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# Restricted Hartree -Fock (RHF) study of schiff base (*N*-[(*Z*)-furan-2-ylmethylidene]-4-methoxyaniline) formation between aromatic amine and furaldehyde

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## ABSTRACT

*Theoretical study based on the Restricted Hartree- Fock calculations (RHF/3-21G) of the formation of Schiff base of para-methoxyaniline with furaldehyde was conducted. The reaction mechanism was found to involve two steps, namely: (1) formation of a carbinolamine and (2) dehydration of the carbinolamine to give the final schiff base, through six-membered ring transition states. The carbinolamine is intermediate and dehydration is rate determining step of the reaction. The formation of Schiff base between the para-methoxyaniline and furadehyde requires the contribution of one auxiliary water molecule as a true reactive in order to facilitate proton transfer, and allows the nucleophilic attack of the incoming amine to carbonyl group.*

**Keywords:** Schiff base, Six-membered ring transition state, Restricted Hartree-Fock.

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## INTRODUCTION

Schiff bases that contain aryl substituents are substantially more stable and more readily synthesized, while those which contain alkyl substituents are relatively unstable. Schiff bases of aliphatic aldehydes are relatively unstable and readily polymerizable [1], while those of aromatic aldehydes having effective conjugation are more stable. Schiff bases derived from aromatic amines and aromatic aldehydes have a wide variety of applications in many fields, *e.g.*, biological, inorganic and analytical chemistry [2-3]. Schiff bases appear to be important intermediates in a number of enzymatic reactions involving interaction of the amino group of an enzyme, usually that of a lysine residue, with a carbonyl group of the substrate [4]. Many biologically important Schiff bases have been reported in the literature possessing, antimicrobial, antibacterial, antifungal, anti-inflammatory, anticonvulsant, antitumor, antihypertensive activity and anti HIV activities [5-13].

The generally accepted mechanism for this reaction was proposed by Snell and Braunstein [14-15]. It consists of the addition of the amine to a carbonyl compound to give an intermediate carbinolamine that loses one molecule of water to produce the imine [16]. Although carbinolamines have proved to be difficult to observe in studies of Schiff base formation, experimental evidence [17-19] supported the occurrence of such intermediate and the location of the rate-limiting step of the whole reaction in its dehydration. Quantum mechanics calculations onto a reactive system can provide a detailed description of the intermediates and transition state geometries involved in the reaction.

A PM3 study regarding Schiff base formation of a pyridoxal 5-phosphate (PLP) analogue with methylamine in gas phase and using two solvation models has been reported [20]. At this level of theory, they concluded that one water molecule has a key role in the reactive complex for the achievement of reliable reaction barriers in the nucleophilic attack of the incoming amine onto the carbon of the carbonyl group [20]. A comprehensive study of Schiff base formation of vitamin B6 analogues using DFT calculations (B3LYP/6-31+G*) were carried out [21]. Vitamin B6 analogues for the gas-phase calculations included one auxiliary water molecule. These calculations result in the description of the geometries of all the intermediates and transition structures along the reaction pathway, which can be divided into three parts: carbinolamine formation, dehydration, and imine formation. The carbinolamine is the main intermediate, and dehydration is the limiting step of the reaction, in accordance with experimental evidence. The details of the mechanism of carbinolamine formation highlights the key role of the auxiliary water molecule of the molecular complex as a true reactive site for allowing the nucleophilic attack of the incoming amine to the carbonyl group [21].

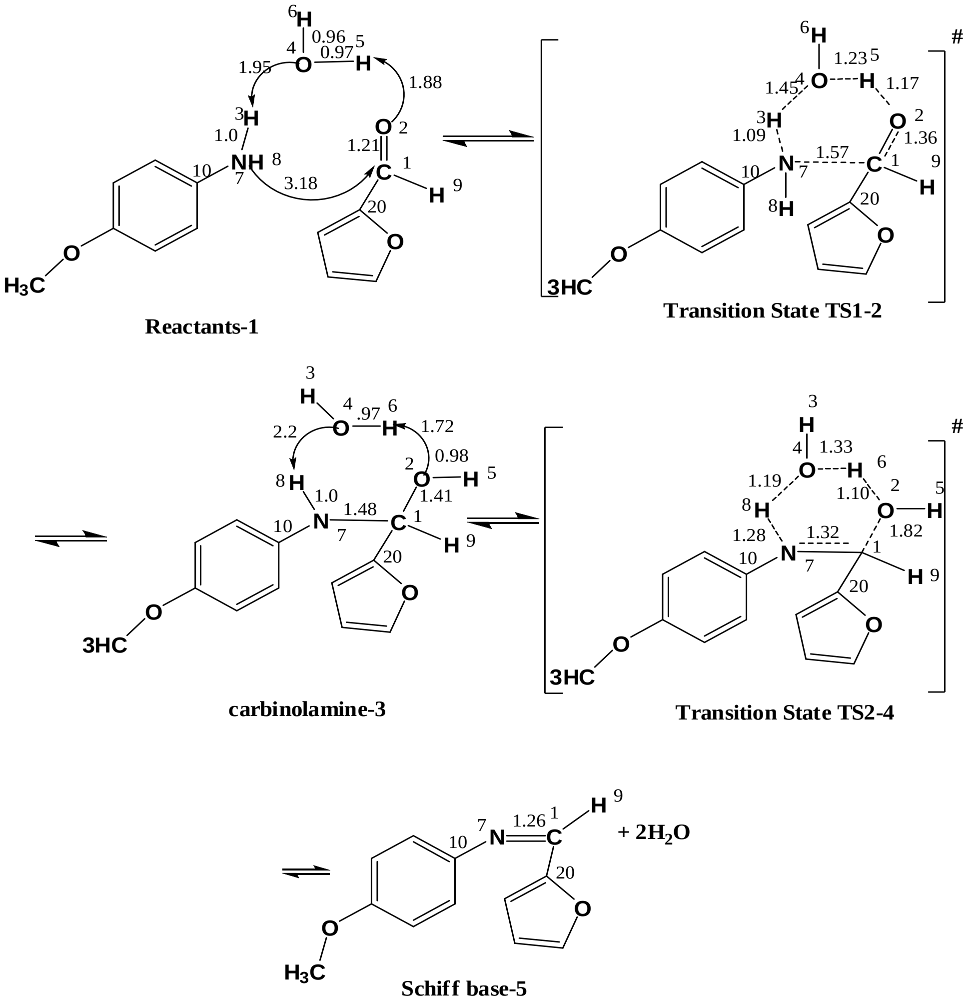
A theoretical study based on density functional theory calculations of the formation of Schiff bases of pyridoxamine analogues with two different aldehydes was carried out [22]. The reaction mechanism was found to involve two steps, namely: (1) formation of a carbinolamine and (2) dehydration of the carbinolamine to give the final imine. The formation of a Schiff base between pyridoxal 5-phosphate (PLP) and an amine or amino acid requires the contribution of an external water molecule in order to facilitate proton transfers [22].

In this work, the reactivity of furaldehyde with para-methoxy-aniline as regards to Schiff base formation will be discussed by means of the description of the energy, the geometry, and the topology of the intermediate and transition state structures involved in such reaction. This information provides a detailed energy profile for Schiff base formation that matches conclusions which have been obtained experimentally.

## MATERIALS AND METHODS

### Method of calculations

A molecular complex consisting of furaldehyde, para-methoxy-aniline and one water molecule was chosen as model compound to study the Schiff base formation. The purpose of including one water molecule in the model molecular complex was not the simulation of water solvation environment but its consideration as reactive species for the processing of the reaction. In the present study Restricted Hartree-Fock (RHF) calculations were performed with the Gaussian03 [23] software packages, running in an Intel Pentum (R) 1.86 GB personal computer. All structures were fully optimized at the Restricted Hartree Fock (RHF) level, using the 3-21G basis set in gas phase. Also, the geometries of the reactants, products, intermediates, and transition states involved in the reactions were all fully optimized by using RHF/3-21G. The structures thus obtained were subjected to vibrational analysis calculations toward their characterization as local minima (all positive force constants) or transition states (one imaginary force constant only). For the later structures, IRC [24] calculations were performed along the transition vector defined by the vibration mode of this imaginary frequency in order to asses that the saddle point structure connected downhill the corresponding forward and backward minima. This methodology allowed the identification of the reaction intermediates and transition state structures along the reaction path. The standard state is 1 atm, which is the default in Gaussian calculations.



**Scheme 1**: **Mechanism of Schiff base formation (*N*-[(*Z*)-furan-2-ylmethylidene]-4-methoxyaniline) between para-methoxy-aniline and furaldehyde**

## RESULTS AND DISCUSSION

The mechanism of the Schiff base formation reactions of para-methoxy-aniline with furaldehyde involves two steps, namely: (1) formation of carbinolamine (1-3 in scheme 1) and (2) dehydration of the carbinolamine to give the imine (3-5 in scheme 1), scheme 1 shows the atoms directly involved in the reaction and the overall process. Figure 1 shows the energy profiles for the process in the gas phase with RHF/3-21G. Tables 1 and 2 show the relative energies, $\Delta H^o$, $\Delta G^o$ and $\Delta S^o$ data for the structures involved .

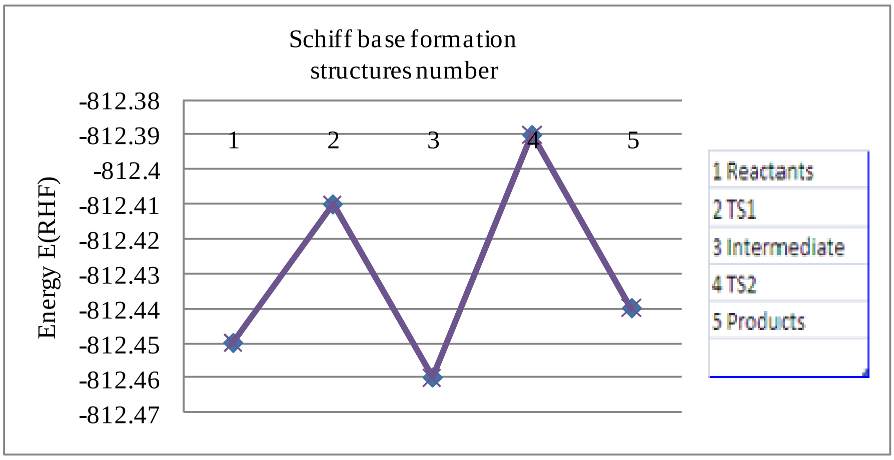


**Figure 1**. **Energy profile for the reaction. Energy is in a.u.**

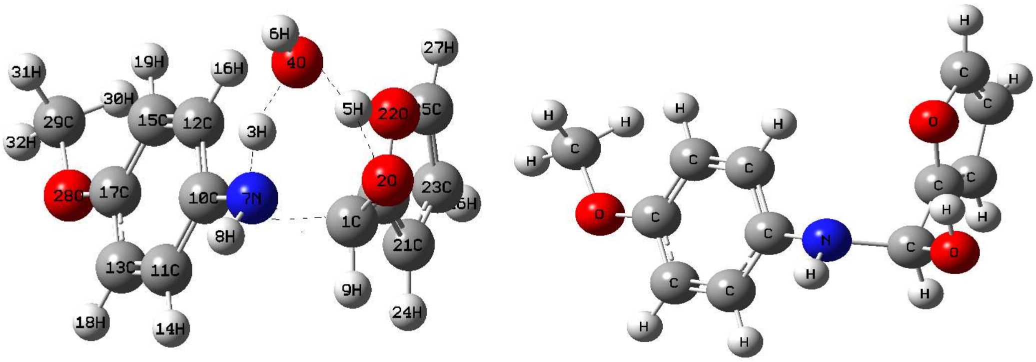
**Table 1. Energies (RHF) for each of the structures of the reaction path from the standard thermochemistry output of a frequency calculation** [a]

| Structure | E(RHF) |
|---|---|
| **1**[b] | -812.450285 |
| **2**[c] | -812.416005 |
| **3**[d] | -812.462736 |
| **4**[e] | -812.392964 |
| **5**[f] | -812.446041 |

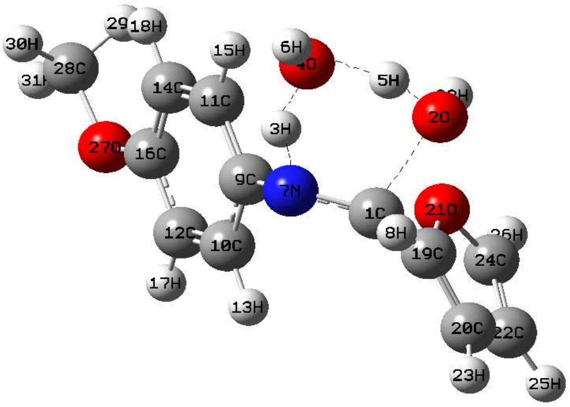
[a] *All structures were fully optimized. Cartesian coordinates of all structures are available as supplementary material. Energy in a.u.*
[b,c,d,e,f] *reactants, cyclic transition state-TS1, intermediate, cyclic transition state-TS2 and product respectively (refer to Scheme 1).*

**Carbinolamine Formation:** The starting point for this concerted step process is structure 1(scheme 1) where the incoming amino group (N7) of the para-methoxyaniline is the site of the nucleophilic attack on the carbonyl carbon in furaldehyde (C1).The amine approach occurs in such a way that the C20-C1-N7 angle is 94.3º(see the relevant geometrical data for all structures in the supporting Information). The distance N7-C1 is 3.18 Å at the start. The existence of auxiliary water molecule in this reaction facilitates the transfer of the amine proton to the water molecule H3…O4 which distance is 1.95 Å. The simultaneous transfer of water proton to aldeyhde oxygen H5…O2 which distance is 1.88 Å (scheme 1 and figure 1). This mechanism occurs via six-membered ring transition state TS1-2 clearly involving the formation of an N7-C1 bond (1.57 Å), H3-O4 bond (1.45 Å) and O2-H5 bond (1.17 Å). Then partial breaking of N7…H3(1.09 Å), O4…H5 bond (1.23 Å) and C1…O2 bond (1.36 Å) occurs.The energy barriers for the reaction of para-methoxy-aniline with furaldehyde to form six-membered ring transition state(TS1) is 21.51 kcal mol$^{-1}$ (table 2), downhill from these transition state structure, the system evolves to the carbinolamine form 3 (scheme1) via the formation of an N7-C1covalent bond and complete transfer of the water proton (H5) to carbonyl oxygen (O2), and complete transfer of amine proton (H3) to water oxygen (O4), scheme 1 and figure 2.

Water has been shown to take part in similar reactions in other simple systems where the energy barrier for carbinolamine formation by proton transfer was found to be reduced if explicit water molecules were used to facilitate proton transfer [22]. On the basis of experimental work on other molecular systems, these protonation reactions are pH-dependent in acid-base equilibria [26-27].



**Transition state -TS1** **intermediate carbinolamine -3**



**Transition state -TS2**

**Figure 2. Optimized structures of six-membered ring transitions states TS1, TS2 and carbinolamine intermediate 3 of the above reaction calculated by RHF/3-21G.**

**Table 2.Calculated energies of reactants, six-membered ring transition states, carbinolamine and products using RHF/3-21G in kcal mol$^{-1}$ $^{a,b}$**

| Compound | ΔE<br>kcal mol$^{-1}$ | ΔG<br>kcal mol$^{-1}$ | ΔH<br>kcal mol$^{-1}$ | ΔS<br>Cal mol$^{-1}$K$^{-1}$ |
|---|---|---|---|---|
| $1^{c}$ | 0 | 0 | 0 | 0 |
| TS1-$2^{d}$ | 21.51 | 26.17 | 1.14 | -0.35 |
| $3^{e}$ | -7.81 | 5.44 | -7.71 | -0.17 |
| TS2-$4^{f}$ | 43.78 | 20.73 | 8.71 | 0.17 |
| $5^{g}$ | 10.47 | 7.55 | 18.95 | 0.16 |

[a] *All structures were fully optimized. Cartesian coordinates of all structures are available as supplementary material.*

[b] *Energies reported relative to the sum of energies of separated reactants.*

[c,d,e,f,g] *Reactants, cyclic transition state-TS1, intermediate, cyclic transition state-TS2 and product respectively (refer to Scheme 1).*

**Schiff base formation:** In this step the carbinolamine is dehydrated to give the corresponding Schiff base through the six-membered ring transition state TS2 (Scheme 1, figure 2) in the presence of the auxiliary water molecule to facilitate the reaction, in which the second amine proton (H8) transfer to water oxygen(O4), simultaneously the water proton (H6) is transfered to hydroxyl oxygen (O2) of carbinolamine , and C1-O2 start to break to release water molecule, this step causes the formation of an imine double bond between C1 and N7. In fact the distance between these two atoms decreases from 1.48Å in structure 3 to 1.32 Å in structure 4 (Scheme 1). The energy barriers for the reaction of carbinolamine with water to form six-membered ring transition state (TS2) is 51.59 kcal mol$^{-1}$ (table 2).

If we consider the energy values (table 2) calculations (RHF/3-21G) show that the initial attack of furaldehyde has energy barrier of 21.51 kcal mol$^{-1}$, where as the potential energy barrier for dehydration of the carbinolamine is 51.59 kcal mol$^{-1}$. This suggests that the carbinolamine deyhdration is the rate-determining step of the process. Similar conclusions for this type of reaction have been drawn from the theoretical and experimental results for other simpler systems [21-22, 28].

If energy Gibbs is considered, RHF calculations show barriers of 26.17 for initial attack and 15.29 kcal mol$^{-1}$ for the dehydration of carbinolamine to form the Schiff base.

## CONCLUSION

On the bases of our Schiff base formation model, water plays a prominent role in all protons transfers, by which the two amine protons were exchanged through two six-membered ring transition states to form carbinolamine intermediate and Schiff base respectively. Dehydration of carbinolamine to form Schiff base is rate-determining step.
The energy barrier for the dehydration step in our system is slightly high relative to other previously studied systems. This may be a result of low level basis sets parameters calculations used in our large system reactions.

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