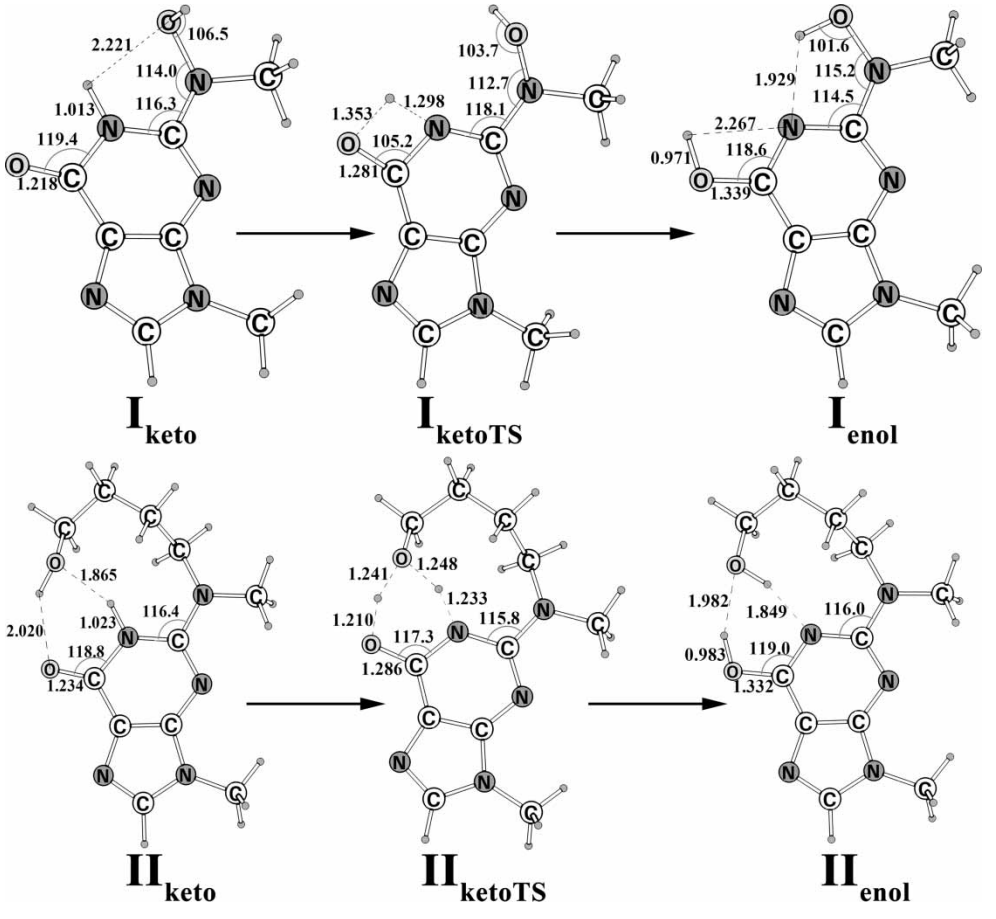


Figure 2. Gas phase intramolecular single and double proton transfer mechanisms of keto→enol tautomerization. Geometrical parameters are calculated for the proton transfer vicinity of 9-methyl-2*N*-substituted guanines at B3LYP/6-31G(d,p) level.

for the corresponding enol/thiol forms. Because of such a relaxation, the values of $\angle N_2-C_2-N_1$ and $\angle N_1-C_6-S_6$ in $II_{thione(thiol)}$ and $III_{thione(thiol)}$ almost approach 120°. These values for tightly bounded $II_{keto(enol)}$ forms are 116° and 119°, respectively.

Despite the fact that structural parameters of W vicinity are affected by the nature of X substituent, the tautomerization process mainly depends on the length of R_2. Gas phase calculations suggest intramolecular single proton transfer mechanism of tautomerization for the tautomers with R_2=OH. For tautomers with $R_2=(CH_2)_4OH$ and $(CH_2)_4SH$, intramolecular double proton transfer proceeds with an assistance of R_2 substituent.

3.1.2. *Microhydrated environment model*

Rich in polar sites, the 9-methyl-2*N*-substituted guanines would form associates with such polar solvent as water. There is also possibility that water from the first solvation shell could be able to assist in the tautomerization process. The simplest model of water-induced tautomerization is based on the one explicit water molecule interacting with the studied species placed at the W vicinity. An inclusion of even one water molecule has a great impact on geometry and tautomerization mechanisms.

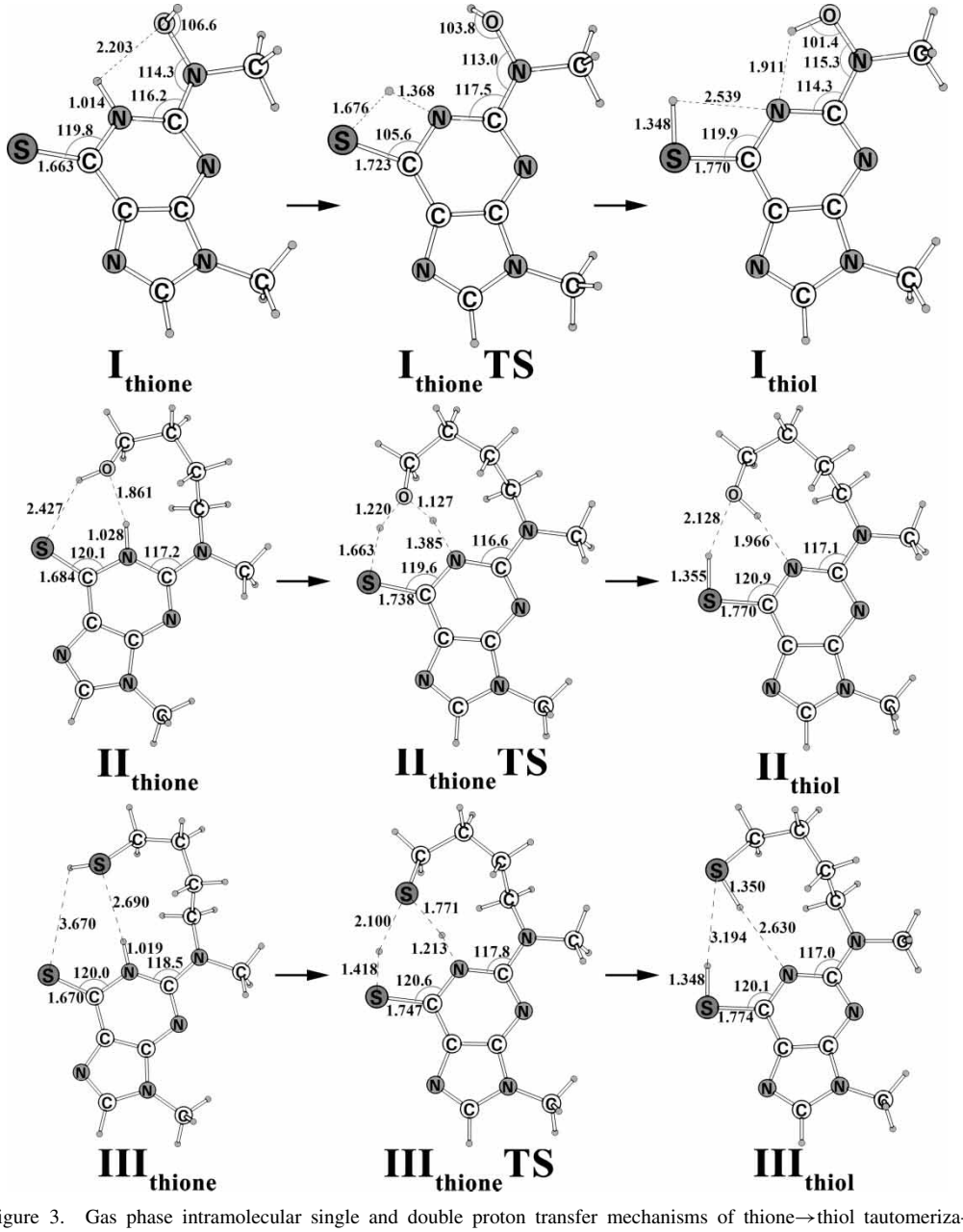


Figure 3. Gas phase intramolecular single and double proton transfer mechanisms of thione→thiol tautomerization. Geometrical parameters are calculated for the proton transfer vicinity of 9-methyl-2*N*-substituted thioguanines at B3LYP/6-31G(d,p) level.

In addition to gas phase trends correlated with the nature of X substituent, we also predicted extra relaxation around the N_2-C_2 bond. In particular, the $\angle N_2-O-H$ formed by short R_2 substituent became wider as a result of microhydration (Figure 4).

In contrast to the predictions for isolated I_{enol} and I_{thiol}, our calculations reveal that stabilization of enol forms (Iw_{enol} and Iw_{thiol}) by water prevents the formation of hydrogen bonds between the short R_2 substituent and the N_1 atom of the ring. An interaction of R_2 substituent of the Iw_{enol}

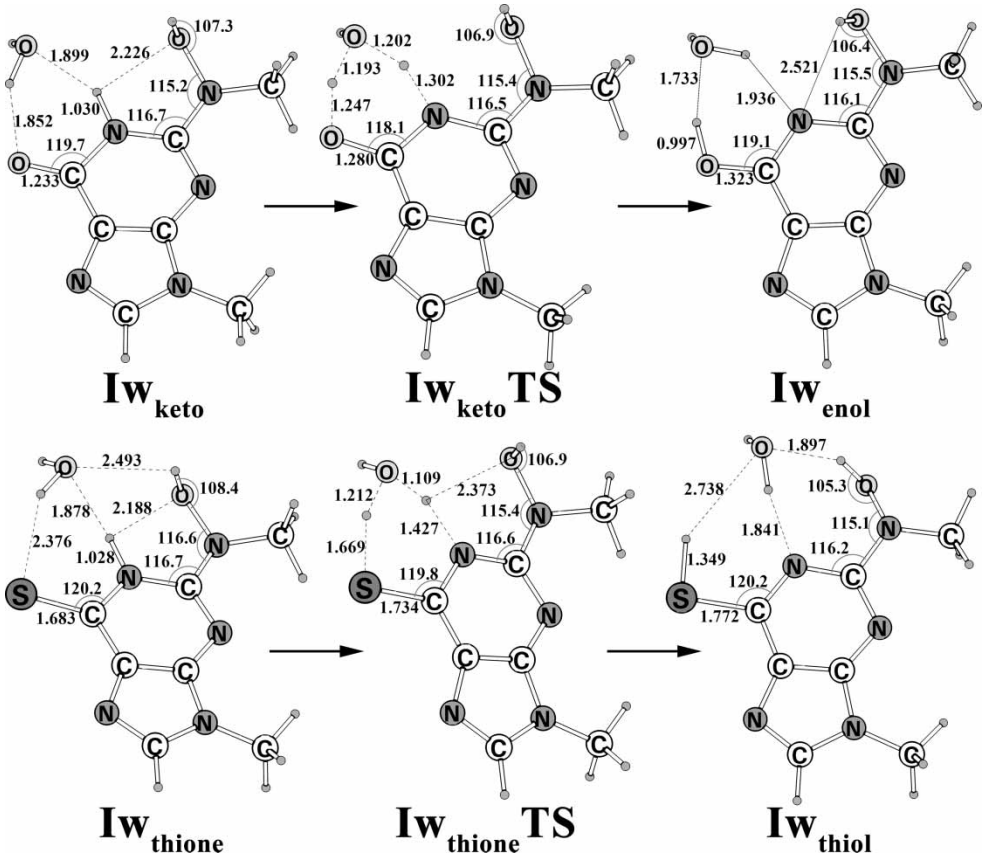


Figure 4. MEM simulations of water-assisted intermolecular double proton transfer mechanism. Geometrical parameters are calculated for the proton transfer vicinity of monohydrated 9-methyl-2-(hydroxy(methyl)amino)-guanines and thioguanines at B3LYP/6-31G(d,p) level.

with water molecule leads to widening of the $\angle N_2-O-H$ because of the repulsion between the hydrogen atoms of R_2 and water. The same type of interaction in Iw_{thiol} and in all monohydrates with long R_2 (Figure 5) results in the formation of an additional hydrogen bond between R_2 and oxygen of water molecule.

A slight increase in the values of $\angle N_1-C_6-X_6$ in all hydrated forms also provides an evidence of relaxation caused by the interaction with water. One can assume that the effect of bulk water on geometry of tautomers would be even more pronounced than that revealed in the case of the MEM model. However, even such a simple, one water molecule model makes possible to reveal a trend of changes and mechanism of tautomerization. If water molecule participates in the intermolecular double proton transfer, there is no room for R_2 substituent. Water molecule behaves as donor and acceptor of protons in all the discussed systems. Some variations exist in those species that form three hydrogen bonds between water and the R_2 substituent in TS.

3.2. *Thermodynamics and kinetics of tautomerization*

The thermodynamical parameters of the investigated tautomerization reactions are listed in Table 1. The energetics of the gas phase model was evaluated using B3LYP and QCISD methods. As expected, the difference in the energy values estimated by those two methods

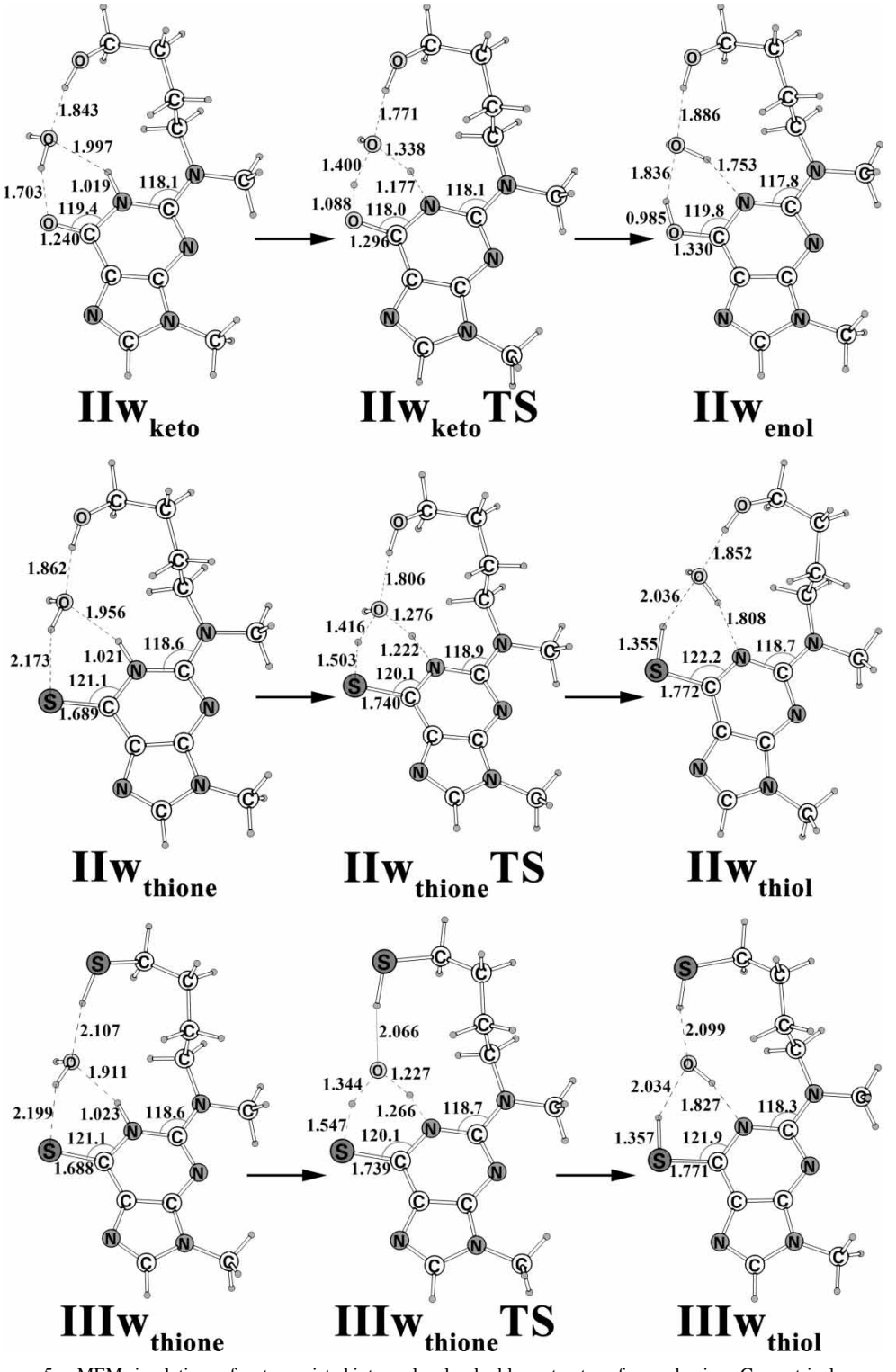


Figure 5. MEM simulations of water-assisted intermolecular double proton transfer mechanism. Geometrical parameters are calculated for the proton transfer vicinity of monohydrated 9-methyl-2-((4-hydroxybutyl)(methyl)amino)-guanines and thioguanines at B3LYP/6-31G(d,p) level.

Table 1. Gibbs free energies, activation free energies, equilibrium constants, and tautomeric concentration ratio in gas phase and in water.

	$\Delta G_{298.15}$ (kcal/mol)			$\Delta G^{\neq}_{298.15}$ (kcal/mol)			K_{eq}, keto↔enol or thione↔thiol			keto/enol or thione/thiol concentration ratio		
	B3LYP/ 6-31G (d,p)	QCISD/ cc-pVDZ// B3LYP/ 6-31G(d,p)	IEFPCM// B3LYP/ 6-31G (d,p)	B3LYP/ 6-31G (d,p)	QCISD/ cc-pVDZ// B3LYP/ 6-31G(d,p)	IEFPCM// B3LYP/ 6-31G (d,p)	B3LYP/ 6-31G (d,p)	QCISD/ cc-pVDZ// B3LYP/ 6-31G(d,p)	IEFPCM// B3LYP/ 6-31G (d,p)	B3LYP/ 6-31G (d,p)	QCISD/ cc-pVDZ// B3LYP/ 6-31G(d,p)	IEFPCM// B3LYP/ 6-31G (d,p)
$I_{keto} \rightarrow I_{enol}$	1.53	2.45		33.53	36.27		7.58×10^{-2}	1.61×10^{-2}		13:1	62:1	
$II_{keto} \rightarrow II_{enol}$	0.83	0.31		10.66	13.77		2.45×10^{-1}	5.90×10^{-1}		4:1	2:1	
$I_{thione} \rightarrow I_{thiol}$	−0.73	−6.27		26.13	25.26		3.44	3.95×10^{4}		1:29	1:39455	
$II_{thione} \rightarrow II_{thiol}$	2.27	−1.90		11.49	12.58		2.17×10^{-2}	2.48×10^{1}		46:1	1:24	
$III_{thione} \rightarrow III_{thiol}$	−2.05	−5.64		12.81	16.35		3.20×10^{1}	1.36×10^{4}		1:32	1:13602	
$Iw_{keto} \rightarrow Iw_{enol}$	2.97		5.90	11.31		13.07	6.66×10^{-3}		4.71×10^{-5}	150:1		21239:1
$IIw_{keto} \rightarrow IIw_{enol}$	5.59		6.77	10.52		12.53	8.04×10^{-5}		1.09×10^{-5}	12442:1		92000:1
$Iw_{thione} \rightarrow Iw_{thiol}$	2.59		8.41	12.06		12.81	1.26×10^{-2}		6.85×10^{-7}	80:1		1460029:1
$IIw_{thione} \rightarrow IIw_{thiol}$	4.21		8.99	12.56		16.51	8.14×10^{-4}		2.55×10^{-7}	1229:1		3914437:1
$IIIw_{thione} \rightarrow IIIw_{thiol}$	3.86		10.64	12.10		15.14	1.47×10^{-3}		1.60×10^{-8}	680:1		62515041:1

($\Delta G_{\mathrm{QCISD}} - \Delta G_{\mathrm{B3LYP}}$) is not uniform. While the difference in predicted ΔG values for $\mathrm{I}_{\mathrm{thione/thiol}}$ system is 5.54 kcal/mol, it amounts to only 0.52 kcal/mol for $\mathrm{II}_{\mathrm{keto/enol}}$. In most cases, ΔG values calculated at the DFT level are above the QCISD ones. However, for $\mathrm{I}_{\mathrm{keto/enol}}$ system, B3LYP Gibbs free energy value is lower than that of predicted by the QCISD method. B3LYP level activation free energies are always lower than the corresponding QCISD ones, except for the $\mathrm{I}_{\mathrm{thione/thiol}}$ system. Similarly to ΔG, the difference in $\Delta G^{\neq}$ values for two methods varies from -0.87 kcal/mol (for $\mathrm{I}_{\mathrm{thione/thiol}}$) to 3.54 kcal/mol (for $\mathrm{III}_{\mathrm{thione/thiol}}$). It is clear that DFT method for most cases provides only a qualitative estimation of energy parameters.

Both applied methods predict high-activation energy for the direct intramolecular proton transfer in the gas phase. The values of activation barrier are slightly affected by the nature of X substituent. For example, a substitution of oxygen by sulfur changes the activation energy from 13.77 kcal/mol (for $\mathrm{II}_{\mathrm{keto/enol}}$) to 12.58 kcal/mol (for $\mathrm{II}_{\mathrm{thione/thiol}}$). The proton transfer barriers are approximately 50% lower for tautomers with long R_2 chain. Long enough R_2 chain assists in proton transfer and stabilizes TS structures by H-bonding with tautomeric sites.

Inclusion of one water molecule significantly reduces the activation barriers only for $\mathrm{I}_{\mathrm{keto/enol}}$ and $\mathrm{I}_{\mathrm{thione/thiol}}$ systems. In TS structures with short R_2, water molecule assists in proton transfer the same way as long R_2 does in the gas phase process. In the other systems, OH group of water replaces a position of XH terminal group of long R_2 substituent. Therefore, the incorporation of water molecule in such systems does not change significantly neither the mechanism nor the activation barrier of proton transfer.

The simulation of bulk solvent effect (hybrid model) revealed increase in energy barriers of tautomerization comparing to the corresponding data from MEM. Partially, such effect can be explained in terms of dipole moment changes $N\mathrm{w}_{\mathrm{keto(or\ thione)}}$ and $N\mathrm{w}_{\mathrm{keto(or\ thione)}}$ TS structures. We use the results of Mulliken (*33*) and Löwdin (*34*) population analysis to calculate the dipole moments of all considered species. Though the differences between these two approaches are within 10%, one should rely on the fact that both methods are able to predict similar trends of changes in dipole moments (Table 2) rather than their absolute values.

In most cases, $N\mathrm{w}_{\mathrm{keto(or\ thione)}}$ tautomers are characterized by the largest dipole moments, while the values corresponding to the TS structures are small. That means that $N\mathrm{w}_{\mathrm{keto(or\ thione)}}$ structures

Table 2. Dipole moments (in debye) of tautomers calculated with charges from Mulliken (Löwdin) population analysis.

	μ, D	
Tautomer	MEM, B3LYP 6-31G(d,p)	Hybrid model, IEFPCM// B3Lyp/6-31G(d,p)
$\mathrm{Iw}_{\mathrm{keto}}$	6.15 (6.41)	8.20 (8.09)
$\mathrm{Iw}_{\mathrm{thione}}$	6.94 (6.82)	10.06 (9.43)
$\mathrm{IIw}_{\mathrm{keto}}$	6.72 (7.22)	9.18 (9.09)
$\mathrm{IIw}_{\mathrm{thione}}$	8.15 (7.97)	11.78 (10.85)
$\mathrm{IIIw}_{\mathrm{thione}}$	8.64 (7.31)	12.68 (10.50)
$\mathrm{Iw}_{\mathrm{keto}}\mathrm{TS}$	5.08 (5.01)	6.76 (6.35)
$\mathrm{Iw}_{\mathrm{thione}}\mathrm{TS}$	5.83 (4.55)	8.29 (6.58)
$\mathrm{IIw}_{\mathrm{keto}}\mathrm{TS}$	7.74 (7.91)	10.13 (9.69)
$\mathrm{IIw}_{\mathrm{thione}}\mathrm{TS}$	8.07 (7.12)	11.00 (9.38)
$\mathrm{IIIw}_{\mathrm{thione}}\mathrm{TS}$	8.17 (6.01)	11.50 (8.55)
$\mathrm{Iw}_{\mathrm{enol}}$	4.35 (3.98)	5.76 (5.10)
$\mathrm{Iw}_{\mathrm{thiol}}$	4.48 (3.59)	5.85 (4.79)
$\mathrm{IIw}_{\mathrm{enol}}$	5.99 (5.53)	7.87 (6.89)
$\mathrm{IIw}_{\mathrm{thiol}}$	6.78 (5.24)	8.95 (6.88)
$\mathrm{IIIw}_{\mathrm{thiol}}$	7.13 (4.50)	9.31 (6.38)

are stabilized in polar solvent (water) compared to the $N\mathrm{w}_{\mathrm{keto(or\ thione)}}$ TS. Thus, stabilization of $N\mathrm{w}_{\mathrm{keto(or\ thione)}}$ structures will reduce $N\mathrm{w}_{\mathrm{keto(or\ thione)}} \rightarrow N\mathrm{w}_{\mathrm{keto(or\ thione)}}$ TS transition in polar solvents.

Dipole moment changes can be also employed for the interpretation of difference in ΔG values of tautomerization obtained using the MEM and hybrid models. The $N\mathrm{w}_{\mathrm{enol(or\ thiol)}}$ structures are less stable in bulk water environment because of smaller dipole moments. As a result, the tautomerization Gibbs free energies increase from MEM to the hybrid model. Based on the DFT values of equilibrium constants and tautomeric concentration ratio, we assume the predominance of $N\mathrm{w}_{\mathrm{keto}}$ and $N\mathrm{w}_{\mathrm{thione}}$ tautomers in aqueous environment. An additional stabilization of keto and thione tautomers by bigger R_2 substituent has been also predicted. Gas phase calculations of isolated forms favor the N_{keto} and N_{thiol} tautomers. These results could be related to the nature of X substituent. Obviously, the effects of substituents become dominant in the gas phase, where solvent effect is lacking. Interestingly, the influence of R_2 substituent is less pronounced than the effect of oxygen substitution by sulfur. Long R_2 substituent shifts equilibrium to the formation of N_{enol} and N_{thione} tautomers, while the short one stabilizes the N_{keto} and N_{thiol} forms.

3.2.1. *Rate constants*

Rate constants provide important characteristics of chemical reactions. Since there are no experimental data for the studied processes, in order to fill these gaps, we estimated rate constants at 298.15 K. The rate constants for the reversible first-order A→ B reaction have been evaluated by means of TS theory expression (*35–37*):

$$k = k^{\mathrm{W}}\delta\frac{k_{\mathrm{B}}T}{h}\frac{Q_{\mathrm{TS}}}{Q_{\mathrm{A}}}\exp\left(-\frac{\Delta G_0^{\neq}}{RT}\right), \tag{3}$$

where Q_{TS} and Q_{A} are the partition functions of the TS and the reactant; k_{B} is a Boltzmann's constant, and h is a Plank's constant; δ is a symmetry number; $\Delta G_0^{\neq}$ is the standard molar Gibbs energy change for the conversion of reactants into an activated complex; T is the temperature; and k^{W} indicates the corresponding Wigner tunneling correction (*38*, *39*):

$$k^{\mathrm{W}} = 1 + \frac{1}{24}\left(\frac{h\nu^{\neq}}{k_{\mathrm{B}}T}\right), \tag{4}$$

where $\nu^{\neq}$ is the imaginary frequency at the saddle point.

The imaginary frequencies of the TS used for the calculation of rate constants, values of Wigner correction factors, and rate constants themselves are listed in Table 3.

Table 3. Proton transfer characteristic: imaginary vibrational frequencies of the TS at the B3LYP/6-31G(d,p) level, Wigner tunneling correction values and quantum tunneling corrected reaction rate constants for the proton transfer reactions.

Reaction	$\varpi_{\mathrm{transfer}}$ (cm^{-1})	k^{w}	k_{quantum} (s^{-1})	Reaction	k_{quantum} (s^{-1})
$\mathrm{I}_{\mathrm{keto}}\rightarrow\mathrm{I}_{\mathrm{enol}}$	*i*1836	4.2756	6.90×10^{-14}	$\mathrm{I}_{\mathrm{enol}}\rightarrow\mathrm{I}_{\mathrm{keto}}$	4.28×10^{-12}
$\mathrm{II}_{\mathrm{keto}}\rightarrow\mathrm{II}_{\mathrm{enol}}$	*I*1491	3.1611	1.59×10^{3}	$\mathrm{II}_{\mathrm{enol}}\rightarrow\mathrm{II}_{\mathrm{keto}}$	2.69×10^{3}
$\mathrm{I}_{\mathrm{thione}}\rightarrow\mathrm{I}_{\mathrm{thiol}}$	*i*1610	3.5182	6.67×10^{-6}	$\mathrm{I}_{\mathrm{thiol}}\rightarrow\mathrm{I}_{\mathrm{thione}}$	1.69×10^{-10}
$\mathrm{II}_{\mathrm{thione}}\rightarrow\mathrm{II}_{\mathrm{thiol}}$	*i*1255	2.5316	9.35×10^{3}	$\mathrm{II}_{\mathrm{thiol}}\rightarrow\mathrm{II}_{\mathrm{thione}}$	3.77×10^{2}
$\mathrm{III}_{\mathrm{thione}}\rightarrow\mathrm{III}_{\mathrm{thiol}}$	*i*748	1.5430	9.95	$\mathrm{III}_{\mathrm{thiol}}\rightarrow\mathrm{III}_{\mathrm{thione}}$	7.30×10^{-4}
$\mathrm{Iw}_{\mathrm{keto}}\rightarrow\mathrm{Iw}_{\mathrm{enol}}$	*i*1499	3.1843	5.17×10^{3}	$\mathrm{Iw}_{\mathrm{enol}}\rightarrow\mathrm{Iw}_{\mathrm{keto}}$	1.10×10^{8}
$\mathrm{IIw}_{\mathrm{keto}}\rightarrow\mathrm{IIw}_{\mathrm{enol}}$	*i*903	1.7917	7.24×10^{3}	$\mathrm{IIw}_{\mathrm{enol}}\rightarrow\mathrm{IIw}_{\mathrm{keto}}$	6.68×10^{8}
$\mathrm{Iw}_{\mathrm{thione}}\rightarrow\mathrm{Iw}_{\mathrm{thiol}}$	*i*1165	2.3185	5.89×10^{3}	$\mathrm{Iw}_{\mathrm{thiol}}\rightarrow\mathrm{Iw}_{\mathrm{thione}}$	8.62×10^{9}
$\mathrm{IIw}_{\mathrm{thione}}\rightarrow\mathrm{IIw}_{\mathrm{thiol}}$	*i*1232	2.4746	1.22×10^{1}	$\mathrm{IIw}_{\mathrm{thiol}}\rightarrow\mathrm{IIw}_{\mathrm{thione}}$	4.78×10^{7}
$\mathrm{IIIw}_{\mathrm{thione}}\rightarrow\mathrm{IIIw}_{\mathrm{thiol}}$	*i*1406	2.9203	1.45×10^{2}	$\mathrm{IIIw}_{\mathrm{thiol}}\rightarrow\mathrm{IIIw}_{\mathrm{thione}}$	9.07×10^{9}

The obtained data indicate that the Wigner correction factors increase the reaction rates from 1.5 to 4.3 times. It is also found that the tunneling effect is significant for the prototropic tautomerism in such compounds. The comparison of the rate constants of forward (keto→enol or hione→thiol) and backward (enol→keto or thiol→thione) reactions revealed fast and slow tautomerization processes. Single proton transfer reactions (systems I and III in gas phase) approach the equilibrium concentrations in about 10^{13}, 10^{7} s (or 10^{8}, 10^{2} days). Such reactions are not of practical importance. In all other cases where double-proton transfer takes place, the equilibriums are reached in a fraction of seconds (approximately 10^{-1} to 10^{-9} s).

4. Conclusions

A comprehensive study of the prototropic tautomerism of the 9-methyl-2*N*-substituted guanines and thioguanines has been carried out. We investigated the effect of the substituents and influence of the polar environment on the mechanism of tautomerization and thermodynamics and kinetics of the tautomeric equilibrium. The principal conclusions can be summarized as follows:

(1) The high energy barrier rules out the possibility of a direct intramolecular gas phase proton transfer in the ground state of $I_{keto} \leftrightarrow I_{enol}$ system. This has been already established for a similar type of tautomers (*18*, *22*). Oxygen substitution by sulfur has a little effect on energy barriers.
(2) Substitution of $-OH$ by longer $-(CH_2)_4OH$ and $-(CH_2)_4SH$ groups at 2*N* position decreases the energy barriers approximately to two-fold.
(3) Aqueous environment also reduces the energy barriers approximately by half for $Iw_{keto} \leftrightarrow Iw_{enol}$ and $Iw_{thione} \leftrightarrow Iw_{thiol}$ tautomerization reactions. Consequently, tautomerization mechanism changes from direct intramolecular single proton to the water-assisted double proton transfer process. Similar pattern has been observed in other works (*18*, *19*). Bulk water environment does not introduce considerable changes to the energy barriers for the $II(or\ III)w_{keto} \rightarrow II(or\ III)w_{enol}$ and $II(or\ III)w_{thione} \rightarrow II(or\ III)w_{thiol}$ transitions.
(4) The calculated equilibrium constants suggest keto and thione species as predominant in the aqueous environment. Isolated keto and thiol tautomers are the dominant species in the gas phase.
(5) Tunneling effect is playing significant role for the studied tautomerization reactions.
(6) By varying the different substituents at 2*N* position, we added new characteristics to the well-known 2*N*-substituted oxo and thioguanines. The substitution of oxygen by sulfur atom in the studied tautomers may increase the probability of their mutation from keto to enol form in the gas phase, while decrease of such probability was observed in the polar solution.

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Supporting information available

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References

(1) Hirao, I. *Cur. Opin. Chem. Biol.* **2006,** *10,* 622.

(2) Sasami, T.; Odawara, Y.; Ohkubo, A.; Sekine, M.; Seio, K. *Tetrahed. Lett.* **2007,** *48,* 5325.
(3) Yasui, M.; Matsui, S.; Ihara, M.; Laxmi, Y.R.; Shibutani, S.; Matsuda, T. *Nucleic Acids Res*. **2001,** *29,* 1994.
(4) Terashima, I.; Matsuda, T.; Fang, T.-W.; Suzuki, N.; Kobayashi, J.; Kohda, K.; Shibutani, S. *Biochem.* **2001,** *40,* 4106.
(5) Caddell, J.M.; Chapman, A.M.; Cooley, B.E.; Downey, B.P.; LeBlanc, M.P.; Jackson, M.M.; O'Connell, T.M.; Phung, H.-M.; Roper, T.D.; Xie, S. *J. Org. Chem*. **2004,** *69,* 3212.
(6) Cristalli, G.; Lambertucci, C.; Taffi, S.; Vittori, S.; Volpini, R. *Curr. Top. Med. Chem.* **2003,** *3,* 387.
(7) Ono, M.; Kawakami, M. *Biochem.* **1977,** *81,* 1247.
(8) Saenger, W. *Principles of Nucleic Acid Structure*; Springer: New York, 1984.
(9) Leszczynski, J. *J. Phys. Chem.* **1993,** *97,* 3520.
(10) Leszczynski, J. *Int. J. Quant. Chem. Q* **1992,** *19,* 43.
(11) Zhanpeisov, N.U.; Cox, W.W.; Leszczynski, J. *J. Phys. Chem. A* **1999,** *103,* 4564.
(12) Sponer, J.; Leszczynski, J.; Hobza, P. *J. Phys. Chem. A* **1997,** *101,* 9489.
(13) Stewart, M.; Leszczynski, J.; Rubin, Y.; Blagoi, Y. *J. Phys. Chem. A* **1997,** *101,* 4753.
(14) Shukla, M.K.; Leszczynski, J. *J. Phys. Chem. A* **2002,** *106,* 8642.
(15) Stepanenko, T.; Lapinski, L.; Nowak, M.J.; Kwiatkowski, J.S.; Leszczynski, J. *Spectrochim. Acta A* **2001,** *57,* 375.
(16) Kang, H.; Lee, K.T.; Jung, B.; Ko, Y.J.; Kim, S.K. *J. Am. Chem. Soc.* **2002,** *124,* 12958.
(17) Padermshoke, A.; Katsumoto, Y.; Aida, M. *J. Phys. Chem. B* **2006,** *110,* 26388.
(18) Hu, X.; Li, H.; Liang, W.; Han, S. *J. Phys. Chem. B* **2005,** *109,* 5935.
(19) Fu, A.; Li, H.; Du, D. *J. Mol. Struct. Theochem*. **2006,** *767,* 51.
(20) Ahn, D.; Lee, S.; Kim, B. *Chem. Phys. Lett*. **2004,** *390,* 384.
(21) Markova, N.; Enchev, V.; Timtcheva, I. *J. Phys. Chem. A* **2005,** *109,* 1881.
(22) Contreras, J.G.; Madariaga, S.T. *J. Phys. Org. Chem.* **2003,** *16,* 47.
(23) Maran, U.; Karelson, M.; Katritzky, A.R. *Int. J. Quant. Chem*. **1996,** *23,* 1765.
(24) Frisch, M.J.; Trucks, G.W.; Schlegel, H.B.; Scuseria, G.E.; Robb, M.A.; Cheeseman, J.R.; Montgomery, J.A., Jr.; Vreven, T.; Kudin, K.N.; Burant, J.C. *et al. Gaussian 03*, Revision C.02; Gaussian: Wallingford, CT, 2004.
(25) Becke, A. *Phys. Rev.A* **1988,** *38,* 3098.
(26) Lee, C.T.; Yang, W.T.; Parr, R.G. *Phys. Rev.B* **1988,** *37,* 785.
(27) Vosko, S.H.; Wilk, L.; Nusair, M. *Can. J. Phys.* **1980,** *58,* 1200.
(28) Atkins, P.W. *Physical Chemistry*, Oxford University Press: Oxford, 1994.
(29) Pople, J.A.; Head-Gordon, M.; Raghavachari, K. *J. Chem. Phys.* **1987,** *87,* 5968.
(30) Cances, E.; Mennucci, B.; Tomasi, J. *J. Chem. Phys.* **1997,** *107,* 3032.
(31) Piacenza, M.; Grimme, S. *J. Comp. Chem.* **25,** *84,* (2003).
(32) Gerega, A.; Lapinski, L.; Nowak, M.J.; Furmanchuk, A.; Leszczynski, J. *J. Phys. Chem. A* **2007,** *111,* 4934.
(33) Mulliken, R.S. *J. Chem. Phys.* **1955,** *23,* 1833 (1955).
(34) Löwdin. P.-O.; *J. Chem. Phys*. **1950,** *18,* 365 (1950).
(35) Iacson, A.D.; Truhlar, D.G. *J. Chem. Phys.* **1989,** *90,* 1007.
(36) Yamada, T.; Fang, T.D.; Taylor, P.H.; Berry, R.J. *J. Phys. Chem. A* **2000,** *104,* 5013.
(37) Tzima, T.D.; Papayannis, D.K.; Melissas, V.S. *J. Chem. Phys.* **2005,** *312,* 169.
(38) Resende, S.M.; Ornellas, F.R. *Chem. Phys. Lett.* **2000,** *318,* 340.
(39) Wigner, E.P. *Z. Phys. Chem. Abt. B* **1932,** *19,* 203.

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Thio- versus oxo-derivatives of DNA bases: theoretical study on possible mutagenic effect of sulfur atom

Al'ona Furmanchuk and Jerzy Leszczynski*

Department of Chemistry, Computational Center for Molecular Structure and Interactions, Jackson State University, Jackson, MS, USA

Supplemental Material

I_{keto}			
7	1.047331	1.242514	−0.091601
6	1.237908	−0.110023	−0.114963
7	0.269613	−0.993308	−0.061933
6	−0.957188	−0.406843	−0.019515
6	−1.282792	0.949938	0.007741
6	−0.218076	1.922530	−0.028359
7	−2.154734	−1.074707	0.032086
6	−3.130692	−0.093383	0.079702
7	−2.649309	1.124300	0.070629
8	−0.242982	3.139827	−0.014229
7	2.551264	−0.544608	−0.273100
6	2.908213	−1.911885	0.062200
8	3.520002	0.393184	0.141365
1	1.862193	1.839809	−0.164911
1	−4.179828	−0.354666	0.126073
1	2.168458	−2.576052	−0.381751
1	2.924943	−2.083136	1.149977
1	3.894678	−2.115213	−0.356405
1	3.518153	0.381636	1.119016
6	−2.339989	−2.514575	−0.016091
1	−2.335563	−2.881168	−1.047591
1	−1.529520	−2.998758	0.531061
1	−3.293138	−2.770428	0.450592
I_{keto}TS			
7	1.080112	1.206979	−0.067752
6	1.232778	−0.133746	−0.105373
7	0.209148	−0.988697	−0.080350
6	−0.987647	−0.376415	−0.034288
6	−1.282405	1.002988	0.008974
6	−0.143684	1.828517	−0.000186
7	−2.209527	−0.999433	−0.009036
6	−3.155766	0.015137	0.049891
7	−2.647339	1.218532	0.060950
8	0.117583	3.082153	0.047712
7	2.514169	−0.642484	−0.267315

(*continued*)

*Corresponding author. Email: jerzy@ccmsi.us

Continued.

6	2.802624	−2.004512	0.162753
8	3.516940	0.246651	0.194285
1	−4.212400	−0.217930	0.077995
1	2.002893	−2.650501	−0.195520
1	2.869356	−2.079110	1.255409
1	3.753124	−2.308708	−0.279271
1	3.910076	0.591413	−0.621587
6	−2.440371	−2.433439	−0.010792
1	−3.496931	−2.622061	−0.208469
1	−1.838359	−2.903486	−0.791255
1	−2.170405	−2.874880	0.953183
1	1.327344	2.479373	−0.007819
I_{enol}			
7	1.133901	1.204332	−0.055567
6	1.239168	−0.151868	−0.098327
7	0.236182	−1.041986	−0.073358
6	−0.955228	−0.442559	−0.029644
6	−1.220574	0.940376	0.007346
6	−0.078322	1.752445	−0.002927
7	−2.190276	−1.044495	−0.000211
6	−3.114787	−0.009223	0.050569
7	−2.583091	1.184812	0.057318
8	−0.175675	3.086657	0.043771
7	2.523813	−0.619804	−0.249898
6	2.915319	−1.945246	0.181237
8	3.546523	0.311765	0.063184
1	−4.176634	−0.217561	0.080578
1	2.134650	−2.642423	−0.117521
1	3.056687	−1.990798	1.269550
1	3.853872	−2.204392	−0.312941
1	3.060670	1.160335	0.015945
6	−2.447359	−2.474651	−0.021388
1	−3.041431	−2.750045	−0.897556
1	−1.484049	−2.983462	−0.068826
1	−2.974079	−2.788940	0.884349
1	0.730521	3.434256	0.021599
II_{keto}			
7	0.375423	−0.428144	−0.073618
6	−0.035251	0.882060	−0.044781
7	−1.308816	1.230019	−0.018799
6	−2.141043	0.159864	−0.012054
6	−1.833296	−1.205055	0.026209
6	−0.449862	−1.581904	−0.004256
7	−3.512673	0.223121	0.011811
6	−3.953366	−1.090542	0.056939
7	−2.983336	−1.968343	0.069780
8	0.084180	−2.693882	0.007336
7	0.956133	1.832312	−0.036294
6	0.564369	3.236470	−0.061607
6	2.277091	1.493661	0.521846
6	3.302367	0.953903	−0.504761
6	4.270597	−0.103712	0.062130
6	3.591340	−1.407210	0.505534
8	2.756522	−1.859411	−0.556592
1	1.342284	−0.669800	−0.305756
1	−5.010219	−1.322118	0.083394
1	1.403930	3.829539	−0.432298
1	−0.286467	3.364309	−0.729801
1	0.275343	3.607902	0.931562
1	2.131498	0.767736	1.329414
1	2.665743	2.397807	0.998918

1	2.769928	0.512365	−1.351547
1	3.880731	1.788453	−0.916388
1	4.836087	0.299005	0.912858
1	5.004528	−0.342535	−0.715706
1	3.003427	−1.249116	1.422321
1	4.361015	−2.154378	0.746218
1	2.079238	−2.489834	−0.235086
6	−4.315114	1.433080	−0.029841
1	−3.675535	2.273469	0.242313
1	−4.721124	1.606710	−1.031726
1	−5.140139	1.360389	0.683054

$II_{keto}TS$

7	0.455934	−0.389145	−0.079508
6	0.019658	0.900768	−0.052731
7	−1.266445	1.252434	−0.040081
6	−2.086197	0.186163	−0.015645
6	−1.755135	−1.179835	0.038333
6	−0.375007	−1.481306	−0.005709
7	−3.458765	0.222613	0.006320
6	−3.874330	−1.100703	0.068610
7	−2.893693	−1.964103	0.091328
8	0.176930	−2.642687	−0.009624
7	0.998325	1.863056	−0.026244
6	0.599096	3.264271	−0.012307
6	2.325276	1.513017	0.514098
6	3.315371	0.901746	−0.511296
6	4.171534	−0.265162	0.026439
6	3.361934	−1.496675	0.477271
8	2.370426	−1.803298	−0.492986
1	1.553598	−0.867514	−0.372280
1	−4.927344	−1.349482	0.099213
1	1.432356	3.872715	−0.372252
1	−0.256585	3.405960	−0.671564
1	0.314153	3.610187	0.991703
1	2.181646	0.825209	1.354737
1	2.743856	2.429628	0.938190
1	2.753403	0.546270	−1.379192
1	3.981706	1.685526	−0.888432
1	4.799843	0.067302	0.864044
1	4.854961	−0.569393	−0.774512
1	2.898183	−1.311892	1.460740
1	4.036754	−2.352288	0.603404
1	1.360725	−2.449700	−0.172357
6	−4.284428	1.416439	−0.050703
1	−3.656181	2.273001	0.196323
1	−4.704401	1.561449	−1.051270
1	−5.099644	1.344582	0.673503

II_{enol}

7	−0.421014	−0.450844	−0.108264
6	0.018864	0.839860	−0.078153
7	1.302474	1.229880	−0.005919
6	2.145595	0.193617	0.011732
6	1.832803	−1.176198	−0.057679
6	0.458550	−1.457875	−0.113097
7	3.517868	0.244510	0.078811
6	3.947709	−1.075704	0.049364
7	2.980858	−1.951307	−0.032679
8	0.005209	−2.709834	−0.154171
7	−0.952272	1.806987	−0.125177
6	−0.577222	3.211919	−0.079657
6	−2.315251	1.451336	−0.531797
6	−3.214975	0.968898	0.628606

(*continued*)

Continued.

6	−4.296542	−0.051505	0.222696
6	−3.737945	−1.360585	−0.364778
8	−2.705742	−1.918628	0.443671
1	5.002864	−1.314539	0.088693
1	−1.426756	3.794033	0.286237
1	0.265404	3.347559	0.597813
1	−0.283706	3.599576	−1.065954
1	−2.247991	0.679537	−1.302544
1	−2.753972	2.332889	−1.009726
1	−2.578632	0.516427	1.394974
1	−3.692708	1.830029	1.109902
1	−4.989641	0.387767	−0.508167
1	−4.889605	−0.288473	1.113575
1	−3.376937	−1.196593	−1.391762
1	−4.536080	−2.107254	−0.424712
6	4.325718	1.447087	0.182264
1	3.678628	2.301559	−0.019278
1	4.752369	1.552922	1.184807
1	5.135421	1.426937	−0.551985
1	−0.977414	−2.696416	−0.137492
1	−1.996224	−1.237939	0.455208
Ithione			
7	1.001431	1.007948	−0.097016
6	1.273915	−0.331283	−0.114807
7	0.358684	−1.273119	−0.063853
6	−0.895438	−0.760141	−0.022950
6	−1.285143	0.586421	0.004688
6	−0.277691	1.595261	−0.029001
7	−2.055038	−1.486519	0.029575
6	−3.077796	−0.551319	0.078917
7	−2.658703	0.687599	0.069989
7	2.609150	−0.682915	−0.263054
6	3.057999	−2.021536	0.077884
8	3.518380	0.322763	0.119122
1	1.783387	1.650388	−0.163082
1	−4.112886	−0.863710	0.125861
1	2.358482	−2.736375	−0.352392
1	3.099312	−2.181203	1.166465
1	4.050324	−2.163277	−0.351887
1	3.534800	0.328180	1.096743
6	−2.171031	−2.934299	−0.016931
1	−2.152424	−3.300272	−1.048312
1	−1.336862	−3.378253	0.528638
1	−3.109361	−3.234374	0.453144
16	−0.424961	3.251700	−0.000277
$I_{thione}TS$			
7	1.128264	0.851732	−0.074598
6	1.174405	−0.498612	−0.105777
7	0.097676	−1.292502	−0.076185
6	−1.051131	−0.607144	−0.035067
6	−1.233122	0.794905	−0.001403
6	−0.054660	1.544561	−0.014755
7	−2.317031	−1.134283	−0.009836
6	−3.179132	−0.045969	0.041892
7	−2.578239	1.113857	0.046199
16	0.386145	3.209004	0.037370
7	2.417977	−1.095009	−0.265460
6	2.615088	−2.474469	0.160552
8	3.483784	−0.281342	0.191066
1	−4.251290	−0.192943	0.068284

1	1.783018	−3.070205	−0.210670
1	2.664441	−2.558999	1.253484
1	3.550627	−2.832996	−0.272131
1	3.879755	0.059266	−0.625318
6	−2.661444	−2.546170	0.008839
1	−3.579886	−2.708384	−0.559311
1	−1.847298	−3.105824	−0.453169
1	−2.802015	−2.906845	1.032754
1	1.653492	2.114428	−0.026893
I_{thiol}			
7	1.100471	0.979548	−0.063715
6	1.280922	−0.369441	−0.099817
7	0.331054	−1.321221	−0.070540
6	−0.889997	−0.794482	−0.031379
6	−1.226591	0.574561	−0.003780
6	−0.143072	1.459432	−0.015804
7	−2.093060	−1.459844	0.001443
6	−3.069079	−0.473284	0.044589
7	−2.598383	0.746904	0.043726
16	−0.412885	3.208258	0.038833
7	2.589574	−0.761588	−0.243389
6	3.065293	−2.056289	0.195526
8	3.554636	0.235222	0.040877
1	−4.118980	−0.735035	0.075177
1	2.327110	−2.803860	−0.089269
1	3.219743	−2.081810	1.282690
1	4.013555	−2.262053	−0.305230
1	3.008956	1.049337	0.008090
6	−2.276997	−2.901778	−0.011817
1	−2.794918	−3.235808	0.891743
1	−2.847868	−3.212959	−0.891328
1	−1.288534	−3.360945	−0.047243
1	0.899536	3.510321	−0.010768
II_{thione}			
7	0.301090	−0.328594	−0.011183
6	−0.059195	1.000579	0.019352
7	−1.321168	1.403141	0.002510
6	−2.195187	0.377341	−0.018001
6	−1.928464	−1.000918	0.030862
6	−0.574575	−1.420429	0.036310
7	−3.561101	0.489070	−0.035652
6	−4.044279	−0.812344	−0.000780
7	−3.107117	−1.721630	0.043243
16	0.032965	−2.990430	0.080056
7	0.951431	1.921563	0.068622
6	0.613652	3.337450	−0.014674
6	2.277903	1.562912	0.589023
6	3.319983	1.227907	−0.499367
6	4.397335	0.222536	−0.052143
6	3.824679	−1.139790	0.364120
8	2.841531	−1.515855	−0.595793
1	1.278905	−0.586675	−0.195866
1	−5.108697	−1.008467	−0.005170
1	1.485788	3.884256	−0.381238
1	−0.214322	3.477906	−0.708312
1	0.317738	3.750067	0.959493
1	2.154499	0.720771	1.275866
1	2.624029	2.399247	1.205731
1	2.800799	0.805516	−1.363161
1	3.801793	2.149095	−0.846335
1	4.991857	0.620666	0.780449

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1	5.089184	0.076501	−0.889020
1	3.385898	−1.088563	1.372216
1	4.634910	−1.880841	0.408728
1	2.327950	−2.297148	−0.296910
6	−4.322026	1.724235	−0.110399
1	−3.697469	2.535625	0.265524
1	−4.613344	1.950549	−1.141277
1	−5.220128	1.643489	0.506144
$II_{thione}TS$			
7	0.411507	−0.270726	−0.027320
6	−0.016637	1.024821	−0.008775
7	−1.297166	1.413730	−0.026776
6	−2.141849	0.376522	−0.017102
6	−1.825738	−0.993365	0.045581
6	−0.458868	−1.325359	0.028501
7	−3.513601	0.436013	−0.024345
6	−3.946214	−0.882771	0.031995
7	−2.978352	−1.758975	0.076840
16	0.161325	−2.948703	0.050178
7	0.958333	1.994098	0.034469
6	0.560216	3.395120	0.004388
6	2.286719	1.666198	0.565234
6	3.311974	1.212995	−0.502185
6	4.263472	0.089828	−0.044755
6	3.542814	−1.195365	0.391085
8	2.494320	−1.500443	−0.540764
1	1.661410	−0.762867	−0.363968
1	−5.002923	−1.117865	0.041557
1	1.415153	3.996840	−0.313704
1	−0.254397	3.531938	−0.706022
1	0.217320	3.755859	0.984776
1	2.165247	0.891750	1.328499
1	2.655704	2.552947	1.089528
1	2.765347	0.865495	−1.383155
1	3.906986	2.070241	−0.836083
1	4.898799	0.426417	0.785383
1	4.935389	−0.144446	−0.877766
1	3.122619	−1.097283	1.401538
1	4.241337	−2.037275	0.407714
1	1.694149	−2.366119	−0.226217
6	−4.320380	1.640854	−0.106298
1	−3.697437	2.486325	0.188520
1	−4.684569	1.807968	−1.125259
1	−5.174008	1.567025	0.571841
II_{thiol}			
7	0.366434	0.348213	−0.151649
6	−0.028824	−0.962757	−0.136422
7	−1.296329	−1.410547	−0.035927
6	−2.182718	−0.420378	0.023588
6	−1.918561	0.959638	−0.026148
6	−0.565360	1.309416	−0.114234
7	−3.550739	−0.522910	0.124375
6	−4.025888	0.781777	0.130899
7	−3.091180	1.691979	0.042065
16	−0.109710	3.019258	−0.169077
7	0.953461	−1.910491	−0.234192
6	0.593744	−3.319555	−0.159631
6	2.324209	−1.537784	−0.581067
6	3.209140	−1.220472	0.641127
6	4.399779	−0.297058	0.331714
6	3.973618	1.064499	−0.248515

8	2.905884	1.655410	0.479087
1	−5.087064	0.983649	0.201503
1	1.504287	−3.903844	−0.013293
1	−0.081172	−3.499890	0.679306
1	0.090944	−3.667428	−1.071888
1	2.273563	−0.675643	−1.248370
1	2.756655	−2.358429	−1.163318
1	2.587076	−0.734950	1.399202
1	3.568171	−2.152722	1.092591
1	5.097317	−0.775669	−0.369653
1	4.953461	−0.132061	1.263096
1	3.712050	0.961425	−1.313625
1	4.814438	1.764150	−0.200165
6	−4.313466	−1.755772	0.220389
1	−3.633907	−2.583378	0.013453
1	−4.734732	−1.883118	1.222465
1	−5.123380	−1.762763	−0.513899
1	1.227622	2.798622	−0.157469
1	2.117399	1.087623	0.349696

III_{thione}

7	−0.014604	−0.362329	0.062737
6	−0.369257	0.970711	0.071933
7	−1.628654	1.374074	0.029173
6	−2.510120	0.353406	−0.014838
6	−2.253581	−1.023514	0.022182
6	−0.901980	−1.459501	0.069892
7	−3.874636	0.477009	−0.063794
6	−4.367368	−0.820820	−0.059772
7	−3.436456	−1.736545	−0.005418
16	−0.303168	−3.017545	0.116803
7	0.625205	1.912409	0.113476
6	0.245704	3.319557	0.039485
6	1.986497	1.609908	0.557812
6	2.995750	1.517719	−0.596836
6	4.386742	1.012590	−0.176357
6	4.407345	−0.342461	0.549737
16	3.443234	−1.607229	−0.399020
1	0.962991	−0.637269	−0.020598
1	−5.432568	−1.009648	−0.093205
1	1.118023	3.898937	−0.271382
1	−0.550957	3.452042	−0.691475
1	−0.110472	3.700958	1.005728
1	1.969650	0.679325	1.130249
1	2.292165	2.390748	1.265850
1	2.580770	0.859997	−1.367262
1	3.102782	2.504056	−1.063845
1	4.869426	1.744860	0.484517
1	5.014715	0.950419	−1.072374
1	3.970538	−0.256784	1.548054
1	5.439091	−0.682737	0.666341
1	3.298278	−2.501150	0.596770
6	−4.624440	1.718093	−0.143721
1	−4.015810	2.517313	0.281376
1	−4.866358	1.972124	−1.181056
1	−5.551058	1.626725	0.427468

III_{thione}TS

7	−0.175352	−0.299962	−0.105563
6	0.209286	1.024033	−0.063137
7	1.483430	1.428432	0.038981
6	2.357102	0.422738	0.028483
6	2.081275	−0.952154	−0.111202

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6	0.733276	−1.311846	−0.159441
7	3.723189	0.510642	0.108139
6	4.191070	−0.795340	0.010872
7	3.250773	−1.691652	−0.121938
16	0.208925	−2.974311	−0.267918
7	−0.764680	1.969188	−0.135518
6	−0.407644	3.371240	0.048189
6	−2.089998	1.681099	−0.702536
6	−3.216320	1.571917	0.341011
6	−4.353850	0.629747	−0.086406
6	−3.899534	−0.800847	−0.442562
16	−2.723621	−1.536244	0.778789
1	−1.279506	−0.661452	0.243585
1	5.252492	−1.005280	0.042081
1	−1.305216	3.919429	0.341942
1	0.343029	3.469169	0.831650
1	−0.003946	3.815187	−0.871603
1	−2.005944	0.754387	−1.270764
1	−2.309633	2.469817	−1.432837
1	−2.786365	1.181973	1.267017
1	−3.623677	2.565462	0.564472
1	−4.895926	1.047854	−0.947467
1	−5.072428	0.581128	0.739376
1	−3.446186	−0.825809	−1.439962
1	−4.777038	−1.451606	−0.491942
1	−1.156801	−2.653983	−0.062452
6	4.498558	1.728689	0.280950
1	3.855613	2.574808	0.036019
1	4.845580	1.832360	1.313557
1	5.360244	1.723250	−0.390640
IIIthiol			
7	−0.051923	−0.319109	−0.463923
6	0.367562	0.975294	−0.342460
7	1.620529	1.385861	−0.054877
6	2.471234	0.370878	0.069545
6	2.183186	−0.998792	−0.063457
6	0.843525	−1.297748	−0.341327
7	3.817253	0.429840	0.350836
6	4.255545	−0.887133	0.370876
7	3.318052	−1.766997	0.129240
16	0.342632	−2.989825	−0.526085
7	−0.568883	1.955110	−0.545692
6	−0.196806	3.344949	−0.319832
6	−1.977938	1.627149	−0.738743
6	−2.778152	1.568536	0.572919
6	−4.224650	1.082230	0.399923
6	−4.381833	−0.321274	−0.202975
16	−3.561999	−1.681562	0.737850
1	5.293019	−1.122146	0.571414
1	−1.003737	3.982850	−0.686793
1	−0.026543	3.566497	0.741679
1	0.722389	3.585715	−0.858018
1	−2.020024	0.667690	−1.253480
1	−2.408699	2.380715	−1.409767
1	−2.252479	0.910284	1.273045
1	−2.791687	2.562799	1.036135
1	−4.773730	1.781097	−0.248319
1	−4.722055	1.105555	1.375809
1	−4.034574	−0.358012	−1.238759
1	−5.438452	−0.602838	−0.214478
6	4.592051	1.636179	0.586117

1	3.936282	2.489473	0.409317
1	4.956535	1.674138	1.617143
1	5.443155	1.689043	−0.098585
1	−0.945727	−2.693016	−0.790826
1	−2.291355	−1.272195	0.533644

Iw_{keto}

7	−1.124536	−0.516426	−0.099446
6	−0.775827	0.803401	−0.118593
7	0.462563	1.248110	−0.068247
6	1.367017	0.239810	−0.027950
6	1.142155	−1.139144	−0.007968
6	−0.213142	−1.607232	−0.029724
7	2.729571	0.390346	0.025830
6	3.249115	−0.894437	0.067335
7	2.335497	−1.830802	0.053777
8	−0.643850	−2.762305	0.007419
7	−1.808706	1.717541	−0.254567
6	−1.644060	3.098025	0.163743
8	−3.093813	1.207960	−0.017103
1	−2.117553	−0.789897	−0.121943
1	4.317710	−1.059485	0.112793
1	−0.666033	3.440475	−0.170292
1	−1.704476	3.208852	1.257349
1	−2.429852	3.691172	−0.306041
1	−3.172028	1.054888	0.945097
6	3.458563	1.646163	−0.012521
1	3.645979	1.966346	−1.042558
1	2.869262	2.413834	0.491156
1	4.412732	1.526808	0.504597
8	−3.336471	−2.221644	0.142312
1	−3.737844	−2.467145	−0.701002
1	−2.488480	−2.718830	0.162453

$Iw_{keto}TS$

7	−1.153183	−0.584982	−0.048852
6	−0.850750	0.732644	−0.111473
7	0.372253	1.255093	−0.090340
6	1.322917	0.305645	−0.034840
6	1.157577	−1.086199	0.020552
6	−0.176323	−1.561068	0.018137
7	2.680318	0.511539	−0.014816
6	3.252198	−0.751559	0.052193
7	2.382445	−1.727286	0.074284
8	−0.549928	−2.784105	0.075665
7	−1.919488	1.609083	−0.248665
6	−1.810495	2.991463	0.183658
8	−3.185670	1.059242	0.001707
1	4.327591	−0.872015	0.078057
1	−0.854735	3.383864	−0.159274
1	−1.861918	3.088678	1.279236
1	−2.629013	3.554066	−0.267610
1	−3.202227	0.802122	0.943902
6	3.354573	1.798311	−0.040059
1	4.129849	1.807029	−0.810684
1	2.610701	2.561662	−0.270324
1	3.808761	2.025096	0.929569
8	−2.885642	−2.265825	0.030797
1	−3.311225	−2.466195	−0.814421
1	−2.286006	−1.227586	−0.059937
1	−1.796466	−2.750766	0.055851

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Iw_{enol}			
7	−1.179501	−0.499635	−0.009221
6	−0.783982	0.787899	−0.104497
7	0.472022	1.251249	−0.108898
6	1.364702	0.258115	−0.039942
6	1.107685	−1.121522	0.047739
6	−0.253828	−1.471884	0.061253
7	2.734202	0.371539	−0.039791
6	3.218934	−0.926097	0.049598
7	2.288619	−1.843068	0.101938
8	−0.648522	−2.731915	0.143699
7	−1.797929	1.731052	−0.239739
6	−1.601518	3.100305	0.206481
8	−3.095074	1.267097	0.036401
1	4.284259	−1.117849	0.066712
1	−0.633823	3.444300	−0.154602
1	−1.624024	3.187114	1.303806
1	−2.397015	3.713720	−0.218970
1	−3.064982	0.883095	0.933275
6	3.493554	1.608878	−0.096814
1	4.298091	1.525657	−0.831842
1	2.813451	2.406734	−0.397163
1	3.922214	1.856631	0.879461
8	−3.295370	−2.263166	−0.085105
1	−3.628532	−2.450879	−0.972388
1	−2.908638	−1.360470	−0.143720
1	−1.644446	−2.756292	0.102548
IIw_{keto}			
7	0.019379	−0.512547	−0.442297
6	0.369011	0.820474	−0.396988
7	1.605222	1.219006	−0.142083
6	2.466399	0.195310	0.044042
6	2.221736	−1.181324	0.026886
6	0.885472	−1.615179	−0.225236
7	3.805098	0.322359	0.315974
6	4.289647	−0.971566	0.447030
7	3.377887	−1.893603	0.282773
8	0.428278	−2.766479	−0.269750
7	−0.602712	1.749337	−0.649726
6	−0.249476	3.158802	−0.496732
6	−2.031931	1.412930	−0.659158
6	−2.655727	1.257774	0.738175
6	−4.173949	1.027276	0.713120
6	−4.597354	−0.355780	0.196826
8	−4.068409	−1.390744	1.002794
1	−0.936435	−0.793284	−0.655331
1	5.334568	−1.151387	0.664310
1	−0.975176	3.759106	−1.050004
1	−0.251192	3.478098	0.553511
1	0.747337	3.331161	−0.899959
1	−2.192309	0.513446	−1.262031
1	−2.535679	2.219777	−1.201591
1	−2.187767	0.418128	1.263645
1	−2.432082	2.161050	1.318086
1	−4.669315	1.803938	0.111910
1	−4.555720	1.131619	1.735168
1	−4.297742	−0.479795	−0.855100
1	−5.695643	−0.411870	0.215331
1	−3.403319	−1.870232	0.476165
8	−2.146022	−2.377701	−0.771624
1	−2.405388	−2.834199	−1.580892

1	−1.256300	−2.749679	−0.521706
6	4.538588	1.568425	0.446156
1	4.466986	2.152722	−0.475007
1	4.138730	2.165813	1.269973
1	5.587050	1.340253	0.644948

$IIw_{keto}TS$

7	−0.024911	−0.527862	−0.445336
6	0.324707	0.798378	−0.387949
7	1.567640	1.219557	−0.137569
6	2.440946	0.220198	0.041047
6	2.199916	−1.164074	0.016479
6	0.871808	−1.544444	−0.234127
7	3.779641	0.345209	0.314714
6	4.264976	−0.951497	0.436842
7	3.358994	−1.877160	0.268782
8	0.431005	−2.762848	−0.276910
7	−0.646410	1.727902	−0.613510
6	−0.293085	3.135895	−0.449339
6	−2.073542	1.378106	−0.636594
6	−2.694978	1.196265	0.757301
6	−4.206055	0.923225	0.730018
6	−4.595276	−0.454090	0.165616
8	−4.009503	−1.512208	0.889871
1	−1.064220	−1.033785	−0.665514
1	5.309510	−1.133132	0.654720
1	−1.090163	3.742797	−0.882557
1	−0.166945	3.413695	0.604598
1	0.643071	3.348324	−0.966182
1	−2.212341	0.479308	−1.240928
1	−2.583493	2.186047	−1.171536
1	−2.203772	0.362516	1.270452
1	−2.496126	2.098663	1.348319
1	−4.726414	1.707556	0.160114
1	−4.582023	0.980995	1.758075
1	−4.337084	−0.511882	−0.904462
1	−5.688823	−0.551489	0.223149
1	−3.233670	−1.828915	0.377128
8	−1.874488	−2.097012	−0.726759
1	−2.169545	−2.313323	−1.621258
1	−0.639006	−2.702420	−0.466908
6	4.517078	1.591373	0.443265
1	5.242512	1.702641	−0.368122
1	3.798225	2.409714	0.394059
1	5.040543	1.629681	1.402317

IIw_{enol}

7	0.002837	−0.574469	−0.377962
6	0.366400	0.743998	−0.351189
7	1.610154	1.208145	−0.137472
6	2.501785	0.230739	0.034552
6	2.269861	−1.153850	0.032595
6	0.933040	−1.523219	−0.178667
7	3.848076	0.370031	0.268909
6	4.343932	−0.921892	0.394375
7	3.441717	−1.857376	0.261871
8	0.578790	−2.805380	−0.179051
7	−0.609358	1.680469	−0.570728
6	−0.252564	3.088174	−0.424089
6	−2.030433	1.337431	−0.630797
6	−2.705391	1.180039	0.742615
6	−4.232882	1.033399	0.669353
6	−4.734576	−0.289630	0.071783

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8	−4.341725	−1.410825	0.839999
1	5.396322	−1.091072	0.583890
1	−1.083760	3.695537	−0.787288
1	−0.043695	3.359849	0.618400
1	0.640791	3.314876	−1.008307
1	−2.148356	0.432259	−1.229244
1	−2.524910	2.139117	−1.190972
1	−2.284453	0.311736	1.261006
1	−2.458332	2.059076	1.350393
1	−4.662645	1.867478	0.094500
1	−4.639418	1.110877	1.684406
1	−4.403983	−0.388011	−0.974919
1	−5.832314	−0.264641	0.047161
1	−3.558566	−1.804880	0.417497
8	−2.080887	−2.248840	−0.667212
1	−2.300518	−2.407635	−1.594771
1	−1.500015	−1.434681	−0.648111
6	4.574565	1.622180	0.374325
1	4.453055	2.210836	−0.538712
1	4.207433	2.210741	1.219695
1	5.633653	1.404550	0.522368
1	−0.396125	−2.877470	−0.298345
Iw_{thione}			
7	−1.032680	−0.256480	−0.193197
6	−0.614769	1.044763	−0.162539
7	0.650030	1.415429	−0.069477
6	1.487182	0.358891	−0.032185
6	1.165830	−1.009309	−0.052199
6	−0.201376	−1.380045	−0.106683
7	2.852658	0.417740	0.060558
6	3.282967	−0.902182	0.087083
7	2.312308	−1.774831	0.027362
16	−0.869107	−2.923880	−0.054493
7	−1.590962	2.009700	−0.265477
6	−1.411155	3.358762	0.236924
8	−2.915211	1.562470	−0.262301
1	−2.043203	−0.443076	−0.204005
1	4.336473	−1.140749	0.154724
1	−0.376163	3.649028	0.062964
1	−1.630328	3.427537	1.312298
1	−2.081142	4.022515	−0.311832
1	−3.111832	1.186467	0.619045
6	3.664971	1.622891	0.090023
1	4.192960	1.764879	−0.857945
1	3.002934	2.472822	0.257546
1	4.393334	1.567589	0.902916
8	−3.607885	−1.251185	0.448070
1	−4.172166	−1.433356	−0.315332
1	−3.001766	−2.025382	0.484429
$Iw_{thione}TS$			
7	−1.122568	−0.228624	−0.052062
6	−0.652765	1.038599	−0.104632
7	0.627439	1.414857	−0.083546
6	1.452766	0.362236	−0.036261
6	1.102290	−0.999492	0.007969
6	−0.272581	−1.302788	0.004596
7	2.824670	0.391258	−0.006996
6	3.224378	−0.937302	0.047791
7	2.235266	−1.791238	0.060676
16	−0.917453	−2.910824	0.071265
7	−1.600454	2.048966	−0.238726

6	−1.312187	3.403837	0.199457
8	−2.926603	1.669825	0.020195
1	4.274573	−1.198156	0.079034
1	−0.320704	3.677559	−0.156865
1	−1.334083	3.500088	1.296328
1	−2.061297	4.066624	−0.235980
1	−2.973646	1.427563	0.965474
6	3.663103	1.577155	−0.056780
1	4.405023	1.553020	0.745651
1	4.176636	1.656825	−1.019901
1	3.020010	2.447882	0.074768
8	−3.301216	−1.405670	−0.027349
1	−3.721883	−1.434914	−0.900335
1	−2.482435	−0.658822	−0.077817
1	−2.460895	−2.277721	0.018372
Iw_{thiol}			
7	−1.060681	0.448875	0.017581
6	−0.752964	−0.878128	−0.025296
7	0.479214	−1.409607	−0.044845
6	1.434105	−0.481913	−0.022814
6	1.258683	0.912632	0.037927
6	−0.072060	1.345517	0.049179
7	2.795317	−0.674124	−0.033609
6	3.353573	0.594758	0.016741
7	2.476953	1.565620	0.060290
16	−0.442278	3.077945	0.084847
7	−1.821557	−1.750296	−0.152115
6	−1.612598	−3.180195	0.000309
8	−2.996270	−1.366172	0.536718
1	4.427926	0.726884	0.021889
1	−0.782085	−3.487718	−0.633422
1	−2.528951	−3.679085	−0.317371
1	−1.390160	−3.456886	1.039632
1	−3.463862	−0.752494	−0.070794
6	3.481872	−1.953882	−0.107434
1	4.252816	−2.016517	0.664642
1	2.742578	−2.738275	0.057899
1	3.941184	−2.098239	−1.089984
8	−3.758990	1.072946	−0.492255
1	−4.142468	1.301297	0.365391
1	−2.794991	0.974986	−0.303303
1	−1.771839	2.908725	−0.070609
IIw_{thione}			
7	−0.091755	0.430979	−0.387962
6	−0.363376	−0.922786	−0.391648
7	−1.579041	−1.404215	−0.162800
6	−2.498384	−0.446707	0.047781
6	−2.319257	0.945284	0.076047
6	−1.019531	1.452577	−0.148013
7	−3.827944	−0.653355	0.303019
6	−4.377698	0.611939	0.470106
7	−3.515172	1.584063	0.344350
16	−0.547511	3.073936	−0.138656
7	0.653490	−1.792119	−0.664832
6	0.356347	−3.221707	−0.580381
6	2.071639	−1.405413	−0.648056
6	2.680656	−1.302860	0.761885
6	4.215049	−1.231723	0.769734
6	4.812510	0.058759	0.189434
8	4.411793	1.206816	0.910089
1	0.856182	0.755026	−0.586619

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1	−5.431961	0.731646	0.684077
1	1.133912	−3.766282	−1.119689
1	0.324348	−3.580278	0.456271
1	−0.611600	−3.424287	−1.036515
1	2.205858	−0.471719	−1.200556
1	2.601499	−2.170862	−1.224371
1	2.281614	−0.421569	1.276315
1	2.361342	−2.177949	1.340367
1	4.632091	−2.093101	0.226945
1	4.557410	−1.318757	1.807267
1	4.561677	0.149313	−0.879601
1	5.907090	−0.012447	0.244902
1	3.673655	1.618417	0.426317
8	2.312802	2.047517	−0.769787
1	2.562367	2.393648	−1.636857
1	1.550546	2.619417	−0.478637
6	−4.499838	−1.938612	0.380916
1	−4.436807	−2.464246	−0.575699
1	−4.042432	−2.561809	1.153606
1	−5.549132	−1.771774	0.629290
$IIw_{thione}TS$			
7	−0.012575	0.432266	−0.392091
6	−0.301976	−0.911892	−0.378395
7	−1.526794	−1.409630	−0.154946
6	−2.452219	−0.471384	0.044300
6	−2.270129	0.923215	0.062675
6	−0.968996	1.384863	−0.161345
7	−3.786230	−0.667487	0.298229
6	−4.329367	0.602979	0.452648
7	−3.464207	1.572600	0.322480
16	−0.534316	3.069555	−0.143141
7	0.701061	−1.804529	−0.619086
6	0.375375	−3.226253	−0.514638
6	2.122476	−1.434222	−0.629282
6	2.745078	−1.306588	0.770385
6	4.269727	−1.119691	0.753985
6	4.751260	0.209337	0.148300
8	4.232962	1.333005	0.825171
1	1.068443	0.957953	−0.614256
1	−5.383186	0.731898	0.663723
1	1.227736	−3.799872	−0.881718
1	0.159448	−3.528643	0.517111
1	−0.502033	−3.458481	−1.119954
1	2.249517	−0.507698	−1.189917
1	2.641154	−2.212051	−1.199413
1	2.291998	−0.457577	1.293697
1	2.497652	−2.206165	1.347385
1	4.746151	−1.952132	0.214603
1	4.630962	−1.167473	1.787835
1	4.512347	0.244072	−0.927760
1	5.846680	0.243807	0.220879
1	3.420586	1.610896	0.354381
8	1.980232	1.845424	−0.710147
1	2.208024	2.017876	−1.635173
1	0.899782	2.712555	−0.417461
6	−4.467974	−1.948932	0.379928
1	−5.174904	−2.070081	−0.446217
1	−3.711714	−2.732173	0.319986
1	−5.003448	−2.038159	1.328858
IIw_{thiol}			
7	−0.040160	0.482816	−0.323888

6	−0.321017	−0.860924	−0.336721
7	−1.539193	−1.412296	−0.157470
6	−2.497104	−0.511625	0.028402
6	−2.346505	0.883299	0.066960
6	−1.041707	1.353919	−0.113885
7	−3.837274	−0.737740	0.239428
6	−4.409353	0.518734	0.390741
7	−3.559875	1.508433	0.297079
16	−0.770979	3.103361	−0.045629
7	0.701272	−1.743390	−0.557688
6	0.396736	−3.169225	−0.461667
6	2.112571	−1.357025	−0.608096
6	2.786819	−1.254446	0.771121
6	4.320434	−1.189279	0.709965
6	4.898392	0.075817	0.057836
8	4.537188	1.255966	0.745850
1	−5.471520	0.625312	0.570270
1	1.293834	−3.731198	−0.725766
1	0.080648	−3.457733	0.547678
1	−0.409640	−3.438053	−1.147839
1	2.206586	−0.420449	−1.155922
1	2.623074	−2.116947	−1.210621
1	2.406667	−0.372912	1.298675
1	2.492275	−2.128058	1.365671
1	4.708925	−2.070285	0.177035
1	4.710136	−1.244381	1.733180
1	4.604073	0.126336	−1.003242
1	5.993931	0.002320	0.071228
1	3.737122	1.611696	0.318102
8	2.253945	2.009294	−0.717195
1	2.363508	2.145966	−1.666853
1	1.520978	1.344886	−0.619661
6	−4.492458	−2.034002	0.290254
1	−5.215656	−2.139237	−0.523832
1	−3.721553	−2.797950	0.183578
1	−5.004018	−2.172031	1.246920
1	0.572987	3.040643	−0.209482

IIIW_{thione}

7	0.371252	0.417671	0.483190
6	0.670599	−0.928322	0.444952
7	1.879707	−1.380449	0.140096
6	2.767928	−0.401693	−0.106987
6	2.557393	0.985417	−0.103122
6	1.263397	1.462381	0.209206
7	4.084799	−0.575291	−0.444611
6	4.596819	0.703703	−0.622564
7	3.721235	1.654156	−0.431096
16	0.762843	3.073142	0.268177
7	−0.310610	−1.826870	0.762382
6	0.032982	−3.245700	0.672275
6	−1.743377	−1.496697	0.757467
6	−2.378205	−1.481243	−0.646751
6	−3.907275	−1.625758	−0.638760
6	−4.708558	−0.476087	−0.012724
16	−4.645866	1.121783	−0.936962
1	−0.565128	0.720788	0.763818
1	5.632738	0.853097	−0.898180
1	−0.725025	−3.816259	1.212639
1	0.075923	−3.602396	−0.364647
1	1.007840	−3.418614	1.126499
1	−1.909292	−0.545920	1.269546

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1	−2.229961	−2.259862	1.374319
1	−2.093665	−0.563755	−1.174021
1	−1.961663	−2.315750	−1.223232
1	−4.172982	−2.549960	−0.102949
1	−4.248040	−1.760067	−1.671198
1	−4.410820	−0.283452	1.021638
1	−5.766724	−0.750284	0.011070
1	−3.569292	1.631249	−0.295593
8	−2.015106	1.920821	1.097197
1	−2.195365	2.211972	2.001166
1	−1.309860	2.542036	0.774415
6	4.783568	−1.843849	−0.565988
1	5.485825	−1.987401	0.261013
1	4.039589	−2.640659	−0.542811
1	5.328799	−1.887556	−1.512268
IIw$_{thione}$TS			
7	0.289378	0.401222	0.469154
6	0.625000	−0.927995	0.420026
7	1.852173	−1.385246	0.135652
6	2.736972	−0.413238	−0.091760
6	2.507516	0.973411	−0.084053
6	1.202435	1.389798	0.209592
7	4.064228	−0.562311	−0.407103
6	4.557573	0.727048	−0.568726
7	3.666928	1.665205	−0.387855
16	0.715681	3.058627	0.247519
7	−0.339085	−1.859988	0.695996
6	0.033059	−3.268213	0.571105
6	−1.773734	−1.551423	0.712530
6	−2.414574	−1.471000	−0.685193
6	−3.947644	−1.565178	−0.670895
6	−4.702443	−0.427894	0.031243
16	−4.577858	1.225497	−0.779232
1	−0.823749	0.919255	0.778560
1	5.595969	0.893795	−0.825022
1	−0.764858	−3.873411	1.005253
1	0.183000	−3.572152	−0.472555
1	0.962118	−3.459612	1.108683
1	−1.941766	−0.626180	1.264788
1	−2.251851	−2.347781	1.293290
1	−2.101031	−0.545024	−1.179348
1	−2.027796	−2.298077	−1.292828
1	−4.240189	−2.509280	−0.185943
1	−4.301954	−1.626511	−1.705719
1	−4.400776	−0.322636	1.077323
1	−5.771479	−0.657864	0.035905
1	−3.401653	1.591457	−0.213304
8	−1.699303	1.763182	0.944588
1	−1.860668	1.899034	1.890187
1	−0.721819	2.625907	0.619780
6	4.784468	−1.818864	−0.528660
1	5.317542	−1.862673	−1.482001
1	5.499554	−1.943455	0.290224
1	4.053531	−2.627110	−0.488735
IIIw$_{thiol}$			
7	0.289056	0.426965	0.444937
6	0.635819	−0.898638	0.419143
7	1.865223	−1.386761	0.155283
6	2.760080	−0.433734	−0.083896
6	2.535485	0.952082	−0.104651
6	1.224088	1.352512	0.175306

7	4.092835	−0.589413	−0.381863
6	4.587601	0.695429	−0.564991
7	3.697382	1.639918	−0.409876
16	0.848291	3.082787	0.156020
7	−0.331738	−1.830108	0.697497
6	0.039070	−3.239474	0.596061
6	−1.764233	−1.520249	0.706603
6	−2.402366	−1.464256	−0.694228
6	−3.932489	−1.596120	−0.687845
6	−4.722644	−0.471760	−0.004410
16	−4.639665	1.172671	−0.842144
1	5.629435	0.853894	−0.812854
1	−0.777702	−3.840315	1.000400
1	0.231321	−3.551162	−0.438603
1	0.945977	−3.433908	1.170274
1	−1.929733	−0.585830	1.240851
1	−2.245641	−2.306876	1.298867
1	−2.106778	−0.535183	−1.193729
1	−1.994056	−2.286451	−1.294659
1	−4.204695	−2.541166	−0.192820
1	−4.279732	−1.680816	−1.723698
1	−4.420263	−0.332270	1.036773
1	−5.783884	−0.734984	0.006477
1	−3.569617	1.636722	−0.158773
8	−2.001445	1.833698	1.223145
1	−1.983246	1.951935	2.181521
1	−1.258969	1.212717	1.015266
6	4.807636	−1.848497	−0.491965
1	4.739795	−2.407905	0.444683
1	4.387227	−2.459716	−1.295192
1	5.856452	−1.641116	−0.710479
1	−0.459942	2.937528	0.485923