
Theoretical Studies on Transimination of Vitamin B6 Analogs

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ABSTRACT: The transimination reaction of vitamin B6 analogs has been studied by semiempirical quantum mechanics calculations (PM3 Hamiltonian) on a model reactive system consisting of the Schiff base made from a pyridoxal-5'-phosphate (PLP) model compound, methylamine and two auxiliary water molecules. The mechanism of this reaction has been theoretically established through the description of the energy and the geometric parameters of the intermediates and transition-state structures in the gas phase and in water solution by means of the use of two different solvation models. The description of the reaction pathway for transimination through the structures that have resulted from the calculations supports the existence of a geminal diamine as the main intermediate. The reaction also involves the occurrence of internal hydrogen transfers and water-mediated hydrogen transfers as rate-limiting steps. This study highlights the key role of water molecules not only in the formation of selected hydrogen bonds but also as true reactives. © 2002 Wiley Periodicals, Inc. *Int J Quantum Chem* 89: 48–56, 2002

Key words: transimination; transaldiminization; vitamin B6 analogs; hydrogen transfers; geminal diamine

Introduction

One of the key reactions of pyridoxal-5'-phosphate (PLP)-dependent enzymes in the metabolism of amino acids is transimination or transaldiminization [1]. Once a PLP Schiff base with an amino group of a Lys residue in the active site of the enzyme is formed, an amino group in the substrate reacts with the imine carbon with the final result of the releasing of the amino group of the Lys and the formation of a

new PLP Schiff base with the substrate amino acid. Thus, this process allows the conversion of external aldimines to internal aldimines and vice versa if the opposite of the reaction is considered.

There is some controversy about the interpretation of experimental data for the proposal of a suitable mechanism for the transimination reaction. A pathway was first proposed by Snell and Jenkins [2], which was based on the formation of a geminal diamine [3–7] as the main intermediate. This approach was supported by further experimental work [8, 9]. On the contrary, there were other explanations for the mechanism of this reaction, which were based on a two-fold addition–elimination, as suggested by other experimental evidence [10, 11].

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Whereas the study of enzymatic transimination from a chemical point of view is extremely difficult because of its high rate and complexity [1], nonenzymatic transimination has been widely studied by using intramolecular and intermolecular chemical model systems. They rely on the formation of geminal diamines as model compounds in a number of UV and NMR spectroscopic studies [12–20]. This work has allowed the determination of the rate and equilibrium constants of various cyclization and tautomerization processes in which geminal diamines are involved. Acid base catalysis and the effect of the solvent on the proton transfer for the occurrence of these reactions have also been studied this way, [1, 21, 22].

Quantum mechanics calculations onto a reactive system can provide a detailed description of the intermediates and transition-state geometries involved in the reaction. As far as PLP is concerned, Nero et al. [23] studied the main PLP intermediates involved in the transaminase mechanism using the AM1 semiempirical molecular orbital method. Alagona et al. [24] focused their interest on the ability of carbanion formation on substrates including PLP. Bach et al. [25] performed *ab initio* calculations regarding the reactivity of decarboxylation in the PLP-dependent transamination process.

The conversion of external aldimines to internal aldimines and vice versa is one of the key steps in the metabolism of amino acids in which the PLP cofactor takes the leading role. The aim of the present work is to describe the reaction mechanism of transimination by performing quantum mechanics calculations on a PLP Schiff base model system in the gas phase and in a water solvation environment. The computation of the energies of the intermediates and transition-state structures involved in the reaction allows the identification of the most stable intermediate for the gas phase and in water solvation. Thus, the results in both environments provide a basis for supporting in a generic fashion one of the two possible mechanisms that the experimental community has proposed. The calculations also highlight the reactive role of the water molecules for the occurrence of the reaction.

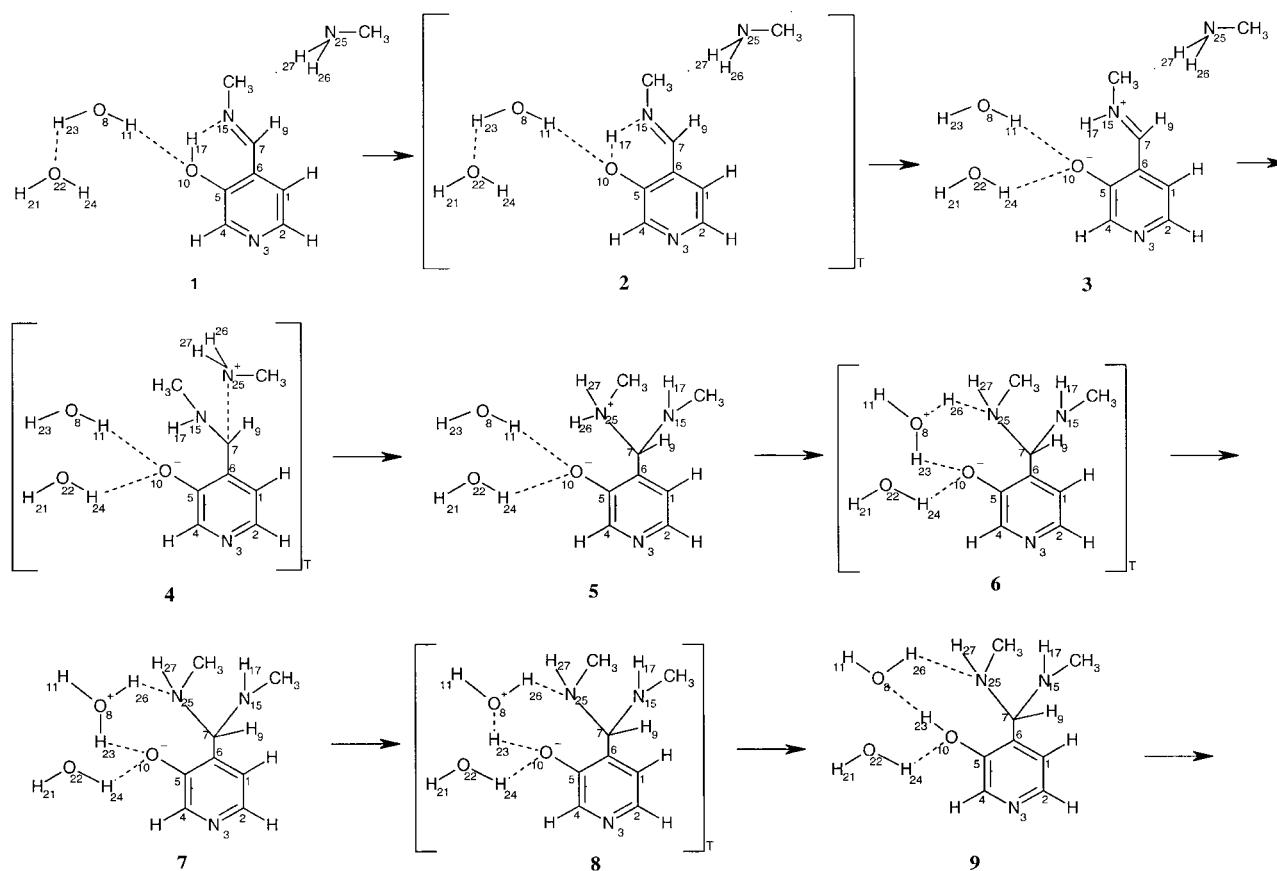
Methodology

A molecular complex of 3-hydroxy-4-(*N*-methylmethylimine)pyridine, methyl amine, and two water molecules (**1** in Scheme 1) was used to simulate the transimination reaction. The former is the Schiff base formed from 3-hydroxy-4-pyridinaldehyde

and methylamine. 3-Hydroxy-4-pyridinaldehyde was used as a model for the cofactor PLP in a theoretical study on the Schiff base formation reaction [26]. When using this molecule, the 2-methyl and 5-phosphate groups are deleted from PLP to deal with a simplified chemical structure in a free enzyme environment. This simplification does not distort the reactivity considered because it is known that 2-methyl and 5-dibasic phosphate anions serve to anchor the cofactor to the active site of the enzyme [27]. Methylamine is the reactive chosen for simulating the amino acid that will be exchanged with the one that is condensed in the PLP Schiff base. When using this model for an amino acid, it is taken into account that the free base form of the alpha amino group is the key point for the progress of the transimination if a nonenzymatic environment is considered.

We included explicit water molecules in the gas-phase study of the mechanism of this reaction. It has been reported that, when performing theoretical reactivity studies for reactions involving a nucleophilic attack on carbonyl carbons with no solvent molecule presence, a nucleophilic approach is carried out with no potential barrier, and energy always decreases until reaching a tetrahedral intermediate [28–31].

The mechanism of the reaction is theoretically established through quantum mechanics calculations using the semiempirical PM3 Hamiltonian [32, 33] included in the AMPAC [34] and MOPAC [35] packages. The use of the PM3 Hamiltonian for semiempirical quantum mechanics calculations has been reported as a suitable method for predicting intermolecular hydrogen bonds between neutral molecules [36] and also appears to predict accurately geometries for neutral hydrogen-bonded complexes involving nitrogen or oxygen [37]. The software was run on a Silicon Graphics Origin 200 computer. After optimization, all the structures were characterized as minima (ground state) or saddle points [transition state (TS)] in the potential energy surface by means of the calculation of the Hessian and further diagonalization of this matrix, which gives the force constants for the molecular system. Ground states were characterized by having all the force constant positives. On the other hand, all transition-state structures showed a unique negative force constant. Internal reaction coordinate [38] calculations following the transition vector of the negative vibrational frequency were also performed for each saddle point to check if the transition-state structures connected the forward and reverse reaction intermediates, respectively.



SCHEME 1. Geminal diamine formation, detachment of the original condensed amine, and Schiff base regeneration steps for the transaldimination reaction.

The effect of the water solvation for the occurrence of the reaction of the system was considered by means of two solvation models. The continuum model consists of the recalculation by means of the PM3 semiempirical Hamiltonian included in the MOPAC package of the optimized gas-phase molecular complex with the COSMO method [39–41]. The supermolecular approach includes the reoptimization and further characterization by vibrational analysis of a molecular complex consisting of the gas-phase structures found surrounded with a periodic box of 30 equilibrated water molecules. Otherwise indicated, transition-states structures for the supermolecular approach were characterized by a single negative constant regarding the vibration considered in the corresponding reaction pathway.

Results and Discussion

Scheme 1 shows the detailed mechanism for the transamination reaction using the molecular com-

plex formed by 3-hydroxy-4-(*N*-methylmethanimine)-pyridine, methylamine, and two water molecules, as it is suggested by the sequence of ground- and transition-state structures. Table I lists the main geometric parameters for structures 1–17 both in the gas-phase (which are equal to those in the continuum solvation model) and in the supermolecular solvation model. The enthalpy of formation profile for the reaction appears in Figure 1 and the value of these energies are listed in Table II. The mechanism can be divided into three parts: geminal diamine formation, detachment of the original condensed amine, and Schiff base regeneration.

GEMINAL DIAMINE FORMATION

The initial molecular complex **1** has one internal hydrogen bond H17—N15 and an external one H11—O10. The occurrence of both hydrogen bonds has the effect of weakening the hydroxyl bond O10—H17. The transfer of H17 to N15 is then accomplished through the transition-state structure (TS) **2**, which evolves to the zwitterionic intermedi-

ate **3**. While the energy gap from **1** to **2** is similar for the gas-phase structure (25.78 kcal/mol) and the continuum solvation approach (22.07 kcal/mol), this energy difference lowers to 17.12 kcal/mol if the explicit solvation model is considered. This can be explained in terms of the stabilization of the transition-state structure that is provided by the water environment. A comparison of the energy differences from TS **2** to **3** in the gas-phase and solvation environments suggests that, once the intermediate **3** is formed with the double hydrogen bonding of two water molecules to O10, the accommodation of additional explicit water molecules around **3** is energetically unfavorable (this energy difference is -7.74 kcal/mol for the explicit solvation model while this value is -19.43 kcal/mol for the gas-phase structures). It is also noticeable that for the hydrogen transfer **1** to **3** the pyridine ring remains flat (the dihedral angle formed by atoms 1, 2, 3, and 4 is 0.0) and the intramolecular distances within the atoms of the ring in the structures in-

The zwitterionic intermediate **3** is the substrate onto which the incoming amine will attack as a nucleophile. As a result of the formation of the ammonium cation on N15, C7 increases its electrophilic character, thus favoring the attack of N25. This situation is described by TS **4**. There, the amine nitrogen N25 approaches C7 by following a path in a plane perpendicular to the flat pyridine ring. The distance C7—N25 is approximately 2.0 Å in TS **4**, whichever environment, gas phase or explicit solvation, is taken into account. Downhill from TS **4**, a zwitterionic intermediate **5** is formed. As happened with the first step **1** to **3**, the geometry of the pyridine ring is not significantly distorted in this step. The π system of the pyridine ring keeps its integrity through the occurrence of the nucleophilic attack of N25 to C7. Also, the double hydrogen bonding from the auxiliary water molecules to O10 is main-

TABLE I

Main geometric parameters for the structures included in the reaction pathway for gas-phase and supermolecular solvation models (the geometry of the structures for the continuum solvation model are the same as those for the gas phase).

Structure	R(15.7)			R(25.7)			R(10.5)			A(15.7.6)			A(25.7.6)			D(15.7.6.1)			D(25.7.6.1)		
	Gas phase	Explicit solvation		Gas phase	Explicit solvation		Gas phase	Explicit solvation		Gas phase	Explicit solvation		Gas phase	Explicit solvation		Gas phase	Explicit solvation		Gas phase	Explicit solvation	
1	1.296	1.297		4.256	4.782		1.361	1.367		118.7	118.6		96.5	73.2		175.1	178.8		-123.4	-127.2	
2	1.317	1.313		4.342	4.890		1.311	1.321		117.1	116.7		104.5	59.7		179.1	-178.3		-129.0	-141.2	
3	1.347	1.330		4.675	4.951		1.256	1.269		121.4	121.3		112.9	114.5		178.8	180.0		-137.1	-142.3	
4	1.373	1.361		1.999	2.084		1.267	1.265		118.9	119.3		98.9	49.0		164.7	165.5		-87.6	-88.2	
5	1.478	1.484		1.586	1.564		1.274	1.281		116.5	115.8		106.2	108.3		146.2	151.1		-99.5	-92.0	
6	1.488	1.491		1.541	1.535		1.293	1.292		114.5	114.0		108.9	110.3		142.6	142.4		-101.4	-100.7	
7	1.492	1.493		1.524	1.520		1.308	1.301		113.9	113.5		110.1	110.2		142.9	142.0		-99.9	-99.3	
8	1.492	1.492		1.519	1.512		1.330	1.326		113.7	114.1		110.4	113.0		141.8	122.8		-100.0	-112.1	
9	1.490	1.506		1.509	1.202		1.369	1.362		116.0	111.4		110.3	112.7		130.3	163.1		-107.3	-72.4	
10	1.534	1.532		1.500	1.500		1.317	1.319		110.5	111.1		113.4	114.1		163.9	176.6		-73.0	-60.0	
11	1.543	1.546		1.502	1.500		1.283	1.287		111.9	112.9		113.8	113.7		159.0	159.3		-77.7	-78.1	
12	2.154	2.077		1.371	1.365		1.253	1.261		50.8	47.6		125.0	123.3		122.9	120.8		-130.4	-129.9	
13	3.377	3.749		1.364	1.348		1.235	1.242		—	—		131.2	130.2		—	—		-158.4	-163.6	
14	4.322	4.280		1.436	1.437		1.226	1.227		—	—		131.1	130.8		—	—		-176.3	-177.9	
15	4.522	4.571		1.349	1.339		1.250	1.260		—	—		121.4	121.6		—	—		-178.8	177.6	
16	5.709	5.831		1.306	1.306		1.297	1.305		—	—		119.4	118.9		—	—		-180.8	174.7	
17	5.854	5.679		1.295	1.296		1.349	1.352		—	—		118.5	118.7		—	—		178.6	178.0	

Structure	R(1.2)			R(2.3)			R(3.4)			R(4.5)			R(5.6)			R(6.1)		
	Gas phase	Explicit solvation		Gas phase	Explicit solvation		Gas phase	Explicit solvation		Gas phase	Explicit solvation		Gas phase	Explicit solvation		Gas phase	Explicit solvation	
1	1.390	1.388		1.358	1.360		1.341	1.347		1.413	1.412		1.409	1.405		1.401	1.397	
2	1.377	1.382		1.374	1.371		1.328	1.332		1.435	1.429		1.421	1.418		1.410	1.406	
3	1.360	1.367		1.398	1.386		1.308	1.316		1.468	1.458		1.445	1.433		1.432	1.419	
4	1.367	1.365		1.388	1.392		1.315	1.315		1.459	1.462		1.435	1.435		1.420	1.419	
5	1.374	1.385		1.379	1.367		1.321	1.328		1.451	1.443		1.429	1.429		1.408	1.400	
6	1.382	1.388		1.368	1.361		1.330	1.336		1.438	1.434		1.422	1.426		1.402	1.395	
7	1.387	1.388		1.362	1.360		1.336	1.334		1.431	1.433		1.419	1.421		1.398	1.397	
8	1.389	1.386		1.359	1.360		1.340	1.340		1.422	1.427		1.413	1.411		1.398	1.402	
9	1.390	1.390		1.355	1.359		1.344	1.343		1.413	1.415		1.404	1.404		1.402	1.401	
10	1.384	1.389		1.365	1.362		1.334	1.337		1.428	1.425		1.415	1.415		1.402	1.400	
11	1.377	1.384		1.374	1.369		1.325	1.329		1.446	1.441		1.424	1.424		1.406	1.402	
12	1.363	1.370		1.394	1.391		1.310	1.318		1.468	1.460		1.468	1.438		1.427	1.420	
13	1.353	1.356		1.406	1.401		1.301	1.304		1.484	1.480		1.459	1.452		1.447	1.442	
14	1.347	1.348		1.415	1.411		1.296	1.297		1.478	1.490		1.478	1.480		1.460	1.462	
15	1.359	1.362		1.400	1.389		1.306	1.311		1.471	1.466		1.449	1.443		1.433	1.428	
16	1.376	1.384		1.375	1.367		1.326	1.334		1.441	1.433		1.420	1.420		1.411	1.404	
17	1.388	1.390		1.360	1.357		1.341	1.343		1.418	1.416		1.409	1.409		1.401	1.401	

Interatomic distances (*R*) are given in Å and angles (*A*, bond angles; *D*, dihedral angles) in degrees.

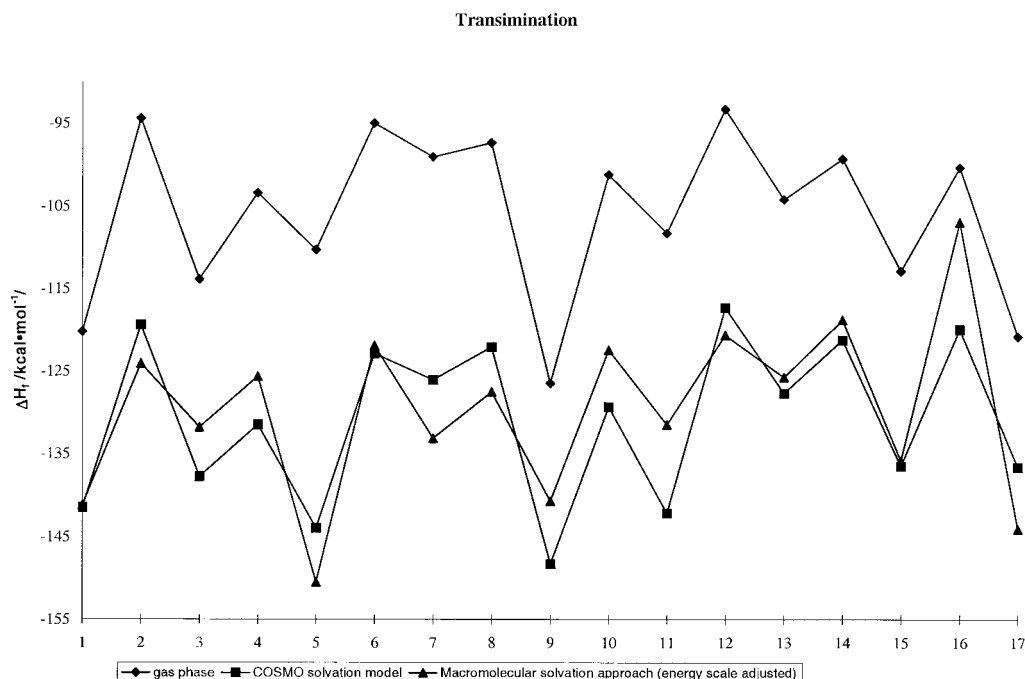


FIGURE 1. The reaction profile for the transimination pathway of the model compound. For this reaction, the standard energy of formation of each structure is plotted as calculated in the gas phase, in the continuum solvation model, and in the supermolecular approach. The energy of the supermolecular approach structures is plotted with a different ordinate scale in such a way that the energy barriers of the transition states can be directly compared from the gas-phase and the Cosmo solvation model.

tained. As TS 4 is a zwitterionic structure, the energy barrier from 3 to TS 4 is about 4 kcal/mol lower for the explicit solvation structure (6.15 kcal/mol) than the gas-phase one (10.45 kcal/mol).

TS 4 evolves to the intermediate 5. The formation of a geminal diamine intermediate requires the deprotonation of N25 in this intermediate and the regeneration of the hydroxyl in O10. This direct transfer of one of the hydrogens of N25 (H26 or H27) to O10 is not favored because of the large distance from each of these two atoms to O10 (3.531 or 3.035 Å) and the orientation of bonds N25—H26 or N25—H27 relative to O10. The presence of the two auxiliary water molecules that form hydrogen bonds with O10 makes this direct transfer even less possible from an electrostatic point of view. However, this double hydrogen bonding to O10 by means of the auxiliary water molecules opens an alternative way for the occurrence of such hydrogen transfer. One of these water molecules becomes a reactive species when TS 6 (Fig. 2) is reached by exchanging one of its hydrogens (H23) for the one (H26) that was bonded to N25. The system evolves to intermediate 7, where a hydronium cation is located in the vicinity of atoms N25 and O10. The energy barrier for the occurrence of this hydrogen

TABLE II
Enthalpy of formation of the structures included in the reaction pathway for gas-phase, continuum solvation, and supermolecular solvation models.

Structure	ΔH (kcal/mol ⁻¹)		
	Gas phase	COSMO solvation method	Periodic box of water molecules
1	-120.21	-141.48	-1941.22
2	-94.43	-119.41	-1924.10
3	-113.86	-137.79	-1931.83
4	-103.41	-131.50	-1925.68
5	-110.32	-143.97	-1950.47
6	-94.98	-122.88	-1921.93
7	-99.05	-126.06	-1933.14
8	-97.34	-122.09	-1927.54
9	-126.50	-148.27	-1940.72
10	-101.22	-129.35	-1922.45
11	-108.30	-142.19	-1931.52
12	-93.28	-117.33	-1920.64
13	-104.19	-127.67	-1925.75
14	-99.30	-121.22	-1918.79
15	-112.86	-136.51	-1935.86
16	-100.33	-119.94	-1906.94
17	-120.78	-136.64	-1944.07

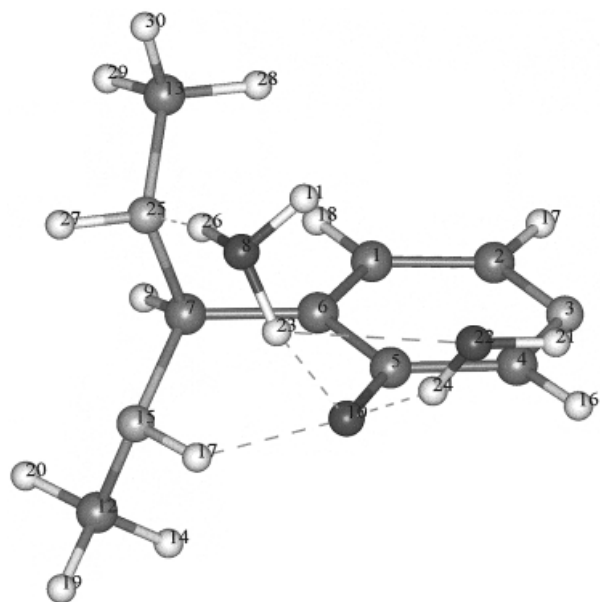


FIGURE 2. Perspective view of TS **6**, in which one water molecule acts as a reactive by exchanging one of its hydrogens with the incoming amine and O10 of the pyridine ring.

transfer mediated by a water molecule (5 to TS **6**) is different for each of the environments considered. The energy differences are lower for the gas-phase structures (15.34 kcal/mol) than for the ones in the continuum model (21.09 kcal/mol) and the explicit solvation model (28.54 kcal/mol). The greater stability of intermediate **5** in water solvation, for both solvation model methods, if compared with the gas-phase structure appears to be the main reason for the surprising high value for this energy barrier. One cannot easily find a reason why in solution this particular zwitterionic structure is more stable than the similar zwitterionic intermediate **3**, which only differs from **5** in the distance of N25 to C7. However, calculations on the explicit solvated system show that the geometry of **5** results in a structure with less charge separation ($\mu = 4.87$ De) than **3** using the explicit solvation model ($\mu = 6.02$ De).

It is known that the use of explicit water molecules for simulating the solvation of reactive species makes difficult the assignment of a ground state as the true minimum because of the flatness of the potential energy hypersurface. IRC calculations forward from TS **2** and reversed from TS **6** led to the reported ground states **3** and **5**. However, additional calculations on intermediate **3** were performed to establish whether the distance of N25 to C7 could distort significantly the solvation sphere of this system in such a way that the energy of the

ground-state structure could dip toward an energy level similar to **5**. The calculations on **3** when increasing N25—C7 show that the energy of the system is only reduced to 3.79 kcal/mol for a distance N25—C7 of 7.54 Å, at the edge of the box of explicit water molecules. Thus, intermediate **5** remains clearly more stable than **3** and this extra stability cannot be related to a preferable disposition of the water molecules around the reactive complex in **5** that results in a structure with less charge separation than in **3**. On the other hand, although a different solvation model as the continuum one is used the difference of stability between **3** and **5** is similar.

Also, the energy gap between intermediates **7** and **5** is lower for the gas-phase structures (11.27 kcal/mol) than for the solvated ones (17.91 kcal/mol in the continuum model and 17.33 kcal/mol for explicit solvation). Thus, water solvation does not provide any stabilization for both transition-state and intermediate structures in this indirect hydrogen transfer despite the fact that all structures involved are zwitterionic. Intermediate **7** reaches TS **8**, which evolves to the geminal diamine intermediate **9** (Fig. 3) through the transfer of H23 from O8 to O10, which regenerates the hydroxyl group in C5. The intermediate **9** is more stable in the overall pathway for the gas-phase structures than in the solvation environment models. Up to three different hydrogen bonds are formed in this structure between the two auxiliary water molecules and the

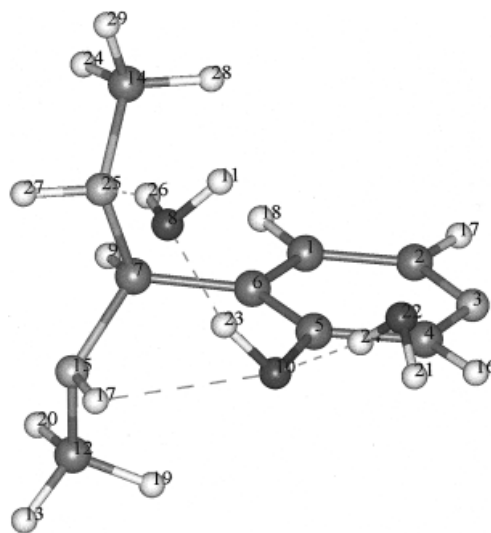


FIGURE 3. Perspective view of geminal diamine **9**. This structure is the main intermediate for model PLP Schiff base formation. Hydrogen bonds are indicated by broken lines.

hydroxyl group and the nitrogen of the incoming amine.

DETACHMENT OF THE ORIGINAL CONDENSED AMINE

From the geminal diamine intermediate **9** the hydrogen bond O8—H23 vanishes when the system evolves to the zwitterionic intermediate **11** by surmounting TS **10**. At this saddle point, the hydrogen transfer from H23 to N15 is allowed to proceed directly, as the distance between both atoms is 1.236 Å. As the starting point **9** is neutral and the hydrogen transfer is performed from an intermolecular polar interaction, the energy barrier for this step is higher if the gas-phase structures are taken into account (25.28 kcal/mol) than if solvation is considered (18.92 and 18.27 kcal/mol for the continuum solvation and explicit solvation models, respectively).

Once N15 is protonated in intermediate **11**, the next step is the detachment of the amine that contains the original nitrogen (N15) in the starting Schiff base. This occurs through TS **12**. In this saddle point, the negative charge on O10 is delocalized through the π system of the pyridine ring and C7 while the bond N15—C7 breaks and C7 loses the tetrahedral character it had in previous structures. Here, note that the geometry of the pyridine ring starts to be distorted (Table I). The dihedral angle formed by atoms 1, 2, 3, and 4 is 3.4°.

SCHIFF BASE REGENERATION

The intermediate that evolves from TS **12** is structure **13**. It can be understood as a protonated imine. H27 needs to be transferred to O10 to regenerate the Schiff base. For this hydrogen transfer to occur, a previous rotational barrier, represented by TS **14**, must be surmounted to allow an adequate geometric disposition of H27 and O10. Here, it has to be noted that the characterization of TS **14** as a transition-state structure has not been possible in the supermolecular water solvation approach because the gradient norm of the optimized structure did not allow the vibrational analysis. In the intermediate zwitterionic structure **15**, the geometry of the aromatic pyridine ring is fully recovered (Table I) and deprotonation of N25 is achieved when the system reaches TS **16**, which evolves to the Schiff base final product **17**. Meanwhile, the amine formed with the nitrogen of the initial Schiff base has been completely removed from the reactive system.

Conclusions

Transimination is known to be a symmetrical reaction. Both reactives and products are equal if the amino acid to be exchanged is the same, as in the present study. However, two different pathways are described for obtaining the geminal diamine that differ in the way by which the hydrogen transfer from the incoming amine to the phenolic oxygen is performed. From **1** to **9**, the pathway is based on the active role of one water molecule as a bridge for the hydrogen transfer when the occurrence of a double hydrogen bonding from the surrounding water molecules to O10 does not allow the internal hydrogen transfer from the incoming amine to this oxygen. Instead, if the reversal of the pathway is considered (from **17** to **9**), the occurrence in TS10 of a single hydrogen bond to O10 from a water molecule makes possible the direct hydrogen transfer from the incoming amine to the phenolic oxygen to yield the geminal diamine **9**.

As can be seen in Table I, there are only slight differences between the main geometric parameters of the structures of the molecular complexes involved in this mechanism when considered in the gas phase or in a solvation environment. On the contrary, as far as energies are considered, the occurrence of solvation modifies the stability of various intermediate and transition-state structures. Experimental work [9] has shown that the rate-determining step for the overall process is the elimination of the amine group once the geminal diamine has been formed. The pathway that is suggested by the intermediate and transition states found in this study is in accordance with this fact, whichever gas-phase or solvation environment is considered for the reactive complex. For both solvation models used, the energy gap for this rate-determining step is approximately 18 kcal/mol (from geminal diamine **9** to TS **10**) and is more related to the hydrogen transfer from the hydroxyl group to the outgoing amine than to the breakage of the C—N bond itself. This is also true for the reversal of the reaction (from **17** to **1**) in which the elimination of the amine group is performed through a water-mediated hydrogen transfer.

Solvent composition plays a major role in the process, as there are involved zwitterionic forms that show lower energy barriers when a water environment is considered than for the gas-phase structures. It must be expected, then, that such zwitterionic molecular complexes react more rapidly than the neutral ones with an increase of the

medium polarity. This is not the case for the water-mediated hydrogen transfer discussed above. For this particular step, although the intermediates and transition-state structures are zwitterionic, the presence of a water environment increases the energy barrier. Thus, the reaction profile for transamination, if water solvation is considered, suggests that the reaction should not proceed significantly in the aqueous media, although it is known that it does at high rates in the enzymatic matrix.

However, the energy results regarding the transition state structures must be taken with great care, as the PM3 Hamiltonian used in the semiempirical calculations is parameterized for ground-state structures. *Ab initio* studies are in progress to get more reliable energy results for the gas-phase transition state structures. Unfortunately, the number of atoms involved in such model systems makes expensive in CPU terms an explicit solvation study at such a level of theory and only continuum models are available in practice.

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