

A computational approach to the synthesis of 1,3,5-thiadiazinane-2-thiones in aqueous medium: theoretical evidence for water-promoted heterocyclization

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Abstract Based on experimental evidence and DFT studies, a probable cyclization route to 1,3,5-thiadiazinane-2-thiones in aqueous medium is proposed. Experimental facts suggest the formation of a {[hydroxymethyl (substituted) carbamothioyl] sulfanyl}methanol intermediate via reaction of dithiocarbamate (DTC) and formaldehyde. Nucleophilic addition of glycine to this intermediate generates an adduct that undergoes intramolecular heterocyclization via an S_N2 reaction. Computational calculations predict an active role of water in the reaction mechanism that promotes intramolecular cyclization.

Keywords Thiadiazinane-2-thione · DFT calculations · Water-promoted heterocyclization

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Introduction

For several years, 1,3,5-thiadiazinane-2-thione (THTT) ring (**1**) has been widely exploited in medicinal chemistry due to its excellent antiprotozoal and antimicrobial properties [1, 2]. The simplicity of the synthetic protocol and the use of readily available starting materials encouraged us to employ this heterocycle as the main core in the synthesis of potent antiparasitic compounds [3, 4].

Synthesis of the THTT ring **1** occurs via formation of the dithiocarbamate (DTC) salt (**2**). Several experimental protocols account for the generation of this key intermediate (Fig. 1). The most common strategy to generate **2** involves a classic nucleophilic addition of primary amines to carbon disulfide in an aqueous medium [1, 2] to yield the corresponding dithiocarbamic acid, which is converted to its salt derivative in the presence of a base. This methodology has also been extended to solid phase synthesis (SPS) protocols [5]. The COOH terminus of the 6-aminohexanoic acid is anchored to the acid-labile SASRIN resin using standard coupling conditions (DIC/DMAP/DMF). Subsequent addition of CS_2/KOH in dioxane yields the desired resin-bound DTC. The presence of this intermediate was confirmed by NMR analysis following cleavage of a small sample in the presence of 3% TFA/DCM. The above strategies proved ineffective when electroacceptor substituents were incorporated at position 3 of the heterocycle ring. In this case, **2** is formed by reaction of a substituted isothiocyanate and an alkaline hydrogensulfide [6]. However, the low commercial availability of substituted isothiocyanates has limited the synthetic scope of this latter process. Addition of formaldehyde and a second primary amine provided the rest of the key building blocks to build the THTT ring. Despite being

Fig 1 Methods to generate the dithiocarbamate (DTC) salt as key intermediate in the synthesis of thiaziazinane-2-thione

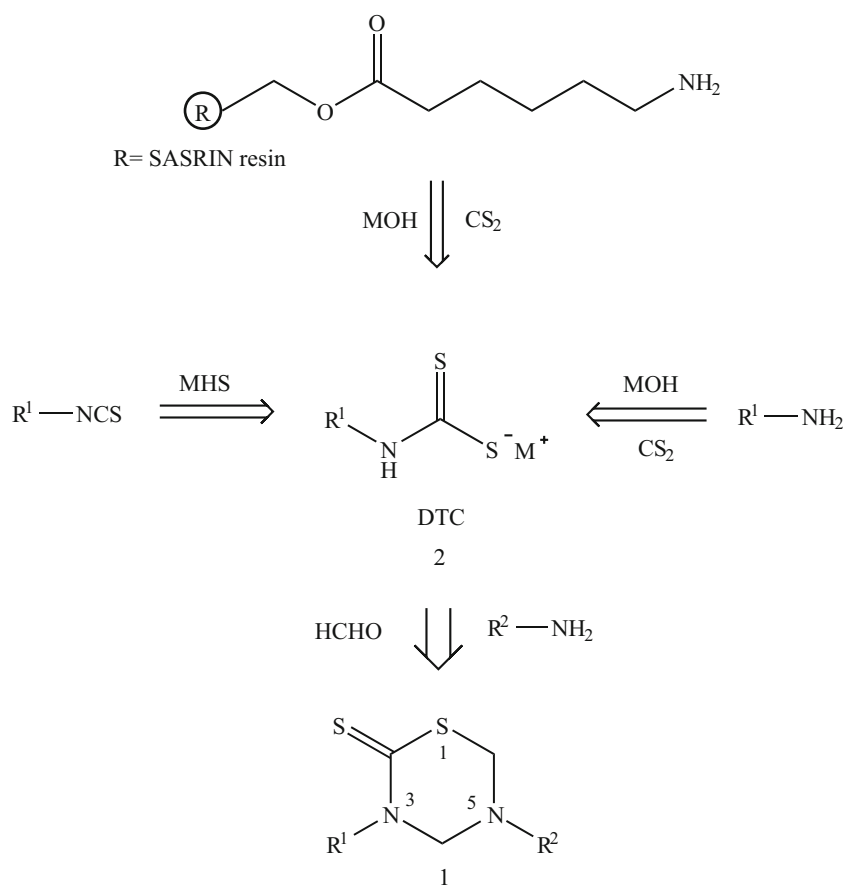
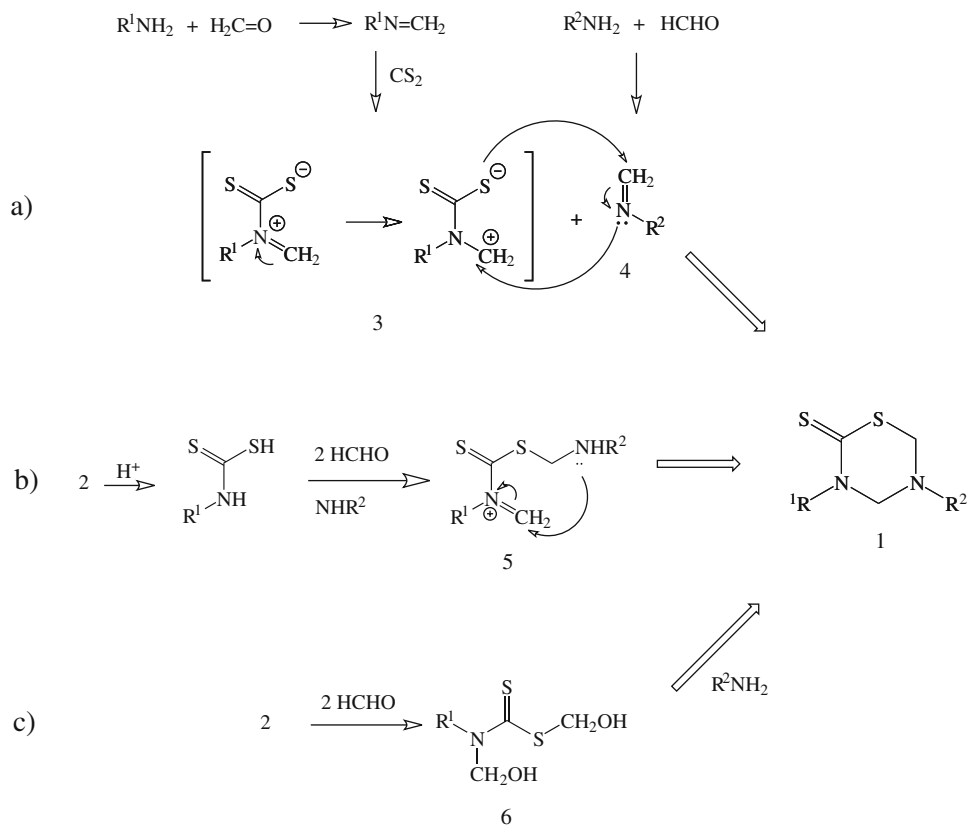


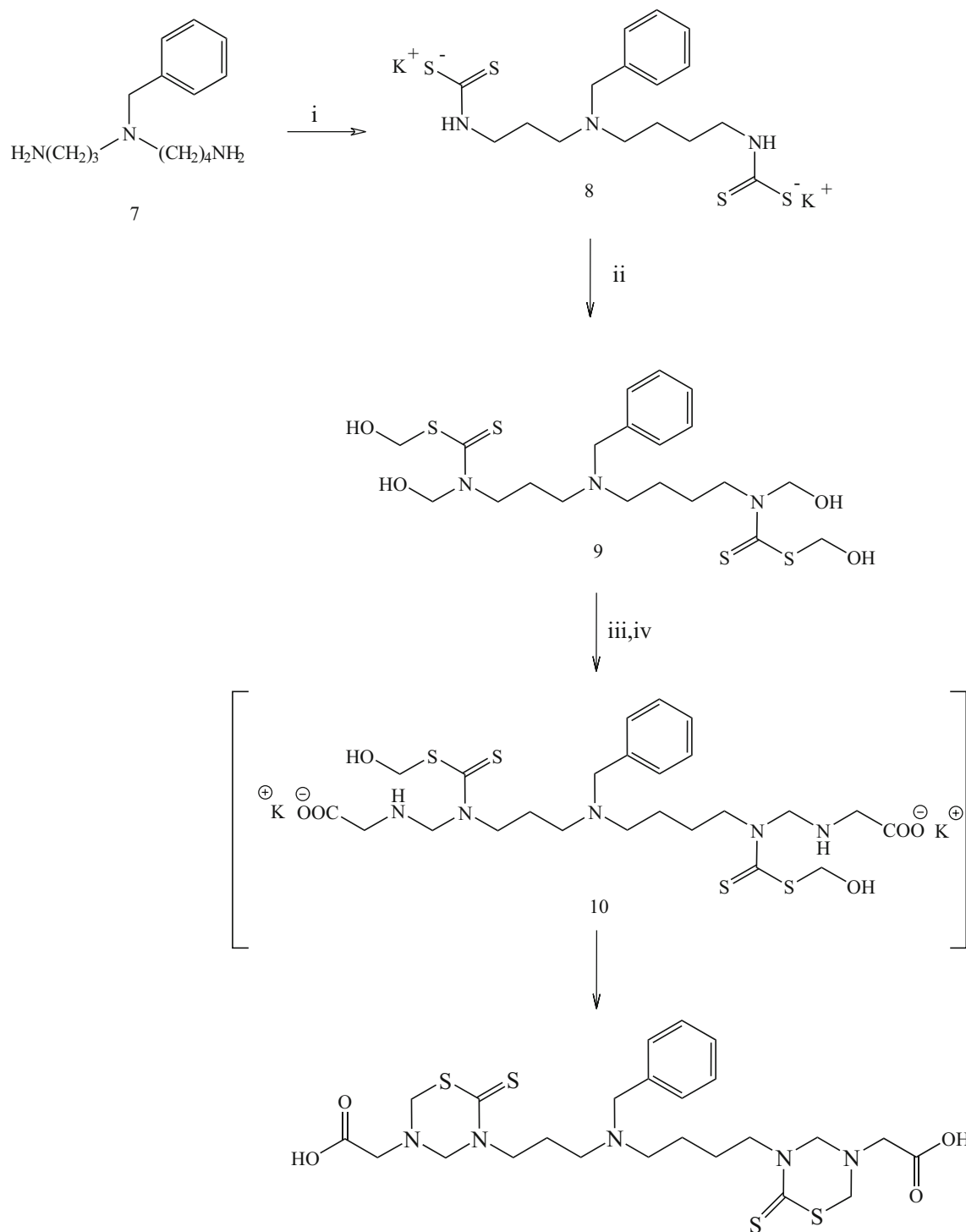
Fig 2 Proposed reaction mechanism for the generation of the thiaziazinone-2-thione ring



considered a multi-component reaction, the reactants are added in a stepwise fashion. An interesting modification to the classical synthetic protocol in the preparation of 2,3-bis(5-alkyl-2-thiono-1,3,5-thiadiazin-3-yl) derivatives was recently reported [7]. According to the authors, formation of the thiadiazinane ring is performed via a one pot domino

reaction between the pre-formed bis-DTC, formaldehyde and the amino acid component.

Undoubtedly, one of the least explored aspects regarding the synthesis of thiadiazinane-2-thiones has been the study of the reaction pathway from the corresponding DTC. In early works, Schorr et al. [8] proposed a 1,4



Scheme 1 Reagents: *i* $\text{H}_2\text{O}/\text{KOH}$ (20%), CS_2 , rt; *ii* HCHO (37%); *iii* $\text{H}_2\text{N-CH}_2\text{-COOK}$, buffer phosphate (pH 7.8); *iv* HCl (7%)

dipolar cycloaddition mechanism (Fig. 2a). Accordingly, the reaction between a primary amine, formaldehyde and CS₂ yielded the dipole **3**, which reacts with the substituted methyldieneamine dipolarophile **4**, generated in situ by condensation of a second primary amine with formaldehyde, to afford **1**. In another approach (Fig. 2b) the preformed DTC is allowed to react simultaneously with formaldehyde and the corresponding amine to produce [substituted(aminomethyl)methanethionyl]methylidenazanium **5** [7]. This species possesses two different reactive centers in the same molecular backbone, a protonated imine and a thiosulfanylmethylamino group. Intramolecular addition of the secondary amino group to the carbon atom of the methylene moiety leads to **1**. Formation of THTT ring **1** via a {[hydroxymethyl (substituted) carbamothioyl] sulfanyl}methanol intermediate **6** [9] is proposed in Fig. 2c. This process involves in situ generation of **6** from the corresponding DTC and formaldehyde followed by condensation with a primary amine. Recently, the isolation and characterization of an analog of **6**, via a crystallization process induced by the presence of KOH, was reported [10], providing strong experimental support to the hypothesis depicted in Fig. 2c. Based on this assumption, and taking into account the importance of a good understanding of the reaction mechanism on the effective exploitation of molecular diversity and the improvement of existing synthetic protocols, we report a preliminary DFT study aimed at predicting the probable cyclization mechanism of the thiadiazinane-2-thione from an intermediate of type **6**. To our knowledge, this is the first computational study of the reaction mechanism of this type of heterocyclic system.

Methods

Geometry optimizations were carried out with the Gaussian 03 suite of programs [11]. First-principle computations with the hybrid functional B3-LYP, corresponding to Becke's three-parameter exchange functional [12] along with the correlation functional developed by Lee, Yang, and Parr [13] ensure a high level of theory. The basis set used was a double split-valence Gaussian basis set [14, 15], augmented by 6-31G* [16]. Geometrical convergence was obtained with at least a tight criterion, without imposed symmetry restrictions. Charges were calculated by using natural bond order (NBO) population analysis using the NBO program as implemented in Gaussian [17, 18]. Transition states were calculated by using the synchronous transit-guided quasi-newton (STQN) method [19]. Frequency calculations were used to confirm the nature of the stationary points. Reported thermochemical properties were calculated at 1 atm and 298.15 K.

Results and discussion

The previously synthesized 2-(5-(4-(benzyl(3-(5-(carboxymethyl)-2-thioxo-1,3,5-thiadiazinan-3-yl)propyl)amino)butyl)-6-thioxo-1,3,5-thiadiazinan-3-yl)acetic acid (**11**) [20] was adopted as a case study. The synthetic route leading to this derivative from the corresponding N⁴-(benzyl)spermidine (**7**) [21] is depicted in Scheme 1.

The initial step involved reaction of the polyamine **7** with CS₂/OH⁻ to afford the expected bis-dithiocarbamate salt **8**. According to Aboul-Fadl et al. [10], condensation of

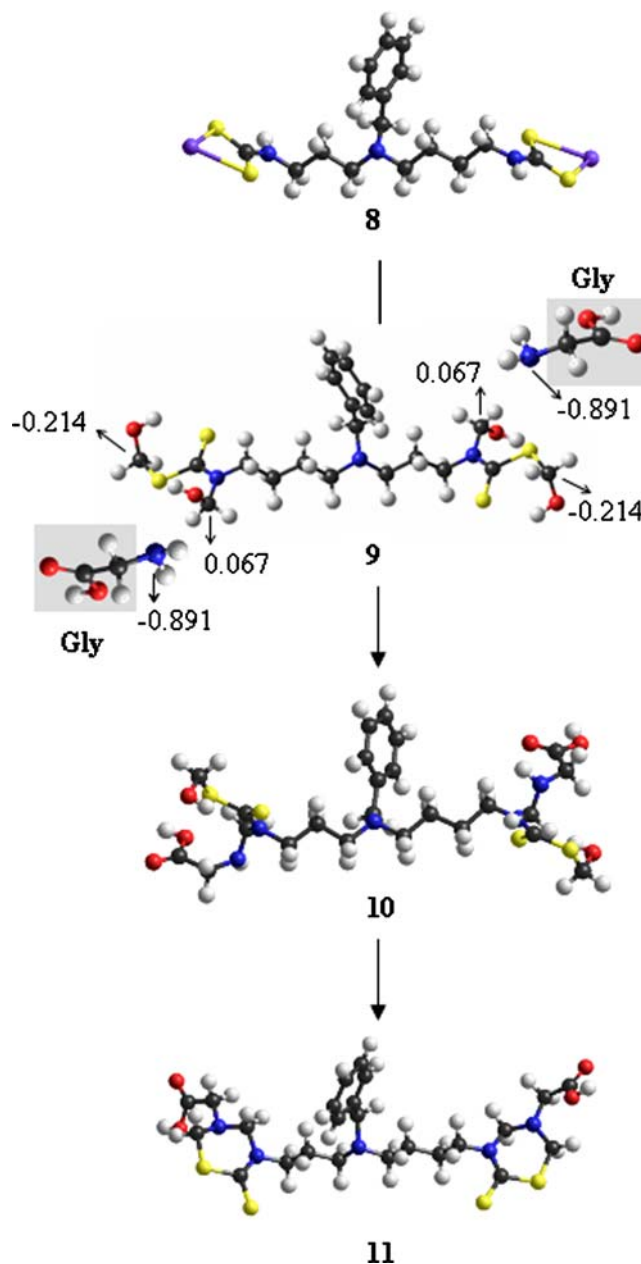
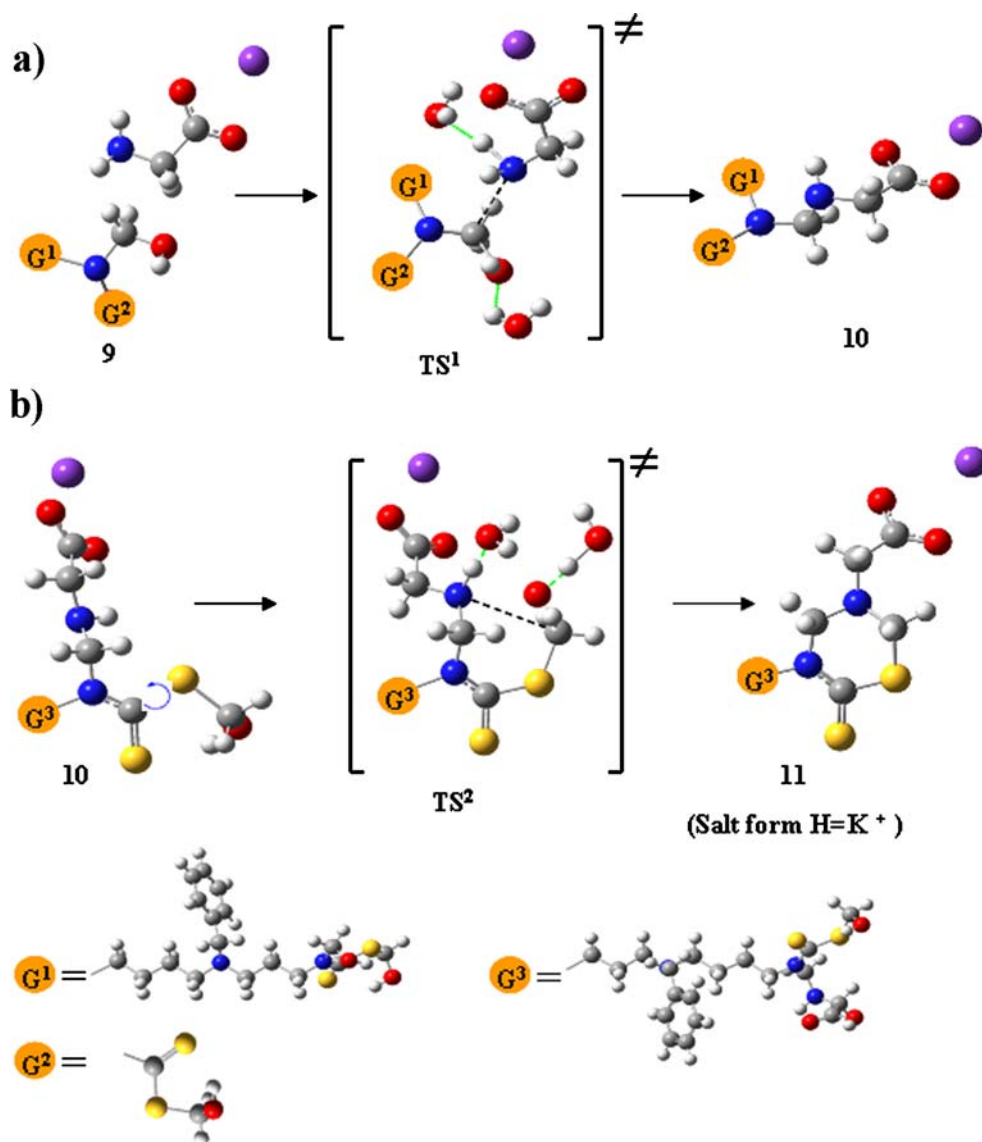


Fig 3 Calculated structures (B3LYP/6-31G*) for all intermediates and the final product, using Gly as amino acid. Gray Carbon; blue nitrogen; yellow sulfur; white hydrogen; red, oxygen and purple potassium

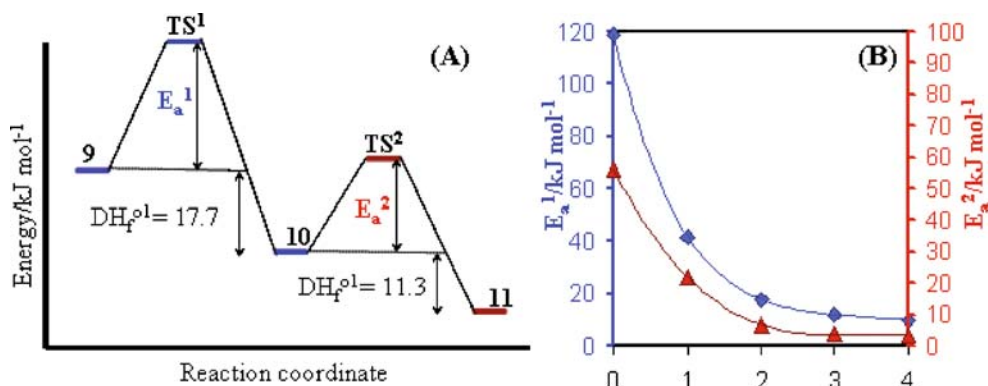
Fig 4 Proposed mechanism (B3LYP/631-G*) for S_N2 reactions (a) and (b), using glycine as amino acid. Water molecules are shown only for transition states. Gray Carbon; blue nitrogen; yellow sulfur; white hydrogen; red, oxygen and purple potassium



8 with formaldehyde is likely to afford [(3-[benzyl(4-hydroxymethyl)([hydroxymethyl]sulfanyl)methanethioyl)amino]butyl)amino]propyl(hydroxymethyl)carbamothioyl sulfanyl]methanol (**9**). With the aim of obtaining mechanistic

information beyond this point, geometry optimization of all proposed intermediates and final compounds was carried out using ab initio/DFT calculations at the B3LYP/6-31G* level of theory (Fig. 3).

Fig 5 a Energy profiles for S_N2 reactions; b decrease in activation energy as a function of the number of water molecules



Initially we focused our attention on the reaction between intermediate **9** and glycine. Despite the asymmetrical nature of the connective spermidyl moiety, the calculated atomic charge distribution of the molecular fragments, located at both ends of structure **9**, was the same. For this intermediate, nucleophilic addition of the amino acid is more likely to occur at the slightly positive carbon atom of the hydroxymethylene moiety directly attached to the nitrogen atom to generate species **10** (see Fig. 3). Interestingly, this adduct has the glycine residues oriented both above and below the plane defined by the polyamine backbone, whereas the predicted structure for compound **11** shows both THTT rings projected in opposite directions with respect to the benzyl moiety, presumably with the aim of minimizing steric hindrance among these bulky molecular fragments. Even though the structures depicted in Fig. 3 were modeled using the glycine it is not expected that the presence of different amino acids residues would induce dramatic conformational changes to the thiadiazinone-2-thione ring.

In order to support the synthetic pathway depicted in Scheme 1, transition state searches were calculated at the same level of theory but using a simplified representation of species **9**, **10** and the potassium salt of **11** as inputs, respectively. The computational study revealed a reaction mechanism where water is actively engaged in the heterocyclization process promoting the S_N2 reactions, Fig. 4a,b. Calculation of transition states TS^1 and TS^2 , and the influence of different solvation stages on the predicted model, provided some theoretical evidence for the proposed mechanism. Figure 5a shows the energy profiles of both reactions with the associated enthalpy of formation ΔH_f . Even though ΔH_f remains constant regardless of the amount of water molecules involved, the activation energy decreases exponentially as a function of the addition of water molecules (Fig. 5b). When one molecule of H_2O is present, it is H-bonded to the leaving amino proton, thus promoting attack of the amino group to the carbon of the S-methyl group. This water molecule decreases the activation energy by almost 50% in both cases. When another water molecule is added (see TS^1 and TS^2 in Fig. 4), it allows for hydration of the hydroxyl group and stabilization of the resulting hydroxide ion by strong solvation. In organic solvents, elimination of naked hydroxide is a very unfavorable process. In water, however, the hydroxide ion can leave with hydrating water molecules and the negative charge can be delocalized in the water cluster. In a real system, a greater number of water molecules would be involved in solvation, lowering the activation energy more efficiently. Recently, direct use of allyl alcohol for the Tsuji-Trost reaction without activators, reported by Kinoshita et al [22], also supported hydroxide elimination assisted by water. As seen in Fig. 5, the activation energy for the first

nucleophilic substitution is significantly larger than that calculated for the second substitution due to the effectiveness of the intramolecular heterocyclization step.

Conclusions

To summarize, based on experimental facts and DFT studies, a probable cyclization route to the 1,3,5-thiadiazinanes-2-thione ring from the corresponding {[hydroxymethyl (substituted) carbamothioyl] sulfanyl}methanol intermediate in aqueous medium is proposed. Notably, water not only contributes to the reaction as a mere solvent, but also plays an active role in the reaction mechanism; both S_N2 reactions are promoted by hydroxide elimination, as a consequence of lowering the activation energy. To our knowledge, this is the first computational study on the formation of the thiadiazinane-2-thione ring.

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