

## RESEARCH ARTICLE

# Theoretical insights into the regioselectivity of a Pictet-Spengler reaction: Transition state structures leading to salsolinol and isosalsolinol

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## Abstract

The mechanism of the cyclization step of the Pictet-Spengler reaction between acetaldehyde and dopamine to give salsolinol and isosalsolinol was studied computationally, using density functional theory. The preferential formation in acidic media of salsolinol, the product of *para*-cyclization, and the requirement of a neutral pH for the formation of the *ortho*-cyclized isosalsolinol are explained in terms of 2 different mechanistic routes with an iminium ion or a phenolate-iminium zwitterion as starting reactants.

## KEYWORDS

DFT calculations, isosalsolinol, Pictet-Spengler of dopamine, regioselectivity, salsolinol

## 1 | INTRODUCTION

The Pictet-Spengler reaction, discovered in 1911, is still one of the most important methods for the construction of the tetrahydroisoquinoline skeleton, present in many molecules of physiological and therapeutic importance.<sup>[1]</sup>

Examples of such molecules are tetrahydro- $\beta$ -carbolines, obtained from starting indole derivatives<sup>[2–4]</sup> or heterocyclic systems obtained by oxa-Pictet-Spengler reactions.<sup>[5]</sup>

Important tetrahydroisoquinolines are obtained by Pictet-Spengler condensation of acetaldehyde, 2-(4-hydroxyphenyl)acetaldehyde or 2-(4,5-dihydroxyphenyl)acetaldehyde with dopamine, epinephrine, and norepinephrine.<sup>[6]</sup>

Salsolinol (1-methyl-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline) (**1**, Figure 1), a dopamine-derived tetrahydroisoquinoline found in brain tissue, has been intensively studied because of its involvement in catechol-aminergic processes.<sup>[7]</sup> Although enzymatic formation of the isomer isosalsolinol (**2**, Figure 1) could in principle be expected, its formation *in vivo* has never been observed. Isosalsolinol is nevertheless an interesting isoquinoline derivative because of its possible role in the biochemistry of alcoholism,<sup>[8]</sup> as it is formed together with salsolinol by a nonenzymatic Pictet-Spengler process.<sup>[9]</sup>

The possibility that isosalsolinol might be a contaminant of salsolinol in these biochemical processes<sup>[10]</sup> led us to attempt the synthesis of isosalsolinol by a Pictet-Spengler reaction. Results were disappointing, and very poor yields of **2** were always obtained. Our synthetic failure in obtaining isosalsolinol by the Pictet-Spengler route prompted us to look for mechanistic reasons for the practically exclusive formation of salsolinol in this reaction.

Bates *et al* had investigated the regioselectivity of the Pictet-Spengler reaction between 3-hydroxyphenethylamines and acetaldehyde or formaldehyde and were able to relate the pH of the medium to the relative yields of the two regioisomeric hydroxylated-1,2,3,4-tetrahydroisoquinoline derivatives.<sup>[11]</sup>

More recently, a one-pot synthesis of tetrahydroisoquinolines in a phosphate buffer was described,<sup>[12]</sup> and mechanisms were proposed involving catalysis by the added phosphate. This report prompted a computational study of the phosphate-mediated Pictet-Spengler reaction of 3-hydroxyphenethylamine with formaldehyde, using *ab initio* and density functional theory (DFT) methods, in the gas phase and in acetonitrile.<sup>[13]</sup>

Although this theoretical work shed light on the role played by the phosphate anion in promoting this reaction,

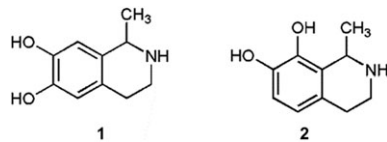


FIGURE 1 Structures of salsolinol (1) and isosalsolinol (2)

the authors concentrated their efforts on the exclusive formation of the *para*-cyclized product, leaving the question of the regioselectivity of this process untouched.

In the present work, we therefore decided to investigate the regioselectivity of this reaction, and Bates' suggestions of possible pH-dependent mechanisms, by means of a DFT study. We employed the Pictet-Spengler condensation of acetaldehyde and dopamine as a model process, emphasizing the regioselective formation of salsolinol and isosalsolinol in water in acidic and neutral medium, respectively.

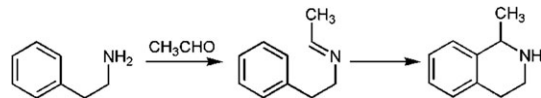
## 2 | COMPUTATIONAL METHODS

The calculations were performed using the Gaussian09 package<sup>[14]</sup> and M062X functional,<sup>[15]</sup> which describes long-range attractive dispersion interactions. Geometries were optimized using the 6-31G(d,p) basis set. Frequency calculations were performed at the same level of theory as the geometry optimization to confirm whether the obtained structures were minima (no imaginary frequency) or transition states (only 1 imaginary frequency). To confirm that all obtained transition states connected the corresponding reactants and products, we performed the intrinsic reaction coordinate calculations in each case. The final free energies reported in this article were obtained from single-point calculations using the larger basis set 6-311++G(2d,2p) corrected for zero-point and thermal effects at 298.15 K, from the frequency calculations and solvation. The latter was calculated as a single-point correction on the optimized structures using the SMD (Solvation Model Density) method for water,<sup>[16]</sup> as implemented in Gaussian09.

Values for  $f_k^-$  were calculated as described in the literature.<sup>[17]</sup> Dual descriptor values ( $\Delta f_k$ ) were calculated from the corresponding fukui functions for electrophilic and nucleophilic attack, from equation  $\Delta f_k = f_k^+ - f_k^-$ .<sup>[18]</sup>

## 3 | RESULTS AND DISCUSSION

The Pictet-Spengler reaction consists of two steps: the initial formation of an imine or an iminium ion, depending on the pH of the medium, and an intramolecular aromatic substitution to produce the six-membered nitrogenated heterocycle.<sup>[19]</sup> These steps are shown in Scheme 1, for the reaction of phenylethylamine with acetaldehyde.



SCHEME 1 Two-step Pictet-Spengler reaction of phenylethylamine with acetaldehyde

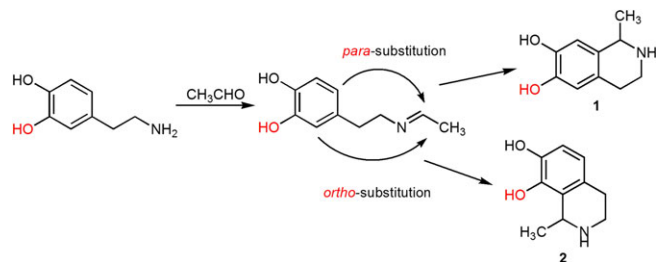
If the starting material contains a substituted aromatic ring such as 3,4-dihydroxyphenethylamine (dopamine), more than one regioisomer may be obtained. In the case of dopamine, these are a *para*- (salsolinol, 1) and *ortho*-substituted (isosalsolinol, 2) tetrahydroisoquinoline derivatives (Scheme 2). The present study will focus on the second step, and on the observed regioselectivity of the aromatic substitution, at acidic pH and at neutral pH.

The proposed mechanisms should account for the following experimental observations:<sup>[11]</sup>

1. At acidic pH, exclusive formation of salsolinols is observed.
2. As the pH of the medium increases, so does the proportion of formed isosalsolinol.
3. At pH 7, it reaches a maximum value of 50%, decreasing to 18% at pH 8.5.

These observations suggest acid-catalyzed processes for the cyclizations. In fact, kinetic studies on the Pictet-Spengler reaction showed that the process is subject to general acid catalysis<sup>[20]</sup> so that we may postulate protonated iminium intermediates as starting materials for the cyclization step. In addition, the fact that *ortho*-cyclization is observed only in more basic media, reaching a maximum at a neutral pH value, also suggests that basic catalysis, with the formation of a phenolate intermediate, is a requirement for the formation of isosalsolinol. We may then postulate a zwitterionic species as the starting material for the *ortho*-cyclization step at pH 7.

The inclusion of water molecules, which play a significant role as general acid and/or base catalysts in these processes, is supported by the fact that the reaction takes place in an aqueous medium. Calculations of chemical processes have often used hydrated supermolecular species that dramatically decrease energy barriers<sup>[21]</sup> and yield results that are much closer to experimental data.<sup>[22]</sup>



SCHEME 2 Formation of salsolinol (1) and isosalsolinol (2) in a Pictet-Spengler reaction with dopamine as starting material

In addition, previous evidence of catalysis by other species<sup>[12]</sup> prompting the successful use of phosphate-mediated supermolecules in a theoretical study of a Pictet-Spengler process<sup>[13]</sup> reinforced our decision to include water molecules as general acid/base catalysts in the present study.

We have therefore analyzed the reaction shown in Scheme 2 in acidic and neutral media, using water molecules as general acid/base catalysts. In the first case, a protonated iminium ion leads exclusively to the *para*-substituted product, the protonated salsolinol. For the reaction at neutral pH, two concomitant pathways are proposed, starting from a phenolate-iminium zwitterion in equilibrium with the corresponding imine and leading to a mixture of zwitterionic salsolinol and isosalsolinol (see Scheme 3).

### 3.1 | Iminium cyclization in an acidic medium

A theoretical rationalization for the exclusive *para*-cyclization of the iminium ion of Scheme 3(a) in an acidic medium was sought by comparing the relative reactivities of its aromatic ring carbons. Two useful theoretical parameters for our purposes were the Fukui function for electrophilic attack ( $f_k^-$ ) at each of the ring atoms<sup>[23]</sup> and the dual descriptor ( $\Delta f_k$ )<sup>[18]</sup> of carbon atoms *ortho* and *para* to the 3-OH group. The sign and magnitude of  $\Delta f_k$  give an indication of the preferred sites for electrophilic or nucleophilic attack in a molecule. Positive values of  $\Delta f_k$  correspond to sites where attack by a nucleophile is favored whereas negative values are an indication of a preferential attack by an electrophile.<sup>[18]</sup>

Calculations led to values of  $f_k^-$  of 0.00 and 0.16 for carbon atoms *ortho* and *para* to the 3-OH group, respectively, indicating that the latter is the preferred site of electrophilic attack. The corresponding values for the dual descriptor were 0.02 and  $-0.12$  (Figure 2). Here again, the negative value of

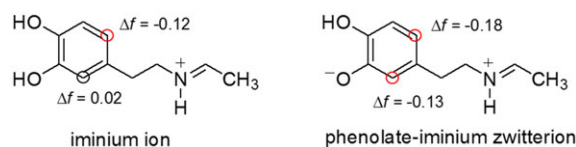


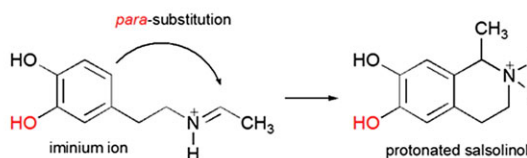
FIGURE 2 Dual descriptor values of carbons *ortho* and *para* to 3-OH

$\Delta f_k$  for the carbon *para*- to the 3-OH group established beyond doubt the exclusive *para*-cyclization observed in acidic medium when the starting species was an iminium ion.

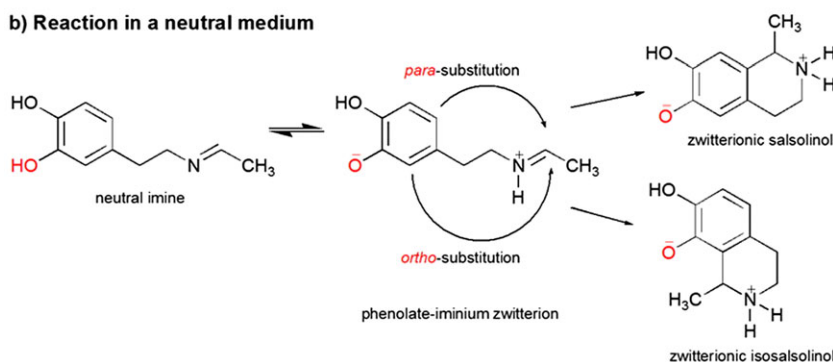
The energy profile for the formation of salsolinol at an acidic pH is shown in Figure 3. Taking into account the fact that the reaction occurs in an aqueous medium, a minimum of two water molecules was added to build a supermolecular hydrated iminium ion as a starting species. The first water molecule helps stabilize the protonated iminium nitrogen, while the second one, hydrogen-bonded to the first, plays a decisive role as a general base catalyst in the second step, corresponding to the rearomatization of the dihydroxyphenyl ring.

The endergonic, rate-determining formation of the intermediate  $\sigma$ -complex takes place via a rather late transition state, TS1-*p(acid)*, where the incipient cyclizing C–C bond distance assumes a value of 1.74 Å, very close to the corresponding distance in the intermediate (1.50 Å). The configuration of the carbon atom *para*- to the 3-OH group in this transition state also departs considerably from its initial  $sp^2$  geometry, assuming a tetrahedral  $sp^3$  configuration very similar to that of the  $\sigma$ -complex intermediate. The two hydrogen-bonded water molecules that solvates the starting iminium adopt a different orientation in the intermediate  $\sigma$ -complex. They act concertedly in the next step, which involves the exergonic aromatization of the cyclized intermediate. By abstracting a proton in the transition state TS2-*p(acid)* from the carbon atom *para*- to the 3-OH group, and transferring

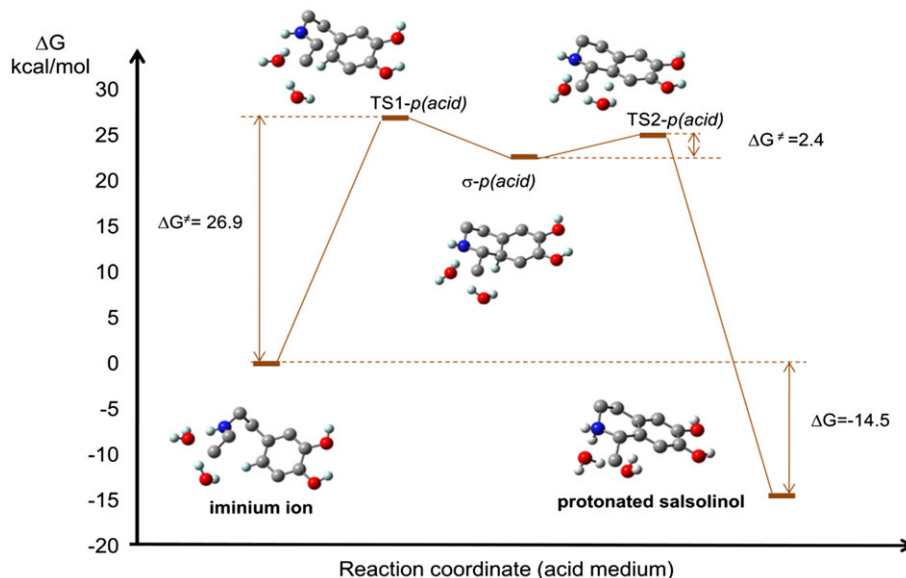
#### a) Reaction in an acidic medium



#### b) Reaction in a neutral medium



SCHEME 3 Proposed pathways for the reaction in an acidic (a) and neutral media (b)



**FIGURE 3** Energy profile for the formation of salsolinol from the iminium ion precursor in acidic medium. For the sake of clarity, not all hydrogen atoms of the solvated species are reproduced

it to the increasingly saturated nitrogen atom, they act both as general base and acid catalysts in this step.

### 3.2 | Imine cyclization in a neutral medium

In a neutral medium, an equilibrium is postulated between the starting imine and a zwitterionic phenolate-iminium, as shown in Scheme 3.

Although this equilibrium should favor the neutral imine, the zwitterionic phenolate-iminium is a much more reactive species. Besides protonation of the imine side chain, which renders it more electrophilic, the phenolate ring system also enhances the reactivity toward the *ortho*- and *para*-aromatic substitution. Thus, according to the Curtin-Hammett principle, both cyclizations at pH 7 should take place from this zwitterionic starting species.

These considerations are reinforced by a comparison of the values of the dual descriptor  $\Delta f_k$  of the carbon atoms *ortho* and *para* to the phenolate oxygen in the zwitterion. In contrast with the iminium cation, the values of  $\Delta f_k$  of the 2 C-atoms were much closer,  $-0.13$  for the C-atom *ortho*-carbon and  $-0.18$  for the *para*-carbon with regard to the phenolate oxygen (Figure 2).

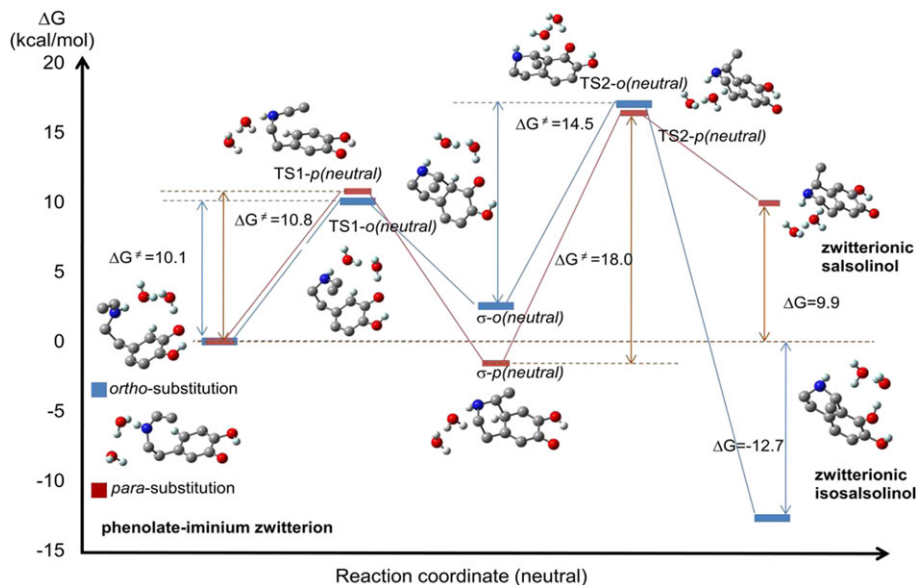
These findings are thus in good agreement with the experimental evidence that *para*-cyclization is exclusively observed from an iminium cation, whereas *ortho*- and *para*-cyclizations compete when the starting species is a zwitterion, as depicted in Scheme 3. Here again, a minimum of two water molecules helped build starting supermolecules for the two processes.

In Figure 4, the energy profiles of the two pathways for the *ortho*- and *para*-cyclizations are compared, starting from hydrated conformations of the zwitterionic phenolate-iminium.

In agreement with the close values of the dual descriptors of the two carbon atoms, the first step, which involves the

internal electrophilic attack of the ring atoms and formation of the intermediate  $\sigma$ -complexes, has similar values of activation free energy to reach the 2 isomeric intermediates (10.1 vs 10.8 kcal/mol). The rate-determining step in both cases is the aromatization of the intermediate  $\sigma$ -complex, a process that is more favored for the *ortho*-cyclization process, with energy barriers of 14.5 vs 18.0 kcal/mol. This is contrast with the previously described energy profile in acidic medium, where endergonic formation of the intermediate  $\sigma$ -complex is the rate-determining step. The reason for this difference stems from the greater stability of complexes  $\sigma$ -*o*(neutral) and  $\sigma$ -*p*(neutral), both of them arenium intermediates that, in contrast with intermediate  $\sigma$ -*p*(acid) in Figure 3, are strongly stabilized by the 2- and 4-oxide anions, respectively.

The rate-determining aromatization of the arenium intermediates is catalyzed by two hydrogen-bound water molecules, which act as a general base catalyst, abstracting a proton from the carbon atoms *ortho* or *para* to the phenoxide oxygen. The difference between the transition free energies  $\Delta G^\ddagger$  of the two isomeric processes (14.5 vs 18.0 kcal/mol) seems a bit too large. The two transition states, TS2-*o*(neutral) and TS2-*p*(neutral), lead to products with an even greater difference in stability (22.6 kcal/mol). Such exaggerated difference is a limitation of the used method of simulation of solvent effects. A neutral supermolecular product (isosalsolinol **2**, hydrated with 2 water molecules) should be largely more stable than its zwitterionic, charge-separated isomer (hydrated salsolinol **1**, in the form of a hydronium-phenolate pair). By applying the principle of microscopic reversibility, if the Hammond postulate is applied to the reverse process, from products to transition states, the exaggerated difference in the stabilities of the products is reflected in an equally exaggerated difference in the stabilities of the corresponding transition states.



**FIGURE 4** Energy profiles for the *ortho*- and *para*-cyclizations from the zwitterionic phenolate-iminium **4**. For the sake of clarity, not all hydrogen atoms of the solvated species are reproduced

In several articles,<sup>[24–27]</sup> Sakaki's model has been applied to correct free energy of reactions studied in solution, obtaining as a result values very close to the ones obtained experimentally, showing the relevance of this model. Sakaki and coworkers proposed to modify the free energy corrections taking in to account the vibrational contribution to entropy only, considering the more restricted movements of the species surrounded by solvent molecules, thus minimizing rotational and translational contributions to free energy. In those articles, intermolecular reactions under study considered changes in the number of species along the reaction coordinate. It is worth to mention that in these studies, the difference between free energy and corrected free energy for vibrational contribution to entropy only is higher than 10 kcal/mol.

By applying Sakaki's model to the calculation of free energy in this work, the corrected  $\Delta G$  values (see Table S1) display smaller differences than the values reported *vide supra* (approximately 0.1 kcal/mol). These results can be attributed to small changes in entropy mainly due to Pictet-Sengler cyclization is an intramolecular reaction, so the number of species along the reaction coordinate remains unchanged. Besides, translational and rotational contributions to entropy are small (see Table S2) and only the vibrational component is larger because the main changes in reactions are bonds rupture and formation.

## 4 | CONCLUSIONS

The present theoretical study of the Pictet-Spengler cyclization step of the reaction between acetaldehyde and dopamine sheds light on the regioselective formation of salsolinol in acidic medium, and on the increased formation of isosalsolinol at neutral pH. Following results from previous kinetic and mechanistic studies in the literature,<sup>[11]</sup> two routes

are proposed: the first, in an acidic medium, starting from an iminium ion and leading exclusively to salsolinol, and the second one, at a neutral pH, starting from a phenolate-iminium zwitterion in equilibrium with the imine and leading to the formation of both salsolinol (**1**) and isosalsolinol (**2**).

The first route involves the formation of the intermediate *para*-substituted  $\sigma$ -complex as the rate-determining step. By contrast, in the second route, aromatization of this intermediate complex becomes the rate-determining step, and the 2 isomers are formed, with some preference for isosalsolinol. The requirements of both a phenolate and a protonated iminium side chain for *ortho*-substitution to take place explain why the competing formation of isosalsolinol is observed at neutral pH. More acidic media protonate the phenolate-iminium zwitterion, leading to the exclusive formation of salsolinol; basic media deprotonate its iminium side chain, making the resulting phenolate unreactive.

Water molecules play a significant role in both pathways, acting as general acid and base catalysts. This role is probably very important in enzymatic processes where amino acid residues may replace the water molecules of the present study, also acting as general acid/base catalysts.<sup>[28]</sup>

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