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REGULAR ARTICLE

A comparative DFT study of the Schiff base formation from acetaldehyde and butylamine, glycine and phosphatidylethanolamine

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Abstract Mechanisms for the formation of the Schiff base from acetaldehyde and butylamine, glycine and phosphatidylethanolamine based on Dmol3/DFT calculations were realized. For the case of phosphatidylethanolamine, calculations were done under periodic boundary conditions, in an amine-phospholipid monolayer model with two molecules of phosphatidylethanolamine by cell. All models contained explicit aqueous solvent. In the three cases, a neutral amino group is used to model the nucleophilic attack on the carbonyl group of acetaldehyde, and water molecules form hydrogen bond networks. These networks were involved in the reactions by performing as proton-transfer carriers, important in some steps of reactions, and stabilizing reaction intermediates. In all the studied reactions, they take place in two steps, namely: (1) formation of a carbinolamine and (2) its dehydration to the Schiff base, being the dehydration the rate-determining step of the process, consistent with available experimental evidence for similar reactions. The main difference between the studied reactions is found in the value for relative free energy for the intermediates and transition states in the second step; these values are lower in the cases of glycine and phosphatidylethanolamine in comparison with butylamine, due the influence of their molecular environments. Based on the results, the aminophospholipid surface environment and carboxylic group of glycine may boost Schiff base formation via a neighboring catalyst effect.

Keywords Monolayer model · Periodic boundary conditions · Schiff base formation · Phospholipids

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1 Introduction

Schiff base (imine) formation is a very important reaction in biological chemistry. This reaction consists of two stages, the first is carbinolamine formation followed by a dehydration step to the formation of the Schiff base. It has been extensively studied in various systems and processes due to its high chemical, biological, and technological relevance [1–7]. One of these processes is the in vivo non-enzymatic glycation that is the covalent binding of a simple reducing sugar to a primary amino group in a biomolecule, producing a Schiff base, whose rearrangement leads to an Amadori product. Non-enzymatic glycation of proteins or Maillard reaction is increased in diabetes mellitus due to hyperglycemia and leads to several complications such as blindness, heart disease, nerve damage, and kidney failure [8, 9], and the Amadori product of the glycation of phosphatidylethanolamine (PE) triggers oxidative modification in lipids via superoxides, promotes vascular disease through their angiogenic action on endothelial cells, and may be involved in the development of diabetes [10, 11]. Previous experimental and theoretical studies by our group allowed Schiff base formation mechanisms for vitamin B_6 analogs and aminophospholipids to be elucidated [12–20], and also, the reactions of sugars and glycation target models with pyridoxamine have been the subject of various studies [21–24].

Upon alcohol consumption, the liver enzyme alcohol dehydrogenase catalyzes the oxidation of ethanol to yield

its primary metabolic product, acetaldehyde (AcH) [25]. Acetaldehyde accumulates and exerts its toxic effects when the enzymatic pathways responsible for oxidizing alcohol become overwhelmed. The electrophilic nature of acetaldehyde renders it highly reactive, enabling it to react with nucleophilic groups from proteins, lipids, DNA, and hormonal biogenic amines forming adducts which may be at least in the early stages of Schiff bases [25–31]. Adducts are pathogenic, because they impair functions of proteins and lipids, promote DNA damage and mutation [29, 32, 33], and increase the generation of reactive oxygen species (ROS) [34, 35]. Consequently, there may be interference of cellular functions, in protein function, gene expression, and DNA integrity, including increased mutagenesis [34, 36–38], breakdown of immune tolerance, and induction of autoantibodies toward the resulting neoantigens [39–43]. Upon ethanol-induced oxidative stress, more abundant amounts and multiple species of adducts may be generated from aldehydic products of lipid peroxidation and through the formation of hybrid adducts. Studies in both human alcoholics and experimental animals have further demonstrated adduct deposition in tissues including the liver, brain, gut, muscle, lungs, and heart thereby aggravating ethanol toxicity in such organs [30, 44–48].

Acetaldehyde adducts could be unstable or stable; in the first case, they are generally Schiff bases whose stability depends on their localization in the modified target or subsequent modifications. For example, hemoglobin adducts with acetaldehyde appear to be stable at 37 °C for up to 14 days, which means that these "stable" Schiff base products can serve as markers of ethanol consumption and explain some clinical consequences of ethanol abuse [49–51]. Stable adducts, on the other hand, are essentially irreversible products whose structures may vary, depending upon the particular target, but Schiff bases always serve as intermediates of these advanced stable products and they also could be used as biomarkers of pathogenic process [52, 53]. Adducts with DNA have been reported as biomarkers, in this case for carcinogenic process related to alcohol consumption such as head and neck cancer, as well as cancer at other sites [54, 55]. In the case of phospholipids, acetaldehyde forms a Schiff base with PE and this adduct could be reduced to the corresponding *N*-ethylphosphatidylethanolamine [56–58].

In all these processes, the speed of formation and stability of these acetaldehyde adducts depend on the chemical environment in which their formation is done [59–61]. In the case of non-enzymatic glycation process where Schiff base formation is also a part, this proceeds faster in lipids than proteins [62]. This can be ascribed to the chemical nature of membrane surfaces. Thus, the interfacial region of a membrane is known to establish electrostatic, hydrophobic, and/or hydrogen bonding interactions with various types of small molecules [63–65]. As a result, some functional groups in membrane surfaces may efficiently enhance the reaction via a neighboring catalyst effect; also, solvated membrane surfaces may provide a favorable environment and lead to a faster reaction [14]. It is known there are differences between the proton mobility in bulk water and membrane/water interface [66–68], and these differences obviously influence in a reaction such as Schiff base formation where several proton transfers are involved. The proton spreading over the membrane is facilitated by the hydrogen-bonded networks at the surface [69]. The membrane-buried layers of these networks can eventually serve as a storage/buffer for protons (proton sponges) [66–70].

Experimental works have shown that various aldehydes and ketones can form Schiff bases with PE [71–73], such as glucose [74] and acetaldehyde [57]. Schiff bases formation from amino acids has been studied extensively [75–77] and particularly from glycine [6, 78–80]. Based on the above studies, the mechanism of the reaction of Schiff base formation has been well understood; it is known that this reaction is generally produced in high yields and that all steps of these reactions are reversible [81]. However, it has not been analyzed the differences in the reaction in relation to the different biochemical environments it could occur.

In a previous work, we have done theoretical studies about the chemical reactivity of on aminophospholipid surfaces [14, 82]; we used density functional theory (DFT) and periodic boundary conditions (PBC's) for the first time to model a portion of the biological membrane surface with a view to investigating its reactivity. In order to gain insight into differences and similarities between the Schiff base formation on aminophospholipid surface and only aqueous solvent environments, now we report a comparative DFT study of the reaction of acetaldehyde, a biochemical prolific reactive carbonyl compound, with butylamine, glycine, and PE. The primary aim of this theoretical study was to elucidate the influence of the chemical environment on the Schiff base formation reaction via an H-atom-transfer mechanism and how it could explain the differences in the speed in other similar reactions.

2 Methodology

In order to make possible DFT calculus, PE surface model was designed from the crystal structure of 1,2-Dilauroyl-DL-phosphatidylethanolamine [83]. The PBC's made possible to obtain a surface model of a layer of phospholipids, useful for studying theoretically, the reaction on an environment different to aqueous solvent. The models for butylamine and glycine, due their more simple structure,

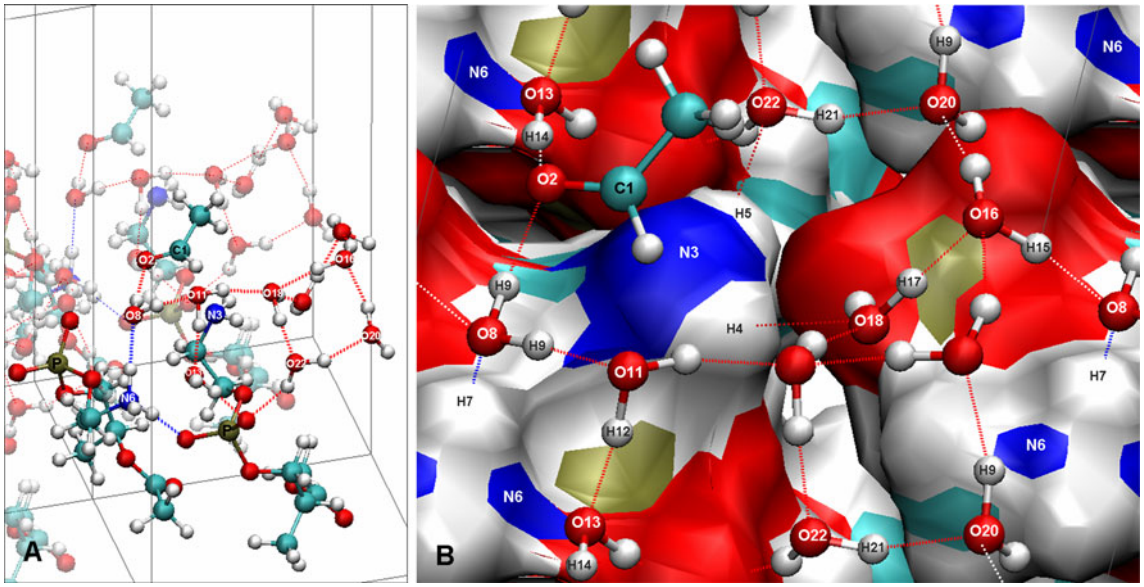


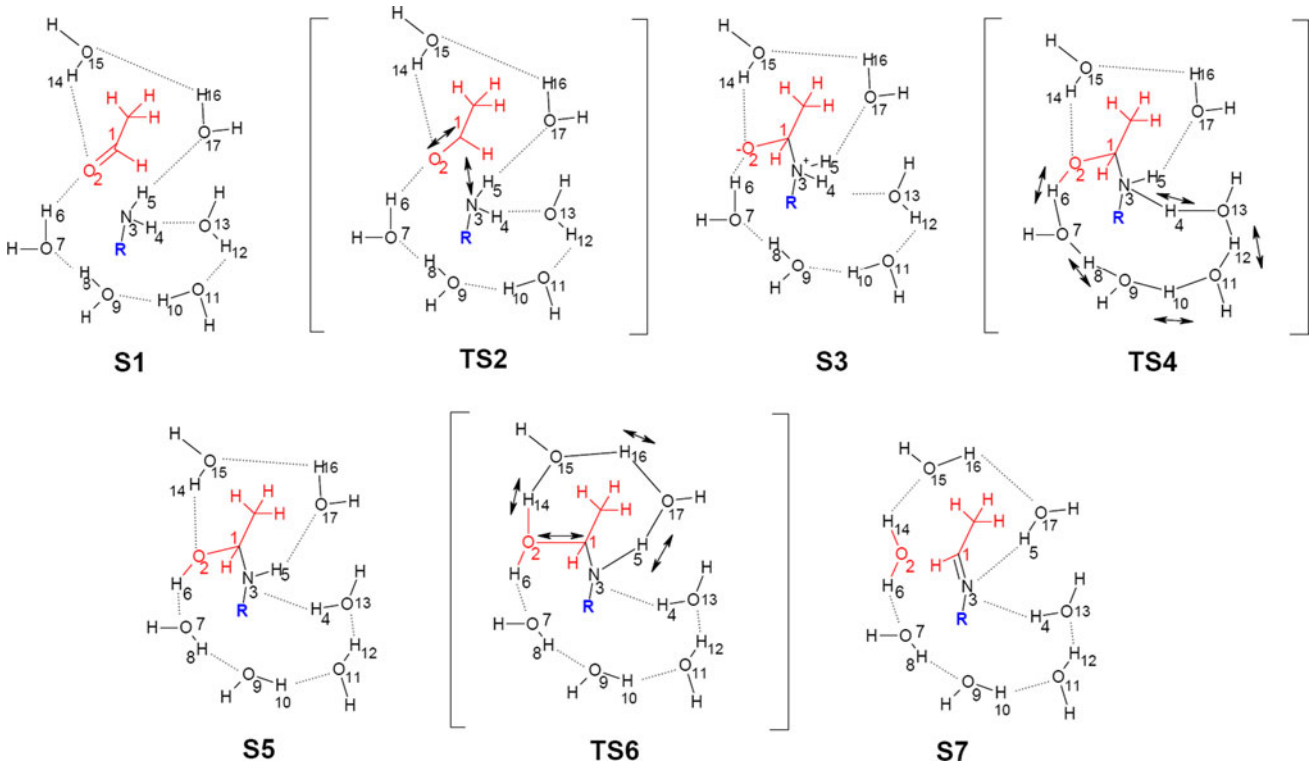
Fig. 1 Periodic model of Phosphatydilethanolamine surface. **a** Section of the initial model for two phosphatidylethanolamine molecules, acetaldehyde and the water hydrogen bond network. **b** A sight of phosphatidylethanolamine surface, reactive atoms are labeled, and *dotted lines* represent hydrogen bonds

were built without PBC's, but also including water molecules as explicit solvent and acetaldehyde.

The PE surface model was represented using a three-dimensionally periodic slab model. The supercell (Fig. 1a) contained two molecules of truncated PE, a molecule of acetaldehyde, and nine water molecules as explicit solvent in a hydrogen bond network along the polar heads of phospholipids. They were chosen as the model compound to study the Schiff base formation on the amino-phospholipids surface. One of the PE molecules had a neutral amine group intended to facilitate modeling of the nucleophilic attack on the carbonyl group of acetaldehyde, and the other had a charged amine group in order to assist some steps of studied reaction acting as proton donor and acceptor. The designed models for the systems with butylamine and glycine included an acetaldehyde molecule and 29 water molecules. The purpose of including this number of water molecules in these molecular models was not exclusively to simulate a water solvation environment; rather, the water molecules were intended to act as reactive species facilitating several steps of studied reaction in the different models.

All of the calculations were performed in the frame of DFT with program package DMol3 of Accelrys, Inc. [84–86], using double numerical with polarization (DNP) basis sets [86] and Perdew–Burke–Ernzerhof (PBE) generalized gradient approximation (GGA) exchange–correlation functional [87, 88]. The DNP numerical basis set is comparable to Gaussian 6-31G(d, p) [89–91], minimizes the basis set superposition error [92], and its accuracy for describing hydrogen bond strengths has been tested, having obtained a good agreement with experimental values [93]. PBE functional has been widely used in the study of great variety of molecular and extended systems, having accuracy for molecular systems, in the prediction of properties such as ionization potentials, electron affinities, and bond distances [94–97]. The maximum number of numerical integration mesh points available in DMol3 was chosen for our computations, and the threshold of density matrix convergence was set to 10^{-6}. A Fermi smearing of 0.005 Hartree and a real-space cutoff of 4.5 Å were also used to improve the computational performance.

The initial models as reactants and the next models for stationary points generated during Schiff base formation in all the cases were modeled in Materials Visualizer and optimized using the conjugated gradient algorithm. Transition state (TS) searches were performed with the complete LST/QST method [98]. In this method, the linear synchronous transit (LST) maximization was performed, followed by an energy minimization in directions conjugating to the reaction pathway to obtain approximated TS. The approximated TS was used to perform quadratic synchronous transit (QST) maximization and then another conjugated gradient minimization was performed. The cycle was repeated until a stationary point was located. The obtained TS was optimized via eigenvector following searching for an energy maximum along one previous selected normal mode and a minimum along all other nodes, using Newton–Raphson method. After this procedure, one transition state was found for each reaction step. Each TS structure was characterized by a vibrational analysis with exactly one imaginary frequency. Mulliken



Scheme 1 Mechanism of Schiff base formation between butylamine and acetaldehyde. *Dotted lines* represent hydrogen bonds (R- = butyle)

population analysis was used to understand the charge flow on-group migration.

3 Results and discussion

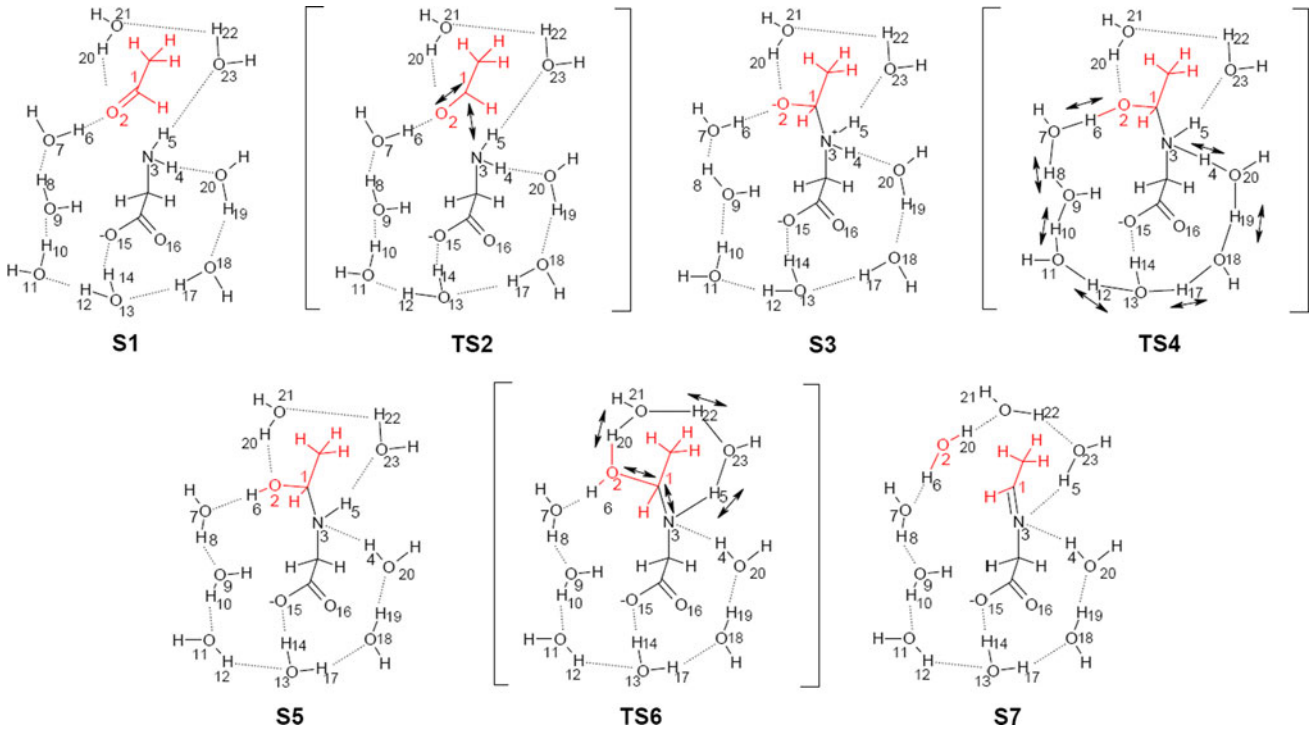
The selection of PE, butylamine, and glycine-like primary amines for studying the Schiff base formation was due to their differences in the adjacent groups, and it could let us evaluate the possible influence of these groups in the reaction. In the case of PE, it is possible to evaluate additionally the influence in the reaction of an environment different to aqueous solvent. PE is one of the major phospholipids of the biological membranes; in comparison with another phospholipids with a primary amine group, it is the most simple and its reaction with acetaldehyde has been probed experimentally [56, 99, 100].

The found structures allowed a detailed chemical pathway for the formation of a Schiff base between acetaldehyde and the three studied primary amines. Schemes 1, 2, and 3 show the atoms directly involved in the reactions and the overall processes. In the three cases, the Schiff base formation essentially involve two steps, namely: carbinolamine formation (structures 1–5 for butylamine and glycine, structures 1–7 in the case of PE surface) and its dehydration to the Schiff base (structures 5–7 for butylamine and glycine, structures 7–11 in the case of PE surface). Table 1 lists the ΔG values for each structure involved in the process, and Fig. 2 shows the comparative free energy profile.

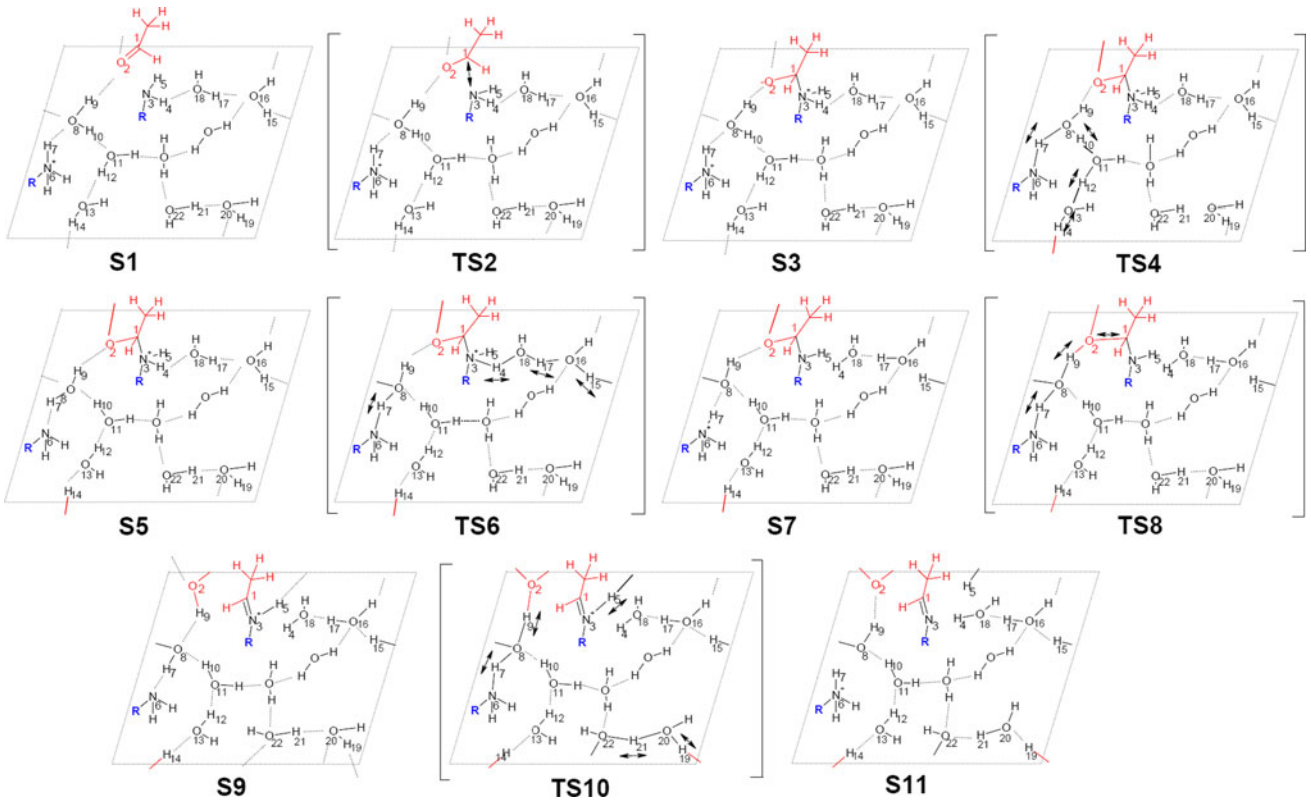
3.1 Carbinolamine formation

The starting point for these stepwise processes are structures S1 (Schemes 1, 2, 3), where the incoming amino groups (N3) of the primary amines are the agent of the nucleophilic attack on the carbonyl carbons in acetaldehyde (C1). The amine approach starts at an N3–C1 distance of 2.70 Å in PE surface (Fig. 1), in the case of glycine this distance is 3.47 Å, and in butylamine is 5.75 Å. These differences could be attributed to the influence of the environment around; in the case of butylamine, water molecules have more freedom for their mobility, having less interactions with the reactive molecules, than the case of glycine that have a carboxylic group, and PE surface where there are several groups acting as hydrogen bond donors or acceptors and stabilizing the hydrogen bonds networks.

The relative energy barriers for direct addition of the amino group to the carbonyl group from acetaldehyde for zwitterionic carbinolamine formation had values of 7.0, 2.4, and 2.5 kcal mol^{-1} for butylamine, glycine, and PE surface, respectively. These values are comparatively low in comparison with the obtained results by other studies.



Scheme 2 Mechanism of Schiff base formation between glycine and acetaldehyde. *Dotted lines* represent hydrogen bonds



Scheme 3 Mechanism of Schiff base formation between a phosphatidylethanolamine monolayer and acetaldehyde, using periodic boundary conditions. *Dotted lines* represent hydrogen bonds

Table 1 Standard free energies of the structures of the reaction paths

Step reaction	Structure	ΔG (Kcal/mol)		Structure	ΔG (Kcal/mol)
		Butylamine	Glycine		Phosphatydilethanolamine
Carbinolamine formation	S1	0.0	0.0	S1	0.0
	TS2	7.0	2.4	TS2	2.5
	S3	2.9	−6.2	S3	−8.5
	TS4	13.3	3.8	TS4	−5.2
				S5	−7.0
				TS6	−3.0
Carbinolamine dehydration	S5	9.3	−4.2	S7	−5.8
	TS6	20.3	13.2	TS8	13.1
	S7	12.5	−5.3	S9	7.0
				TS10	11.6
				S11	−5.7

In the reaction between dimethylamine and propanal, the $\Delta G^{\neq}$ barrier has value of 38.4 kcal mol^{-1} after ab initio gas-phase calculations, but the addition of two molecules of dimethylamine or methanol reduces this barrier till values of 7.2 and 10.9 kcal mol^{-1}, respectively, showing the catalytic effect of the reagent or the co-catalyst for stabilizing the transition states [101]. The relative energy barrier for the addition of pyridoxamine analog to carbonyl compounds as acetaldehyde and glycolaldehyde had also low values of 9.7 and 10.1 kcal mol^{-1} using DFT level of theory gas-phase calculations [102]. The same tendency is appreciated for the addition of pyridoxamine to glyoxylic acid [103] and methylamine to pyridoxal [104], with relative energy barriers of 3.9 and 7.9 kcal mol^{-1}, respectively. In these cases, the catalytic effect could be attributed to the stabilization of transition states through structural resonance or assistance of other molecules like water solvent or polar groups of reagents. In the case of the studied systems by us, the stabilization of transition states can be ascribed to the presence in the models of an explicit solvent that forms hydrogen bonds with the reactants and products alike, thereby facilitating addition of the amino group to the carbonyl carbon. The water molecules can be also involved in the three studied reactions by stabilizing zwitterions forms of the carbinolamine. However, the zwitterionic form of the carbinolamine from butylamine is less stable than formed by reaction with glycine and PE (Fig. 2), and it could be due to the presence in the last cases of charged groups, carboxylate group in glycine, and phosphate group in PE which stabilize this intermediate.

Structure S3 is in the three cases a zwitterionic form of the carbinolamine. Atom O2, which is negatively charged, is explicitly solvated with water molecules via hydrogen bonds. It is the first point where appears more differences between the reactions in butylamine and glycine versus PE surface. Due to inclusion of another amine charged PE in

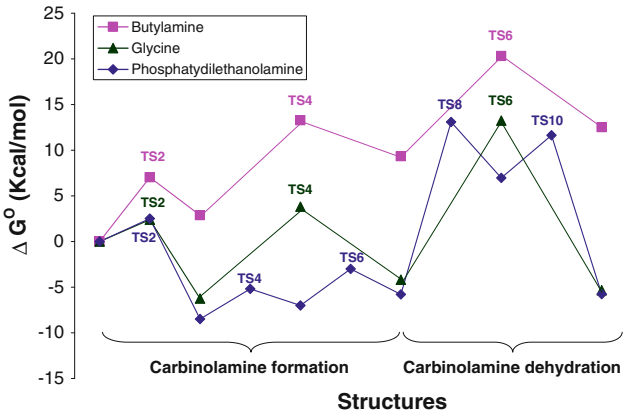


Fig. 2 Free energy profile for the reaction

the model of the surface, it could act as proton donor or acceptor in the different steps of the reaction, acting as an acid catalytic group. In the case of butylamine and glycine, being alone surrounded by solvent molecules, the proton transfers only could be done having final proton donors or acceptors, groups of reactive molecules. In the reaction with butylamine and glycine, the formation of a neutral form of carbinolamine is direct, and without a positive charged carbinolamine intermediate, having only one transition state (TS4). The transfer of proton from N3 to O2 is done through hydrogen bond chains of four water molecules in the case of butylamine and six in glycine. It could be added that in the case of glycine, some of this water molecules form hydrogen bonds with oxygen atoms of carboxylic group of glycine (Scheme 2), interaction absent for butylamine (Scheme 1).

In the case of reaction on PE surface, this part of the reaction is realized through two transition states (TS4 and TS6), first, the zwitterionic form of carbinolamine is converted into a positive charged form by transfer of proton

from a charged amine group of the another PE molecule through a hydrogen bond chain of three water molecules that facilitates protonation of the charged oxygen (O2). The PBC's allow proton H14 to cleave its bond to O13 and be transferred from one face of the unit cell to the opposite face in order to bond to O2 (Scheme 3). Then, the charged form of carbinolamine gives up a proton to the amine group of the another PE molecule that had been deprotonated in the before point of the reaction (from N3 to N6), through a hydrogen bond chain of three water molecules via a concerted transition state (TS6), forming the neutral form of carbinolamine (S7) (Scheme 3). Water has been shown to take part in similar reactions in other simple systems where the energy barrier for carbinolamine formation by proton transfer via a "Grotthuss mechanism" was found to be reduced if explicit water molecules were used to facilitate proton transfer [105]. Based on experimental work on other molecular systems, these protonation reactions are pH-dependent in acid–base equilibria [106–111].

In the three studied reactions, proton transfers are done through a chain of water molecules because the long distance between the possible proton donors and acceptors, playing the solvation water molecules a reactant role. Proton transfer on PE surface takes place via TS4 and TS6, with very low energy barriers, 3.3 and 3.4 kcal/mol, respectively, in comparison with the energy barriers for the direct proton transfer in butylamine and glycine without the positive carbinolamine intermediate, 10.4 and 10.1 kcal/mol, respectively. These differences could be attributed to the presence of polar and charged groups in the PE surface, which impose limitations on the mobility of the water molecules on its surface, polarizing them and also the reactive molecules. It is known interfaces between biological membranes and water solvent environment adopt a dielectric constant (ε) significantly lower than in the aqueous phase [112–115]. In some biological membranes, it has been determined the network of hydrogen bonds on the surface of the PE membrane can serve as a storage mechanism in solution proton (proton sponge), allowing the released proton may remain for a time along the membrane surface before being dissipated in the aqueous medium of "bulk" of water [66, 70]. This result could also explain experimental evidence that say the kinetics of lipid glycation is little faster than that of protein glycation [116].

3.2 Dehydration

The next step in the reaction is dehydration of the carbinolamine to the corresponding Schiff base, which involves the concerted release of the hydroxyl group from carbinolamine and the transfer of one hydrogen from a donor atom, in the case of glycine and butylamine from charged nitrogen N3 from the same carbinolamine through a chain of two water molecules (Schemes 1, 2; Figs. 3, 4) forming directly the neutral form of Schiff base. In the case of PE surface, this happens through two transition states (TS8 and TS10): at first, a proton transfer from the protonated amino group, and in the second, phospholipid chain to hydroxyl group O2-H14 are done, through a water molecule to give the leaving water molecule and the protonated form of Schiff base the iminium ion S9 (Scheme 3; Fig. 5). Then, N3 atom in intermediate S9 is deprotonated, being N6 atom of the second PE molecule the final proton acceptor, restoring in this way, its initial, charged amino group. Four

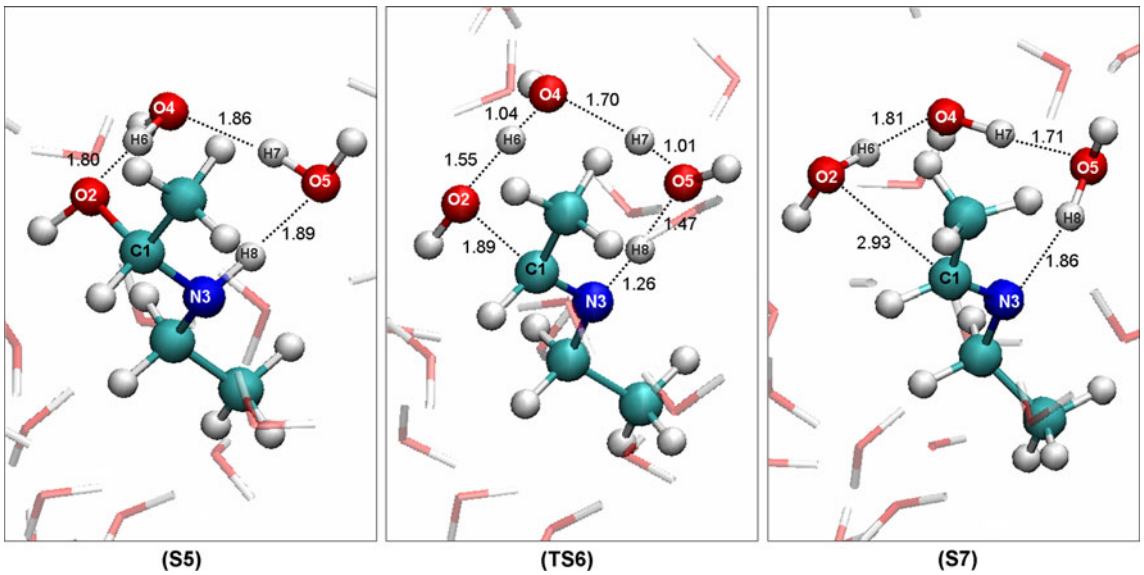


Fig. 3 The pathway for dehydration of carbinolamine molecule from reaction with butylamine. (S5) Carbinolamine; (TS6) transition state; (S7) Neutral Schiff base

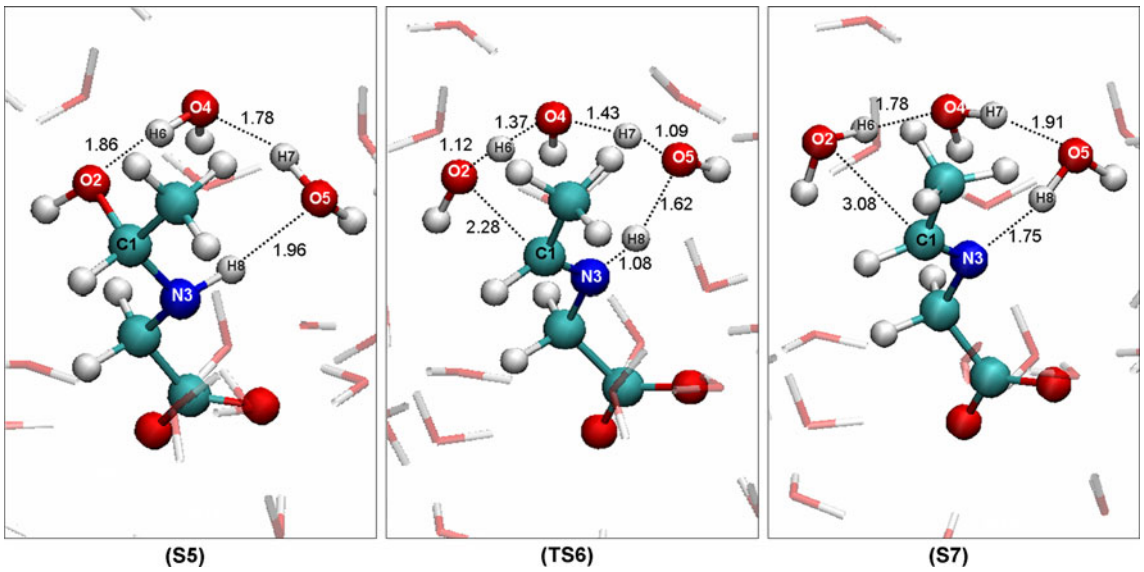


Fig. 4 The pathway for dehydration of carbinolamine molecule from reaction with glycine. (S5) Carbinolamine; (TS6) transition state; (S7) Neutral Schiff base

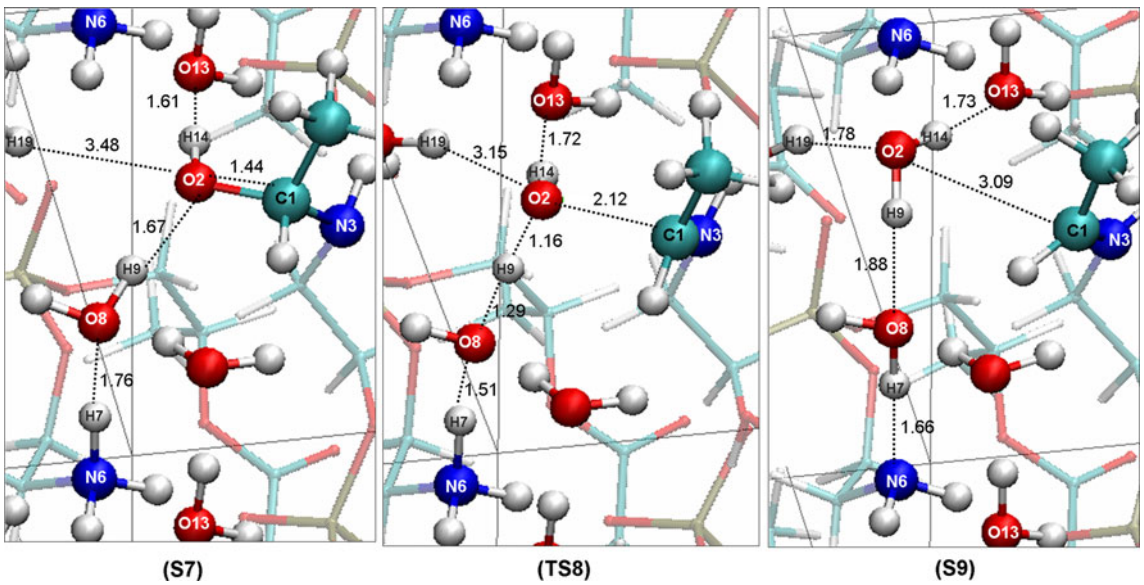


Fig. 5 The pathway for dehydration of carbinolamine molecule from reaction with phosphatidylethanolamine. (S7) Carbinolamine; (TS8) transition state; (S9) iminium ion product

water molecules networked by hydrogen bonds act as a bridge to facilitate the passage of protons through a concerted transition state (TS10 in Scheme 3). This step additionally causes the formation of an imine double bond between C1 and N3, the distance between which is thereby reduced from 1.47 (S7) to 1.29 Å (S11).

As in other molecular systems [102–104, 107], carbinolamine dehydration in the three cases butylamine, glycine, and PE surface is the rate-determining step in the formation of the Schiff base, with an free energy barrier of 11.0, 17.4, and 18.9 kcal mol^{-1}, respectively (Fig. 2). Additionally, in PE surface, obtaining the neutral form of Schiff base from its positive charged form is also subject to a free energy small barrier (4.6 kcal mol^{-1}, Fig. 2). With the exception of heterocyclic systems, the iminium ions are known to be unstable [117], so that the conversion of the positive Schiff base intermediate S9 to its neutral form (S11) is a favorable process. These neutral carbinolamines from glycine and PE (S5 and S7, respectively) have approximately similar values for their values of ΔG (Fig. 2).

There are other systems for Schiff base formation where the barriers for dehydration step are higher than the obtained by us. In the reaction between dimethylamine and propanal, the dehydration step has a $\Delta G^{\neq}$ barrier from 57.5 kcal mol^{-1} after ab initio gas-phase calculations [101]. The assistance of other molecules was necessary, like two methanol molecules, in order to reduce this $\Delta G^{\neq}$ barrier to 32.6 kcal mol^{-1}, showing the importance of the assistance of other molecules for making possible this step of the reaction. However, in certain systems, the free energy barrier for the dehydration step could be slightly lower than the obtained barriers in the reactions between acetaldehyde and glycine or PE. This may be a result of the additional assistance in these systems, provided by other chemical groups from the reagent molecules. A DFT study in the gas phase of the irreversible transamination between glyoxylic acid and pyridoxamine analog showed a value of 16.9 kcal mol^{-1} for relative energy barrier for dehydration step, and it has revealed that a carboxylic group in the amino acid acts as a proton donor facilitating water elimination and also that a phenol group in pyridoxamine analog helps stabilize the system [103]. A DFT study of the Schiff base formation between a pyridoxamine analog and acetaldehyde or glycolaldehyde in the gas phase provided relative energy barriers from 10 to 15 kcal mol^{-1}, depending of used correlation functional for calculus. Inclusion of solvent effects through CPCM implicit solvent method also reduced slightly the energy barriers. In this system, a phenolic hydroxyl group was found to act as a proton donor to the carbinolamine hydroxyl group in order to produce the leaving water molecule [102]. The intramolecular assistance for the dehydration step has been also determined experimentally for the case of the reaction between a cyclohexene-1–carboxaldehyde and glycine or aspartic acid in aqueous solution [118]. In this work, it was found an important acceleration of the reaction with these two amino acids in comparison with the reaction with aliphatic amines, it was attributed to intramolecular general base catalysis of water attack by the internal carboxyl groups, having also determined that this behavior is exceedingly efficient in a relatively nonpolar solvent mixture [119].

In the three theoretically studied reactions for Schiff base formation, water plays a prominent role in all proton transfers, acting as bridge along which protons are transferred through water molecules networked by hydrogen bonds. Water can influence the reaction barrier by electrostatic stabilization of ionic transition structures and other reaction intermediates, formation of a strong hydrogen bond, and acting as a proton-transfer carrier. Moreover, the whole reaction mechanism is governed to a great extent by the network of hydrogen bonds in the different intermediates formed upon condensation of acetaldehyde with the amino group in butylamine, glycine, and PE surface. In the three cases, the water molecules take part in the reaction by performing proton transfer and stabilizing the reactants and intermediates.

As can be seen in Fig. 2 and Table 1, the intermediate molecules and Schiff base products from butylamine are less stable than products from glycine or PE. This result could be attributed to the experimentally probed instability of aliphatic imines, in comparison with imines with other substituents, as consequence of it, aliphatic imines were not possible to isolate, having been studied less than other imines [120, 121]. A comparative experimental study of reactivity of different amines in their reaction benzaldehyde as carbonyl compound showed the increasing of reaction equilibrium constants from <10 M^{-1} in aromatic amines to around 10^3 M^{-1} for aliphatic amines [122]. This fact could be related to the high values for relative free energies of intermediates from butylamine reaction, in comparison with glycine and PE (Fig. 2; Table 1).

Differences in whole processes could be also attributed to the influence of intramolecular and intermolecular groups that could participate catalytically in the reactions. It has been shown glycine carboxylic group can even participate in an intramolecular general acid catalysis [123]. For the reaction on PE surfaces, there is a general acid catalysis, but intermolecular and mediated by charged amine group of other PE molecule, making the process longer but more effective, reducing free energy barriers for carbinolamine formation in its neutral form. Catalysis by general acids has been also reported for other aldehyde amine reactions [110, 111, 124, 125], and the influence of the environment of phospholipids surfaces in the proton transfers has been probed experimentally by other studies [126, 127]. Additionally, weak interactions as Van der Waals forces between reactive molecules and water-PE surface contribute to stabilize the intermediates and products of the reactions and could also influence in the organization of interfacial water molecules.

In PE surfaces, each PE molecule also possesses a phosphate group that may play a role in this reaction. We probed a phosphate group as proton acceptor; without obtaining any stable species, probably due its too low pK_a, the experimental value for which in PE is 0.5 [128]. However, phosphate anion might enhance Schiff base formation via another way, a neighboring catalyst effect; in fact, we found it to form hydrogen bonds with water molecules in the network connecting donor and acceptor protons, and amino groups of PE (Fig. 1), in different steps of the studied mechanism. Phosphate groups could facilitate accumulation of H_2O on the membrane surface and raising local concentrations as a result (as found in previous studies, negatively charged phosphate groups are tightly solvated by an average of four water molecules

each) [129]. Together other polar and charged groups of PE surface, it is also able to polarize water bonds through interaction with them [130], which may facilitate the role of solvation water molecules as bridges for the proton exchange between donor and acceptor protons in the reaction, and exerting a passive catalytic effect by stabilizing charge in various reaction intermediates through direct electrostatic interactions with the positively charged groups produced in the different reaction steps. The Schiff base formation reaction between on a model PE surface and acetaldehyde provides a simple means for illustrating the catalytic potential of phospholipid groups in cell membranes and their solvating water molecules to enhance a reactions that happen in their surface via a neighboring catalyst effect. The designed model of PE surface could be used for studying other reactions on PE surface at the DFT level. Considering the chemical environments where these reactions proceed, reaction mechanisms could be explained in terms of polarization and electronic transfer effects that are turned on and off along the reaction coordinate [131].

Despite the advantage of the reaction on PE surface, this study also showed the efficiency of acetaldehyde as carbonyl compound for Schiff base formation, reacting with different molecules with a free amine group. Our results are also agreed with the extent promiscuity of acetaldehyde to react with a great deal of kind of molecules with amine groups in biological systems. The produced adducts, when acetaldehyde modify proteins, lipids, or nuclei acids, have been implicated not only in carcinogenic process and processes related to tobacco and ethanol abuse [132, 133], but also in the pathogenesis of vascular disease and aging [134].

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