Theoretical Study of the Mechanism of the Formation of Azomethine Ylide from Isatine and Sarcosine and Its Reactivity in 1,3-Dipolar Cycloaddition Reaction with 7-Oxabenzonorbornadiene †

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† Dedicated to Professor Ronald N. Warrener on the occasion of his 90th birthday.

Abstract: The reaction mechanism of the formation of azomethine ylides from isatins and sarcosine is addressed in the literature in a general manner. This computational study aims to explore the mechanistic steps for this reaction in detail and to assess the reactivity of formed ylide in a 1,3-dipolar cycloaddition reaction with 7-oxabenzonorbornadiene. For this purpose, density functional theory (DFT) calculations at the M06-2X(SMD,EtOH)/6-31G(d,p) level were employed. The results indicate that CO2 elimination is the rate-determining step, the activation barrier for 1,3-dipolar cycloaddition is lower, and the formed ylide will readily react with dipolarophiles. The substitution of isatine with electron-withdrawal groups slightly decreases the activation barrier for ylide formation.

Keywords: 1,3-dipolar cycloadditions; DFT calculations; isatine; azomethine ylide; reaction mechanism

1. Introduction

The synthetic utility of azomethine ylides in the formation of heterocyclic molecules via their involvement in 1,3-dipolar cycloaddition with olefinic bonds has been well recognized and explored in numerous reactions [1,2]. An important strategy for the synthesis of complex structures possessing pyrrolidine rings is via 1,3-dipolar cycloadditions of azomethine ylides that are generated in situ from carbonyl compounds and appropriate amino acids. This approach has found wide applications, such as functionalization of fullerences through the Prato reaction, in which aldehydes and sarcosine (N-methylglycine, 2) are employed [3]. Similarly, isatine (1) and sarcosine (2) have been used as precursors for the in situ generation of azomethine ylide reagent for subsequent 1,3-dipolar cycloaddition with the C=C bond of 7-oxabenzonorbornadiene (3) and its derivatives [4]. The reaction is shown in black color in Figure 1a. It is important to note that the reaction benefits from polar (alcoholic) solvents such as ethanol and methanol, while lower yields can be achieved with less polar solvents.

While the syntheses of pyrrolidines utilizing the formation of azomethine ylides from carbonyl compounds and sarcosine have been described, mechanistic studies are scarce. As far as we are aware, published computational studies are focused on the regio- and stereoselectivities of 1,3-dipolar cycloadditions [5,6], while studies which explore the full reaction mechanism and, particularly, the formation of azomethine ylides are rather limited [7].

In the literature, the reaction mechanism is, in general, just briefly outlined. For example, the proposed reaction mechanism (red color, Figure 1a) involves the formation...
of cyclic intermediate 5 via dehydration in the first step, followed by opening of the 5-membered ring and decarboxylation. Once formed, azomethine ylide 7 reacts with 7-oxabenzonorbornadiene 3, resulting in the formation of adduct 4. Also, a more detailed mechanism of the formation of azomethine ylides from modified glycine and aldehydes (containing the desired R" group) was proposed by Henderson et al. [8] (Figure 1b). The latter mechanism could be utilized for the description of the formation of azomethine ylide from isatine and sarcosine as well. This is exactly the main goal of this study. We reinvestigate the reaction mechanism of the model reaction in detail using DFT calculations. The effect of functionalization of isatine in position C6 (the numbering scheme is given in Figure 1a) is studied as well.

Figure 1. (a) Model reaction (black) studied herein with reaction mechanism (red) from Ref. [4]. (b) Mechanism of formation of azomethine ylide from modified glycines and aldehydes from Ref. [8].

2. Results and Discussion

Mechanistic investigations of the reaction were started by geometry optimization of reactants: isatine 1, sarcosine 2, and 7-oxabenzonorbornadiene 3 (Figure 2). Contrary to 1 and 3, sarcosine is conformationally flexible, and several minima on the potential energy surface were found (2, 2a–2d, Figure 2). The most stable structure (global minimum 2) had an intramolecular hydrogen bond between the amino nitrogen atom (N12) and the hydrogen (H17) atom from the carboxylic group.

Although other stretched-out structures 2a–2d (found as local minima on the potential energy surface of 2) are a few kcal mol\(^{-1}\) less stable, they have better nucleophilic properties. The nucleophilic power of the N12 atom in these structures was evaluated from calculated values of the condensed-to-atoms Fukui functions (\(f\)) (see Figure 2). Parr and Yang proposed that a larger Fukui function value at an atom favors its reactivity [9,10]. Therefore, it is assumed that a stretched molecule is better for the formation of the van der Waals complex when isatine and sarcosine are in favorable orientation for the first reaction step. Indeed, in
structure 15 (Figure 3), a lone pair from N12 is in electrostatic interaction with a positively charged C3 atom from the carbonyl group on isatine, and also, a new H bond between H17 and O11 is formed. This orientation allows for the simultaneous closing of the bond between C3 and N12 atoms and the proton transfer of H17 from O16 to O11. In the TS1 structure, the C3-N12 bond length is 1.979 Å, and in intermediate zwitterion structure 16, it assumes a value of 1.558 Å. At the same time, the distance between O11 and H17 decreases from 1.463 in TS1 to 1.051 Å in 16, confirming the simultaneous occurrence of these two geometrical changes (Figure 3 and Table 1).

![Figure 2](image)

**Figure 2.** Optimized structures of reactants by M06-2X/6-31G(d,p) methods using SMD(EtOH) solvation model (relative energies of different conformers of sarcosine 2 are given in kcal mol\(^{-1}\) in parentheses). The condensed-to-atoms Fukui functions (\(f\)) for selected atoms are given as well.

**Table 1.** List of transition structures and their imaginary frequencies.

<table>
<thead>
<tr>
<th>Transition</th>
<th>Structure</th>
<th>Freq/cm(^{-1})</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>TS1</td>
<td><img src="image" alt="TS1" /></td>
<td>−179.8</td>
<td>Nucleophilic addition + simultaneous proton shift</td>
</tr>
<tr>
<td>TS2</td>
<td><img src="image" alt="TS2" /></td>
<td>−69.9</td>
<td>Rotation around the C13-N12 bond</td>
</tr>
<tr>
<td>TS3</td>
<td><img src="image" alt="TS3" /></td>
<td>−931.0</td>
<td>Proton transfer</td>
</tr>
<tr>
<td>TS4</td>
<td><img src="image" alt="TS4" /></td>
<td>−403.0</td>
<td>Rotation of OH group—rotation around the C3-O11 bond</td>
</tr>
<tr>
<td>TS5</td>
<td><img src="image" alt="TS5" /></td>
<td>−85.2</td>
<td>N12 pyramidalization</td>
</tr>
</tbody>
</table>
Table 1. Cont.

<table>
<thead>
<tr>
<th>Transition</th>
<th>Structure</th>
<th>Freq/cm(^{-1})</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>TS6</td>
<td><img src="image" alt="Structure" /></td>
<td>-344.8</td>
<td>H(_2)O cleavage</td>
</tr>
<tr>
<td>TS7</td>
<td><img src="image" alt="Structure" /></td>
<td>-575.2</td>
<td>Decarboxylation</td>
</tr>
</tbody>
</table>

Figure 3. Stationary points along the reaction path describing the generation of azomethine ylide (22) from isatine 1 optimized with the M06-2X(SMD,EtOH)/6-31G(d,p) method. Selected geometry parameters are given in Å.

Inspection of the energy profile along the reaction path leading to the generation of azomethine ylide (22), as shown in Figure 4, reveals that the energy barrier for the primary nucleophilic addition of sarcosine to 1 is only 6.1 kcal mol\(^{-1}\). The relative Gibbs free energy of addition product 16 is 1.5 kcal mol\(^{-1}\). The corresponding addition of 1 to the other isatine carbonyl group (C2=O10) was also considered. Although the C2 atom had a larger Hirsfeld positive partial atomic charge (0.277|e\(^{-}\)|) than the C3 atom (0.196|e\(^{-}\)|), indicating higher electrostatic interactions with the N12 reactive center, the calculated
values of Fukui functions for the C2 atom were smaller (see Figure 2) by 0.071, meaning that
the electrons received in the nucleophilic addition of sarcosine to the C2=O carbonyl group
were poorly accommodated. Indeed, it was energetically more demanding, with an energy
barrier of 10.1 kcal mol\(^{-1}\), which indicates high regioselectivity of the first mechanistic step.
This is consistent with the high regioselectivity of this reaction, which was experimentally
observed earlier [4], and therefore, this direction of the potential energy surface will not be
considered further.

Charge separation within intermediate 16, proven by the calculated high total dipole
moment (17.95 Debye), could be minimized by rotation around the C13-N12 bond via
TS2 to 17, where the carboxyl group was oriented toward H18 from the NH bond and energetically favorable second proton transfer via TS3 to structure 18. The dipole moment
in structure 18 drastically decreased with respect to 16, to 8.2 Debye. Structure 18 was
the most stable intermediate (7.8 and 6.3 kcal mol\(^{-1}\) more stable than zwitterion 16 and the
starting van der Waals complex 15, respectively) (Figure 4). Before the dehydration step,
two minor intramolecular conformational changes should occur. One is OH group rotation
around the C3-O11 bond (see TS4, Figure 3 and Table 1) to achieve better orientation of
the oxygen lone pair toward H18 from the COOH group in structure 19. The second one is pyramidalization on the N12 (see TS5, Figure 3 and Table 1). In the resulting structure
20, the distance between O11 and H18 decreased to 1.660 Å. This interaction facilitated the
dissociation of the C3-O11 bond via TS6 because the H18 proton transfer to the OH group
formed a leaving water molecule and initiated dehydration. The C-O distance in the TS6
was 1.905 Å, and is shown to stretch further to 2.711 Å in structure 21. The intermediate 21
was zwitterionic, with a total dipole moment of 19.52 Debye. The last step in the reaction
path for azomethine ylide was decarboxylation. It can be described with TS7. The most
important geometrical changes along the decarboxylation path were C13-C14, N12-C13
distances, and O16-C14-O15 valence angle. While the C13-C14 bond lengths increased in
the sequence 1.552, 2.113, and 3.018 Å, the N-C13 lengths decreased in the order 1.467, 1.348,
and 1.299 Å in structures 21, TS7, and 22, respectively (Figure 3). The angle O16-C14-O15
gradually expanded due to the formation of linear atom arrangement in the CO\(_2\) molecule.
Energy barriers for H\(_2\)O and CO\(_2\) cleavages were 15.2 and 16.1 kcal mol\(^{-1}\) in structures 20
and 21, respectively. Finally, based on the relative free energies calculated for all transition
structures along the reaction pathway (Figure 4), one can conclude that the decarboxylation
step was the key step that determined the energetics of azomethine ylide formation, starting
with complex 15. The overall process was endergonic, since \(G_{rel}(22) = 6.0\) kcal mol\(^{-1}\).
Azomethine ylide within structure 22, generated through the reaction path described in Figures 3 and 4, corresponds to azomethine ylide structure 23 (see Figure 5). The formation of the other isomer 7 (less stable by 0.8 kcal mol\(^{-1}\)), which is related to 23 via \(E/Z\) isomerization, started with van der Waals complex 24 and ended with structure 25 (see Figure 6). The details of the reaction path between 24 and 25 are given in Figures S1 and S2 in the Supplementary Materials. The reaction path, as found before, involved nucleophilic addition to the carbonyl bond, several intramolecular proton transfers, and conformational changes, followed by dehydration and decarboxylation. The values of the relative free energies of significant TS structures are also comparable. Hence, it appears that, mechanistically, there is no difference between the formation of azomethine ylides 7 and 23. Thermodynamically, there is a slight difference: starting van der Waals complex 24 is 0.8 kcal mol\(^{-1}\) less stable than 25.

![Figure 5. Optimized structures of two possible isomers of azomethine ylide by M06-2X/6-31G(d,p) methods using SMD(EtOH) solvation model.](image)

![Figure 6. Energy minima 24 and 25 optimized with M06-2X(SMD,EtOH)/6-31G(d,p) method. Selected geometry parameters are given in Å. All details on the reaction path between 24 and 25 are given in Figures S1 and S2 in Supplementary Materials.](image)

The mechanism for the formation of azomethine ylide described herein differs from the mechanism proposed by Parthasarathy et al. [4]. To test whether it is possible to form the cyclic intermediate 5 via dehydration in the first step of the reaction, as assumed, we calculated the TS8 structure (Figure 7). The intrinsic reaction coordinate (IRC) following in a reversed direction gave the van der Waals complex 26. On the other side, IRC calculation in the forward direction gave the structure 27, which corresponds to the water-coordinated intermediate 5. This means that the TS8 is, indeed, the transition structure for synchronous addition and dehydration. Further stationary points and the energy profile for generating azomethine ylide after the formation of intermediate 27 are given in Figures 7 and 8, respectively. The processes that follow were relocation of water molecule on very flat part of the potential energy surface via TS9; pyramidalization of the N12 atom via TS10; ring opening by means of C3-O11 bond dissociation via TS11; and, lastly, decarboxylation via TS12. We note in passing that, in the complex intermediate structure 31 produced in the later step, azomethine ylide assumed the conformation equivalent to 23 (the same configuration was already found in the outcome of a previously described reaction path in Figures 3 and 4, structure 22). The slight difference in electronic energies between the two complexes 31 and 22 was due to different H\(_2\)O position. The data presented in Figure 8 illustrate that the TS8 was the highest-energy transition structure \((G_{rel}(TS8) = 30.5 \text{ kcal mol}\(^{-1}\) above complex 26), and activation of this reaction path (associated with the TS8) is very improbable.
The next point of great interest to us is the effect of substitution in the C6 position of isatine 1 on the reactivity of ylide formation for the planned application of isatins as cycloaddition delivery reagents for guanidine functionality [11]. The influence of substituents at C6 was assessed by examination of the decarboxylation reaction—the rate-determining step defined by TS7. The relative energies for TS7 and 22 with the amino (TS7a, 22a),
nitro (TS7b, 22b), and guanidino (TS7c, 22c) groups, with respect to the corresponding 21a, 21b, and 21c structures, respectively, are given in Table 2. Due to the high basicity of guanidines [12], it was likely that the guanidine functional group would be protonated. Therefore, the effect of protonation of the guanidino group in structures TS7d, 21d, and 22d was studied as well.

Table 2. Relative Gibbs free energies in kcal mol\(^{-1}\) of transition structures (TS7–TS7d) for decarboxylation step in the formation of key intermediates 22–22d. Relative energies with respect to reactants are given as well.

<table>
<thead>
<tr>
<th></th>
<th>TS7</th>
<th>22</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>(\Delta q(C1))</td>
<td>(\Delta q(C1))</td>
</tr>
<tr>
<td>(\Delta G_{rel}^1)</td>
<td>(\Delta G_{rel}^2)</td>
<td>(\Delta G_{rel}^1)</td>
</tr>
<tr>
<td>R=H</td>
<td>16.1</td>
<td>26.0</td>
</tr>
<tr>
<td>R=NH(_2)</td>
<td>16.4</td>
<td>26.0</td>
</tr>
<tr>
<td>R=NO(_2)</td>
<td>12.0</td>
<td>23.0</td>
</tr>
<tr>
<td>R=GU</td>
<td>14.8</td>
<td>24.3</td>
</tr>
<tr>
<td>(\text{R=GUH}^+)</td>
<td>13.1</td>
<td>21.2</td>
</tr>
</tbody>
</table>

\(^1\) with respect to 21; \(^2\) with respect to reactants.

During the cleavage of CO\(_2\) from 21, a substantial redistribution of atomic charges took place. For instance, the positive partial charge on the C1 atom increased by 0.12 and 0.20 |e\(^-\)| in TS7 and structure 22, respectively (see \(\Delta q(C1)\) in Table 2). This decrease was not affected by substitution, probably because the substituents attached on the C6 were far from the reaction center. Subsequently, the influence of different functional groups on the reactivity of decarboxylation was low. The obtained activation energies were in the 12.0–16.4 kcal mol\(^{-1}\) range. The largest effects were noticed for nitro (-NO\(_2\)) and protonated guanidino (-NHC(NH\(_2\))\(^2\)+) substituents. In those cases, the calculated energy barriers were decreased by 4.1 and 3.0 kcal mol\(^{-1}\), respectively, showing that an electron-withdrawing group favorably affects the reactivity.

Once the mechanism of azomethine ylide intermediate formation was established, we next turned to study its 1,3-dipolar cycloaddition with the 7-oxabenzonorbornadiene 3. It is well known that due to the slight endo-pyramidalization of the C20-C21 double bond in 3 [13], cycloadditions preferentially take place in the exo fashion [14]. Therefore, the azomethine ylide 22 was oriented toward 3 on the exo side for the optimization of complex structures 32 and 33 (Figure 9). In both structures, the C20-C21 bond was more than 3 Å distant from the ylide plane. Corresponding transition structures for cycloaddition TS13 and TS14 were located at 9.1 and 10.5 kcal mol\(^{-1}\) above 32 minimum. Further shortening of these distances led to the formation of new carbon–carbon bonds in the final adduct 34. The minima 34 was the most stable structure \(\Delta G_{rel}(34) = -46.6\) kcal mol\(^{-1}\). The calculated stereospecificity of the cycloaddition was in full agreement with the experimentally observed structures of cycloadducts 34 [4] and the formation of a single product. Employing the energies of stationary points along the reaction path for 1,3-dipolar cycloaddition of 7-oxabenzonorbornadiene 3 with azomethine ylide, it can be concluded that the 1,3-dipolar cycloaddition reaction of azomethine ylide 22 and 7-oxabenzonorbornadiene 3 is a very exergonal step, and also, it is less energy-demanding than the decarboxylation step for the generation of 22. This conclusion is additionally corroborated by calculations where CO\(_2\)
and H₂O molecules were deleted from the first coordination sphere, resulting in a slightly smaller energy barrier for cycloaddition of 8.4 kcal mol⁻¹.

Figure 9. Energy profile and structures of stationary points along the reaction path describing 1,3-dipolar cycloaddition of 7-oxabenzonorbornadiene with azomethine ylide. Gibbs free energies at M06-2X(SMD,EtOH)/6-31G(d,p) level of theory are given relative to structure 32. Selected geometry parameters are given in Å.

The thermodynamic stability of structures 32 and TS13 with respect to 33 and TS14, respectively, can be rationalized by electrostatic interactions of the oxa bridge (electronegative O) with the positive N12 atom from ylide. This interaction is favorable; it influences 32 and TS13 structures, where the oxa bridge and NCH₃ groups are oriented on the same side in space. The opposite holds for 33 and TS14, since the oxa bridge and NCH₃ groups are oriented on different sides in space, decreasing their interaction through space. To better understand these interactions, additional calculations involving norbornene (36) and 7-oxanorbornene (37) dienophiles were conducted (see Figure 10).

Figure 10. TS structures for 1,3-dipolar cycloaddition of azomethine ylide 22 with norbornene 36 and 7-oxanorbornene 37 (TS15 and TS16, respectively), optimized with the M06-2X(SMD,EtOH)/6-31G(d,p) method. Selected geometry parameters are given in Å.

In contrast to the oxa bridge, the local charges on the CH₂ bridge in norbornene were positive, and its interaction with N13 was unfavorable. Indeed, it was found that, in
the reaction of norbornene 36 with the azomethine ylide 22 in transition structure TS15 (Figure 10), the CH₂ bridge oriented on the opposite side of NCH₃ from ylide was in a preferred orientation. The reaction was still very exergonic, since product 39 was 51.7 and 39.4 kcal mol⁻¹, respectively, more stable than the TS15 and structure 38 (van der Waals complex between 22 and 36). It should be noted that TS15 as 2.4 kcal mol⁻¹ less stable than TS7 (TS for decarboxylation); therefore, in the case of norbornene, cycloaddition is a rate-determining step on the reaction path. The high energy of TS15, thus, follows norbornene’s experimental inertness [4]. To quantify the oxa bridge’s importance for the reaction, we compared the energy of TS15 with TS for cycloaddition with 7-oxanorbornene TS16 (Figure 10). Substitution of CH₂ with O stabilized the TS by 3.8 kcal mol⁻¹ and was beneficial for the reaction.

In this study, the solvent effect was considered by the implicit SMD solvation model. However, the solvent molecule (EtOH) was able to directly form hydrogen bonds with some transition structures and intermediates, particularly zwitterionic structures with large dipole moments, such as 16 or 21. It could also facilitate intramolecular proton transfers to some extent. However, we should point out that, for the key reaction steps (decarboxylation and cycloaddition), extensive additional effects upon explicit EtOH inclusion in the reactive site are not expected because, in that case, the microsolvation is already taken into account via the present H₂O molecule, which possesses better solvation properties than EtOH.

3. Materials and Methods

The M06-2X DFT functional developed by Truhlar et al. [15] was used to optimize the structures of reactants, transition states, intermediates, and products. The XYZ coordinates of all structures are given in Table S1 in Supplementary Materials. The selected method has very good performance in applications involving main-group thermochemistry, kinetics, electronic excitation energies, and noncovalent interactions [9]. It is designed to include dispersion effects at an electronic level and to work quite well for weakly bound systems at their equilibrium distances [16,17]. The M06-2X density functional is used in conjunction with the Pople’s double-ζ basis set 6-31G(d,p) [18,19]. The solvent effects during the optimizations were included using the SMD method [20], and ethanol was used as a solvent with default parameters as defined in the Gaussian16 [21] software package. Ethanol was selected because, in non-alcoholic solvents, the products of the reaction were generated in lower yields [4]. No symmetry constraints were imposed. Vibrational analysis was performed, and all structures were characterized either as minima without imaginary frequencies or as transition state structures with one imaginary frequency. The total energy of each stationary point on the surface of the potential energy was corrected by unscaled ZPV energy. The association of products with reactants via transition structures was confirmed by intrinsic reaction coordinate (IRC) calculations. Partial atomic charges were extracted from the Hirshfeld population analysis [22]. Condensed Fukui functions [23] on the selected reacting atoms in reactants were calculated as the difference between Hirshfeld atomic charges of neutral and radical anion (for atoms as electrophiles) or radical cation (for atoms as a nucleophile) species at the geometries of the neutral minima. In IRC calculations, vibrational analyses, and in single-point calculations for population analysis, the M06-2X functional was used as well. The Gaussian16 [21] software package was used to perform quantum-mechanical calculations, and the initial structures were generated using the Molden package [24].

4. Conclusions

The DFT theoretical investigation of the formation of azomethine ylide from isatine and sarcosine and its reactivity in a 1,3-dipolar cycloaddition reaction with 7-oxabenzenorbornadiene enabled detailed elucidation of the reaction mechanism. It is shown in this study that the reaction started with the simultaneous nucleophilic addition of sarcosine to carbonyl group of isatine (C3=O11) and proton transfer from O16 to O11. Further, several conformational changes (rotations and pyramidalization) and proton transfers were followed by dehydra-
tion and decarboxylation, which led to the formation of azomethine ylide intermediate. We showed that proposed cyclic intermediates in the literature (structures 5 or 12) were not included in the mechanism. The CO₂ cleavage was recognized as the rate-determining step, which could be expedited by substitution in position C6 of isatine with electron-withdrawing groups such as -NO₂ and protonated guanidine. Finally, the last reaction step, where the 1,3-dipolar cycloaddition of azomethine ylide and 7-oxabenzonorbornadiene produced a stable fused spiro pyrrolidine-oxindole product, was energetically advantageous due to beneficial interactions of the oxa bridge with ylide N12 atom.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/ijms25126524/s1.

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References

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