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Proceeding Paper

DFT Study on Ring-Chain Isomerism of Semicarbazones †

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Abstract: The conversion of semicarbazones to 1,2,4-triazolidin-3-ones and vice versa (ring-chain isomerism) was studied by the DFT B3LYP/6-311++G(d,p) method. The thermodynamic and kinetic characteristics of this reaction were calculated and discussed.

Keywords: semicarbazones; 1,2,4-triazolidin-3-ones; ring-chain isomerism; DFT calculations

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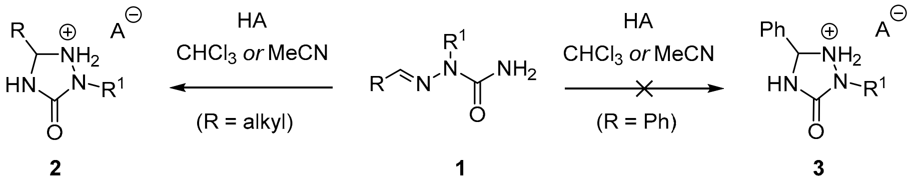
1. Introduction

Ring-chain isomerism is a phenomenon in which a molecule can exist in either cyclic or acyclic isomeric forms [1,2]. This type of isomerism is of great importance for understanding the structural features of various organic compounds and their chemical transformations. One of two principal pathways of chain-to-ring conversion involves intramolecular addition of a functional group to a polar multiple bond. The reverse reaction of elimination leads to the conversion of a cyclic compound into its acyclic isomer. Ring-to-chain transformation of functionalized hydrazones (and vice versa) (for review, see ref. [3]), in particular, aldehyde semicarbazones/1,2,4-triazolidin-3-ones interconversion is an important example of ring-chain isomerism from both practical and theoretical points of view. Indeed, aldehyde semicarbazones are readily available compounds and their closed-ring isomerization followed by oxidative aromatization of the formed 1,2,4-triazolidin-3-ones could give access to 2,4-dihydro-3*H*-1,2,4-triazol-3-ones possessing various useful properties [4–8]. However, the cyclization of aldehyde semicarbazones to 1,2,4-triazolidin-3-ones still remains practically unexplored. There is only one report on the study of the ring-chain isomerism of semicarbazones of aromatic aldehydes using ^{1}H NMR spectroscopy [9]. The authors demonstrated that all the 36 tested compounds in DMSO-d_6 solution exist only in acyclic semicarbazone form. This form is also the only one in CF_3COOD solution, except for 4 compounds of the series of 2,4-dimethyl-substituted semicarbazones, which give mixtures of the starting material with the corresponding 1,2,4-triazolidin-3-ones. It should be noted that all the experiments were performed in NMR tubes without isolating products. To the best of our knowledge, no preparative works on the chain-to-ring isomerization of any aldehyde semicarbazones into 1,2,4-triazolidin-3-ones have been described. There are a few reports on the one-pot syntheses of 1,2,4-triazolidin-3-ones by the reaction of some aromatic aldehydes with semicarbazide in the presence of complex catalysts [10–12], where the intermediate formation of semicarbazones followed by their cyclization is hypothesized. However, analysis of the reported spectroscopic data for the products obtained showed that, in at least in two studies (refs. [11,12]), these products were the corresponding semicarbazones and not 1,2,4-triazolidin-3-ones. It should be noted that one of these article [12] was retracted by the authors. Thus, the study of semicarbazones/1,2,4-triazolidin-3-ones interconversion remains a challenge for synthetic and theoretical chemistry. In continuation of our interest on ring-chain isomerism [13–15] and synthesis of polyaza compounds based on semicarbazones [16–19], we initiated a research program aimed to study the isomerization of semicarbazones into 1,2,4-triazolidin-3-ones.

Our preliminary experimental data showed that the cyclization of 2-alkylsubstituted semicarbazones of benzaldehyde **1** (R = Ph) does not proceed under various acidic conditions. In contrast, 2-alkylsubstituted semicarbazones of aliphatic aldehydes **1** (R = alkyl) completely cyclized under the action of very strong Brønsted acids (TfOH, HCl) in aprotic solvents at room temperature to give the corresponding salts of the N1-protonated 1,2,4-triazolidin-3-ones **2** (Scheme 1).



R = Et, Pr, *i*-Pr, Ph; R^1 = alkyl.

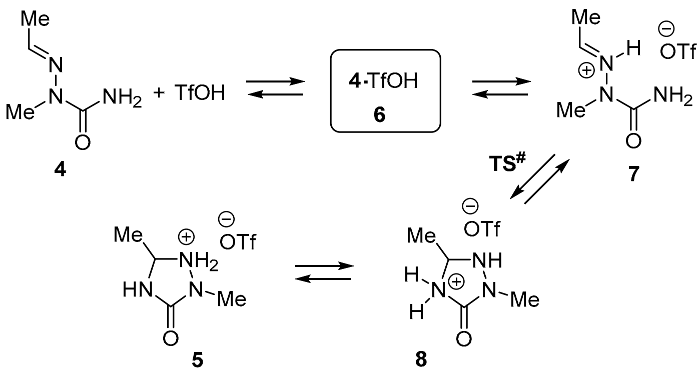
HA = Bronsted acid (TfOH, HCl, TsOH)

Scheme 1. Acid-promoted cyclization of 2-alkylsubstituted semicarbazones **1** to 1,2,4-triazolidin-3-ones **2** and **3**.

Herein, we report on the DFT B3LYP/6-311++G(d,p) study of the ring-chain isomerism of 2-alkylsubstituted semicarbazones. A plausible mechanism of this reaction is discussed. A comparison of chain-to-ring isomerization for 2-alkylsemicarbazones of aliphatic and aromatic aldehydes is presented.

2. Results and Discussion

Cyclization of 2-alkylsubstituted semicarbazones of aliphatic aldehydes was studied by the DFT B3LYP/6-311++G(d,p) method using ethanal 2-methylsemicarbazone (**4**) as a model compound and triflic acid as a promoter. Thermodynamic and kinetic parameters for the TfOH-promoted transformation of semicarbazone **4** into triazolidine salt **5** (Scheme 2) in $CHCl_3$ and MeCN solutions were calculated employing the polarizable continuum model. Table 1 and Figure 1 show the obtained results.



Scheme 2. TfOH-promoted cyclization of ethanal 2-methylsemicarbazone (**4**) to triazolidine salt **5**.

The calculations showed that the first step of the reaction involves the formation of the pre-reaction complex of semicarbazone **4** with TfOH (intermediate **6**) followed by the proton transfer to give triflate **7**. Noteworthy, the protonation leads to a significant change of the conformation via rotation around the N-N bond. Indeed, in $CHCl_3$ solution, the C=N-N-C dihedral angle in the most stable conformation of semicarbazone **4** is −179.46°, and in the intermediate **7** this angle is −94.58°. In MeCN solution, these angles are −179.49° and −99.42°, respectively (Figure 2a). This change is explained by a strong repulsion between the C=NH proton and one of the protons of the NH_2 group in the planar conformation of salt **7**.

Table 1. Relative electronic (ΔE, kcal/mol) and Gibbs free energies (ΔG, kcal/mol) of the transition state (**TS**#), the most stable stereoisomers of the intermediates **6–8**, and the final product **5** [a].

Compound or Transition State	$CHCl_3$ Solution		MeCN Solution	
	ΔE	ΔG	ΔE	ΔG
Pre-reaction complex of semicarbazone **4** with TfOH (intermediate **6**)	0.00	0.00	0.00	0.00
Triflate of protonated semicarbazone **4** (intermediate **7**)	−13.38	−9.63	−15.45	−11.88
Transition state (**TS**#)	1.56	6.31	−0.15	4.25
Triflate of N4-protonated triazolidinone (intermediate **8**)	−10.72	−4.23	−12.61	−5.77
Triflate of N1-protonated triazolidinone (product **5**)	−15.38	−9.31	−17.95	−12.98

[a] Calculations were performed at the B3LYP/6-311++G(d,p) level. Free energies at 298 K and 1 atm.

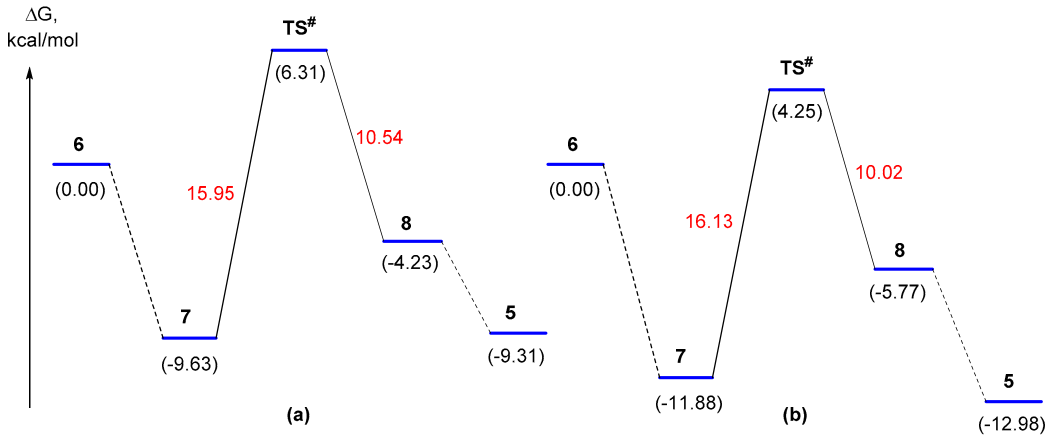


Figure 1. Energy diagram (B3LYP/6-311++G(d,p)) for the TfOH-promoted transformation of semicarbazone **4** into triazolidine salt **5** in $CHCl_3$ solution (**a**), and in MeCN solution (**b**).

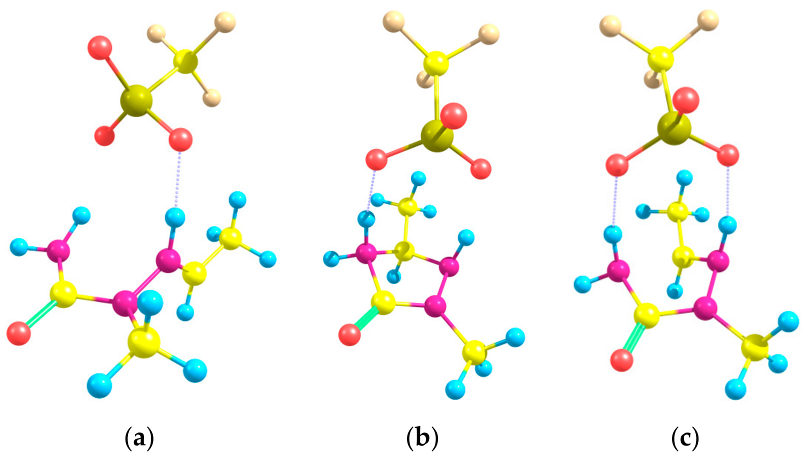


Figure 2. Optimized geometries for (**a**) intermediate **7**, (**b**) intermediate **8**, and (**c**) transition state **TS**# of the **7** to **8** conversion according to the DFT B3LYP/6-311++G(d,p) calculations in MeCN solution.

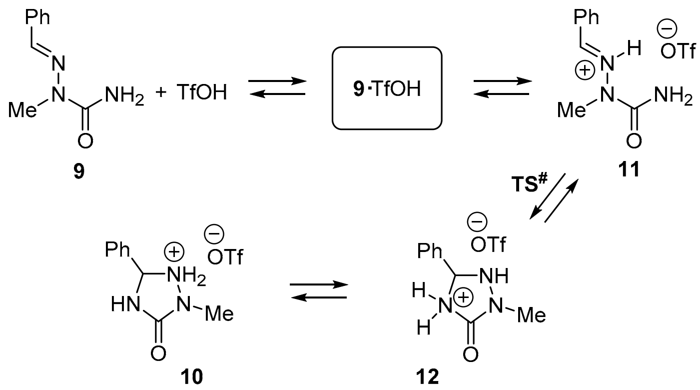
Interestingly, two oxygen atoms of the triflate anion in the formed non-planar conformation of salt **7** form two hydrogen bonds with the C=NH proton and one of the NH_2

protons. It should be noted that the described conformation of the intermediate **7** significantly facilitates its subsequent cyclization. The cyclization proceeds via the transition state **TS**$^{\#}$ (Figure 2c) to give the N4-protonated triazolidinone triflate (intermediate **8**) where two oxygen atoms of the triflate anion form two hydrogen bonds with the $N_{(1)}$-H and $N_{(4)}$-H protons (Figure 2b). The IRC analysis demonstrated that the found transition state connects the desired minima. The calculated activation barrier for the **7** → **8** transformation is rather low ($\Delta G^{\#}$ = 15.95 kcal/mol in $CHCl_3$, $\Delta G^{\#}$ = 16.13 kcal/mol in MeCN). The final step of the reaction involves the proton transfer from the $N_{(4)}$ nitrogen to the $N_{(1)}$ nitrogen to give more stable compound, the target product **5**.

Transformation of semicarbazone **7** to triazolidinone **5** is thermodynamically favorable (ΔG = −1.10 kcal/mol) in MeCN and unfavorable (ΔG = 0.30 kcal/mol) in $CHCl_3$ solution. However, precipitation of the cyclization products in $CHCl_3$ (our experimental data) undoubtedly changes the thermodynamic characteristics of the reaction resulting in its completion.

The DFT calculations also showed that Brønsted acid is required for cyclization of aliphatic aldehyde semicarbazones to the corresponding triazolidin-3-ones. For example, the cyclization of semicarbazone **4** to 2,5-dimethyl-1,2,4-triazolidin-3-one without an acidic promoter is thermodynamically very unfavorable (ΔG = 7.17 kcal/mol in $CHCl_3$, ΔG = 6.77 kcal/mol in MeCN).

In contrast to aliphatic aldehyde semicarbazones, no cyclization products formed from benzaldehyde semicarbazones in the presence of very strong Brønsted acid (vide supra). To explain this difference, we performed the DFT B3LYP/6-311++G(d,p) calculations using benzaldehyde 2-methylsemicarbazone (**9**) as a model compound. Thermodynamic and kinetic parameters for the TfOH-promoted transformation of semicarbazone **9** into triazolidine salt **10** (Scheme 3) in MeCN solution were estimated employing the polarizable continuum model.



Scheme 3. TfOH-promoted cyclization of benzaldehyde 2-methylsemicarbazone (**9**) to triazolidinone salt **10**.

The calculations showed that the cyclization of the intermediate salt **11** proceeds via the transition state **TS**$^{\#}$ to give the N4-protonated triazolidinone triflate **12** followed by proton transfer affording the final product **10**. The IRC analysis demonstrated that the found transition state connects the desired minima. The activation barrier $\Delta G^{\#}$ for the **11** → **12** transformation is low (19.67 kcal/mol in MeCN) (Figure 3).

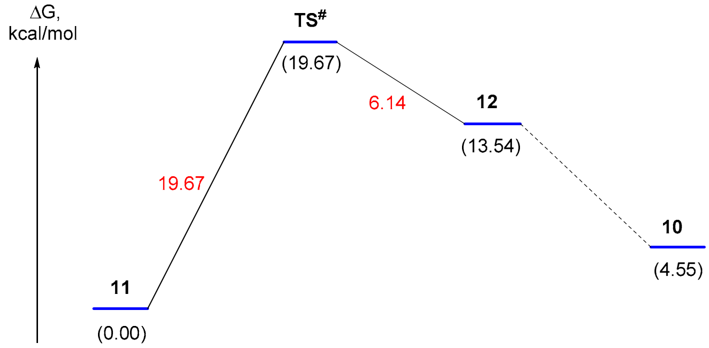


Figure 3. Energy diagram for the transformation of triflate **11** into triazolidine triflate **10** in MeCN solution.

However, the transformation of semicarbazone hydrotriflate **11** to triazolidinone salt **10** is thermodynamically unfavorable in MeCN (ΔG = 4.55 kcal/mol). This can be explained by the collapse of the π-π conjugation between the benzene ring and the C=N bond during the reaction.

3. Conclusions

In summary, aldehyde semicarbazones/1,2,4-triazolidin-3-ones chain-ring isomerism was first studied by the DFT B3LYP/6-311++G(d,p) method. Aliphatic aldehyde semicarbazones in the presence of very strong Brønsted acids (TfOH, HCl) in aprotic solvents ($CHCl_3$, MeCN) undergo protonation at the $N_{(1)}$ nitrogen, and the salts formed are completely cyclized at room temperature to give the corresponding salts of the N1-protonated 1,2,4-triazolidin-3-ones. The DFT calculations performed for the reaction of ethanal 2-methylsemicarbazone as a model compound with TfOH showed that the activation barrier of the cyclization is rather low (15.95 kcal/mol in $CHCl_3$, 16.13 kcal/mol in MeCN). From the thermodynamic viewpoint, the reaction in MeCN solution is favorable (ΔG = −1.10 kcal/mol) and in $CHCl_3$ solution is unfavorable (ΔG = 0.30 kcal/mol), however, precipitation of the product in $CHCl_3$ shifts the equilibrium towards the N1-protonated 1,2,4-triazolidin-3-one triflates. In contrast to aliphatic aldehyde semicarbazones, the cyclization of benzaldehyde semicarbazones does not proceed in the presence of very strong Brønsted acids, which is explained by unfavorable thermodynamics of this reaction. The DFT calculations performed for the reaction of benzaldehyde 2-methylsemicarbazone with TfOH in MeCN showed positive change in the Gibbs free energy (ΔG = 4.55 kcal/mol) with low activation barrier ($\Delta G^{\#}$ = 19.67 kcal/mol).

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