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Structural and energetics aspects of a proposed mechanism for the phosphate-mediated Pictet–Spengler cyclization reaction: A computational study

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ABSTRACT

A proposed phosphate-mediated mechanism for the Pictet–Spengler cyclization reaction is systematically examined using DFT and *ab initio* methods both in vacuum and in acetonitrile solution. In particular, the condensation reaction of either phenethylamine or 3-hydroxyphenethylamine with formaldehyde to yield the corresponding tetrahydroisoquinoline products was investigated. One mechanistic pathway involves a pre-reaction complex between an iminium cation and a phosphate ion (either dihydrogen phosphate or hydrogen phosphate), a post-reaction complex between the tetrahydroisoquinoline product and the protonated phosphate, and a single transition state complex connecting the pre- and post-reaction complexes. Energy barriers for the reaction system to transition from the pre- to the post-reaction complexes are lower with dihydrogen phosphate rather than with hydrogen phosphate, and in solution rather than in vacuum. Accordingly, the MP2/6-31++G(d,p) calculated lowest energy barriers in solution are 20.83 kcal/mol (3-hydroxyphenetylamine) and 28.77 kcal/mol (phenethylamine). Another mechanistic pathway was also considered for the reaction in acetonitrile solution of the 3-hydroxyphenethylamine substrate. In this case, a third molecule (a solvent molecule, or another phosphate anion) was added to interact with the hydroxy group of the pre- and post-reaction dimer complexes of the iminium cation with the phosphate anion. For all trimer complexes considered, the reaction appears to proceed through a two-step mechanism. The lowest energy path for the reaction occurs when the third molecule added is hydrogen phosphate, with an MP2/6-31++G(d,p) calculated energy barrier of 12.49 kcal/mol in the rate determining step.

1. Introduction

Over a century since its discovery, the Pictet–Spengler reaction remains a prime reaction for the synthesis of tetrahydroisoquinolines from phenethylamines and tetrahydro-β-carbolines to tryptamines [1–3]. The tetrahydroisoquinoline moiety is found in many natural alkaloids and synthetic organic compounds with varied biological activity [4,5]. The Pictet–Spengler reaction is a multistep sequence in which the aromatic ethylamine first condenses with an aldehyde to form an iminium cation which then forms a six-membered heterocyclic ring by a two-step electrophilic aromatic substitution. In general, indoles react under mild conditions and phenethylamines (Fig. 1) require strong acids and high temperature [2,6,7]. However, 3-hydroxy-phenethylamines are observed to react to tetrahydroisoquinolines under mild, aqueous conditions and by enzyme catalysis [3,8–10].

Recently, Pesnot et al. reported on the specific role played by a phosphate buffer to promote the Pictet–Spengler reaction with 3-hydroxy-phenethylamines [8]. These authors carried out the reaction of various phenethylamines and aldehydes in various buffers at pH 6. Particularly striking was the finding that the reaction only occurs for phenethylamines that contain a protic electron releasing substituent (either OH or NH_2) in position 3 of the aromatic ring and that phosphate and related organophosphates were the most effective catalysts. No analogous specificity for the acid–base catalyst has been observed in indole Pictet–Spengler reactions. In light of their experimental results, Pesnot et al. proposed two possible mechanisms to rationalize the unique role of phosphate in the reaction after iminium cation formation (See scheme 2 in Ref. [8]). In both mechanisms, phosphate-mediated deprotonation of the aryl substituent was proposed to catalyze cyclization by increasing the nucleophilicity of the para position of the aromatic ring. The critical role of this deprotonation explains the lack of reactivity observed in phenethylamines lacking the 3-position substituent. However, the experimental data presented was

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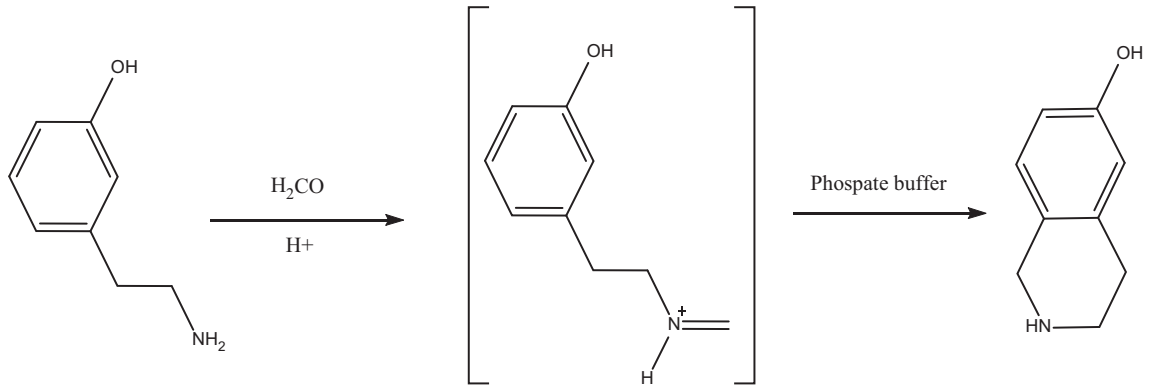

Fig. 1. Reaction scheme showing the formation of an iminium intermediate ion (in brackets) and its subsequent conversion to the Pictet–Spengler condensation product in phosphate buffer.

insufficient to conclude whether complete deprotonation is required or if the electron-donating group alone was sufficient.

After cyclization, any general base catalyst could potentially perform the role of base to deprotonate the ring and restore aromaticity (path b, scheme 2 in Ref. [8]). However, Pesnot et al. proposed a unique role to phosphate ion. A highly reactive aminophosphate intermediate was suggested to form via phosphate attack on the iminium intermediate based on the recent precedent of nucleophilic phosphate addition to cyanamide at pH 7.0 [11]. Upon deprotonation of the 3-substituent, the unique structure of the animophosphate was proposed to facilitate both cyclization and deprotonation to restore aromaticity in one step via a 6-membered ring intermediate (path a, scheme 2 in Ref. [8]).

Prior theoretical studies of the Pictet–Spengler reaction have focused on the cyclization step either in indole reactions or to rationalization of stereochemistry [12–18]. A significant limitation to the synthetic utility of the Pictet–Spengler reaction is control of product stereochemistry [3]. One successful approach to stereochemical control is the use of chiral phosphate catalysts [19–21]. The notable success of diastereoselective phosphate catalysts warrants an investigation into the catalytic mechanism of this ion. To the best of our knowledge, no computational investigation has examined either the role of phosphate catalysis or electron enrichment of the phenethylamine ring in the Pictet–Spengler reaction or related electrophilic aromatic substitution reactions.

The primary purpose of the present work is to report a systematic computational investigation of a plausible phosphate-mediated mechanism of the Pictet–Spengler cyclization reaction of 3-hydroxyphenethylamine. The role of the 3-hydroxy group is investigated through comparison of phenethylamine and 3-hydroxyphenethylamine. Additionally, this work investigates the proposal that phosphate ions uniquely catalyze the two-step cyclization and deprotonation sequence in a single step.

2. Computational details

For all species considered in this study, the B3LYP hybrid functional [22–24] along with the 6-31++G(d,p) basis set was used for geometry optimizations and frequency calculations using the GAUSSIAN 09 program [25]. Moreover, transition states were found using the STQN method (Opt = QST2 or Opt = QST3) [26,27]. Intrinsic reaction coordinate (IRC) calculations using the B3LYP/6-31++G(d,p) method were performed to confirm whether a given transition state truly connected the two minima of interest. Solvent effects were taken into account using the polarized continuum method (PCM) with acetonitrile as the solvent [28]. Single-point energy calculations were carried out on the B3LYP optimized geometries with the MP2 method level [29–33].

Prior to investigating the role of the phosphate ions, the conformational stability of the iminium cation was examined. The purpose of the conformational search was to find low energy conformations of the cation that might interact with the phosphate bases ($H_2PO_4^-$ and HPO_4^{2-}) in a way that favors the formation of the corresponding Pictet–Spengler reaction product, as shown schematically in Fig. 1. For this purpose, the potential energy space resulting from rotations about the N—C bond (D1), and the adjacent C—C bond (D2) respectively was explored using the Opt = ModRedundant option. Accordingly, for a given value of one dihedral angle, the other dihedral angle was varied from 0° to 300° in 60° increments, resulting in a total of 36 points of the conformational space spanned by the two dihedral angles considered, D1 and D2.

Seven distinct minimum energy conformations were identified through relaxed scanning, and their relative energies as well as their corresponding dihedral angles are presented in Table 1. For convenience, the different iminium conformations are denoted ICn, with n increasing from 1 to 7 in accordance with the increasing energy of the conformations. Inspection of Table 1 shows that all minima lie close (within 3.8 kcal/mol) to one another. Full geometry optimization resulted in small changes in D2. Sizeable changes in D1 are, however, observed for the four lowest energy conformations. Upon full geometry optimization, all minima lie within 5.1 kcal/mol of IC2 which is now the most stable conformation followed by IC1. The energy ranking for the other conformations remains unchanged. The absence of any imaginary frequencies in the fully optimized conformations confirmed their nature as minimum energy structures. The fully optimized geometries of the seven minimum iminium ion conformations are shown in Fig. 2. Inspection of Fig. 2 shows that IC2, in addition to being the lowest

Table 1
Iminium ion minimum energy conformations found using scanning and full geometry optimizations at the B3LYP/6-31++G(d,p) level. Dihedral angles, D1 and D2, in degrees; relative energies, ΔE, in kcal/mol.

Conformation	Relaxed scan			Fully optimized		
	D1	D2	ΔE	D1	D2	ΔE
IC1	60	300	0.00	39	306	0.00
IC2	240	300	0.51	266	302	−0.61
IC3	300	60	0.56	319	52	0.69
IC4	60	60	1.26	95	60	0.80
IC5	300	180	2.95	299	180	3.65
IC6	60	180	3.06	60	182	3.77
IC7	180	180	3.78	179	182	4.50