Res Chem Intermed (2015) 41:9835–9843
DOI 10.1007/s11164-015-1987-4

Role of hydroxyl groups on the aromatic ring in the reactivity and selectivity of the reaction of β-phenylethylamines with non-enolizable aldehydes

Rodolfo Quevedo[1] · Christian Díaz-Oviedo[1] · Yovanny Quevedo-Acosta[1]

Received: 26 October 2014 / Accepted: 22 February 2015 / Published online: 24 March 2015

Abstract The influence of hydroxyl groups on the β-phenylethylamine aromatic ring was studied during its reaction with non-enolizable aldehydes. Computational calculations established that the degree of hydroxylation generates differences in the activation patterns of the ring (different reaction pathways) and in the nucleophilicity of the nitrogen atoms (different reaction yields). Cyclic aminals, benzoxazinephanes, or tetrahydroisoquinolines were obtained in the reaction with formaldehyde, and Schiff's bases or tetrahydroisoquinolines were produced in the reaction with other non-enolizable aldehydes. The product obtained depends on the degree of hydroxylation of the ring of the starting phenylethylamine.

Keywords Dopamine · Tyramine · Phenethylamine · Aldehyde · Aromatic Mannich reaction

Introduction

The Pictet–Spengler reaction involves the formation of an imine or iminium ion from an aldehyde and a β-arylethylamine followed by cyclization through an intramolecular aromatic electrophilic substitution in the presence of a catalyst [1–3]. Commonly, the amines used have benzene or indole rings as an aromatic nucleus, forming 1,2,3,4-tetrahydroisoquinolines (THIQ) and 1,2,3,4-tetrahydro-β-carbolines (THBC), respectively. Because the THIQs and the THBCs are nuclei with multiple biological activities, the Pictet–Spengler reaction is considered to be of great importance in the synthesis and biosynthesis of alkaloids and other nitrogenated derivates [4–9].

✉ Rodolfo Quevedo
arquevedop@unal.edu.co

[1] Departamento de Química, Facultad de Ciencias, Universidad Nacional de Colombia, Sede Bogotá, Carrera 30 No. 45-03, Bogotá, Colombia

Dopamine (3,4-dihydroxyphenethylamine) is one of the most used phenylethylamines in the Pictet–Spengler reaction because the high activation of the ring favors its reaction with carbonyl compounds, even under physiological conditions. Recently, the regioselective synthesis of 6,7-dihydroxylated THIQs from dopamine and non-enolizable aldehydes was reported. When the reaction was performed with 3,4-dimethoxyphenethylamine (less activated ring than dopamine) and 3-nitrobenzaldehyde, an intermediate Schiff base was obtained. This cyclization was only possible under strong conditions (reflux in strong acid medium) [10].

The importance of the hydroxyl group on the C-3 of the phenylethylamine ring in the reaction course became evident in a recent study of the reaction between 4-hydroxyphenylethylamines (tyramine and L-tyrosine esters) and formaldehyde. This reaction did not produce the expected THIQs but instead led to the formation of benzoxazinephane-type macrocyclic compounds (2 units of 3,4-dihydro-2*H*-1,3-benzoxazine bonded by ethylene bridges) through a double Mannich-type aromatic reaction [11].

In this work, the effect of hydroxyl groups on the aromatic ring was studied in the reaction course of β-phenylethylamines with non-enolizable aldehydes, selecting the following as model amines: phenethylamine **1** (non-hydroxylated ring), tyramine **2** (4-hydroxylated ring) and dopamine **3** (3,4-dihydroxylated ring).

Experimental

General

Ethanol was fractionally distilled at atmospheric pressure. Chloroform and methanol were dried over 5-Å molecular sieves. All other chemicals were used as commercially available (Alfa Aesar, Panreac). All reactions were conducted with continuous magnetic stirring in oven-dried glassware. Reactions were monitored by TLC until completion using silica gel-coated glass plates (Merck Kieselgel 60). The plates were visualized under iodine vapors.

The nuclear magnetic resonance (NMR) ^{1}H and ^{13}C spectra were collected using a Bruker Avance 400 spectrometer (400 MHz for ^{1}H and 100 MHz for ^{13}C) using the residual signal of the solvent as a reference. All of the chemical shifts are reported as δ values (ppm). The melting points were determined in an electrothermal apparatus (Mel-Temp) with open capillaries, and the reported results are not corrected. The Fourier transform infrared spectroscopy (FT-IR) spectra were obtained using a Nicolet iS10 spectrometer (Thermo Fisher Scientific) in 1 % KBr pellets.

Mass spectra were recorded on a Shimadzu LCMS-IT-TOF instrument using electrospray ionization (ESI). Samples were dissolved in a 90:10:1 acetonitrile/water/formic acid mixture and directly injected. The instrument was operated in positive mode with the following parameters: CDL temperature, 200 °C; heating block, 200 °C; nebulizer (N2) flow, 1.5 l/min; detector voltage, 1.69 kV; scan range, *m/z* 100–500.

Ab initio calculations were performed with the Firefly QC package (version 8.0), which is partially based on the GAMESS (US) code, with a level of theory DFT-B3LYP and 6-31G(d,p) as basis.

Reaction of phenethylamine 1 with formaldehyde

Formaldehyde 37 % (2.5 mmol) was added to a solution of **1** (300 mg, 2.5 mmol) in methanol (5 ml) and then the mixture was stirred at room temperature for 60 h and the solvent was evaporated under reduced pressure.

1,3,5-triphenethylhexahydro-1,3,5-triazine **4** Light-yellow viscous liquid. Yield: 96 %, bp = 130 °C, refractive index 20 °C: $n = 1.6956$, ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.24 (15H, m), 3.44 (6H, br s), 2.73 (8H, m). ^{13}C NMR (100 MHz, $CDCl_3$): δ 140.3, 128.7, 128.3, 126.0, 74.4, 54.5, 34.5. FT-IR (KBr) cm^{-1}: 3,027, 2,929, 1,674, 1,600. ESI-HRMS: *m/z* 399.2590 ($[M]^{\cdot+}$, calc. 399.2669), 422.2440 ($[M + Na]^+$, calc. 422.2567), 438.1825 ($[M + K]^+$, calc. 438.2306).

General procedure for the reaction of phenethylamine 1 with non-enolizable aldehydes

The aldehyde (× mol) was added to a solution of phenethylamine **1** (× mol) in methanol. The mixture was stirred at room for 48 h. The resulting solid was filtrated and dried in an oven at 60 °C overnight to give the desired product.

N-(3-nitrobenzylidene)-2-phenylethanamine **8a** Dark orange viscous liquid. Yield: 94 %, ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.52 (1H, t, $J = 1.8$ Hz), 8.25 (1H, dd, $J = 8.2$ Hz and 2.3 Hz, 1.0 Hz), 8.19 (1H, s), 8.03 (1H, d, $J = 7.7$ Hz), 7.57 (1H, t, $J = 7.9$), 7.32–7.17 (5H, m), 3.92 (2H, t, $J = 7.3$ Hz), 3.04 (2H, t, $J = 7.3$ Hz). ^{13}C NMR (100 MHz, CDCl3): δ 158.8, 148.6, 139.5, 137.8, 133.4, 129.6, 129.0, 128.4, 126.3, 125.0, 122.8, 63.0, 37.2. FT-IR (KBr) cm^{-1}: 3,085, 3,027, 2,927, 2,849, 1,648, 1,615. ESI-HRMS: *m/z* 255.1091 ($[M + H]^+$, calc. 255.1089).

N-(4-hydroxy-3-methoxybenzylidene)-2-phenylethanamine **8b** Purple solid. Yield: 98 %, mp = 110–113 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.04 (1H, s), 7.43 (1H, d, $J = 1.8$ Hz), 7.31–7.16 (5H, m), 7.03 (1H, dd, $J = 8.1$ Hz and 1.8 Hz), 6.89 (1H, d, 8.1 Hz), 3.88 (3H, s), 3.82 (2H, t, $J = 7.6$ Hz), 3.00 (2H, t, $J = 7.6$ Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 161.7, 148.7, 147.3, 139.8, 129.0, 128.4, 126.1, 124.0, 114.2, 108.4, 62.8, 55.9, 50.6, 37.6. FT-IR (KBr) cm^{-1}: 3027, 1644, 1591. ESI-HRMS: *m/z* 256.1665 ($[M + H]^+$, calc. 256.1293).

1,4-*bis*(*N*-phenethyliminomethyl)benzene **8c** White solid. Yield 100 %, mp = 123–125 °C. White solid. mp = 123–125 °C. ^{1}H NMR (400 MHz, CDCl3): δ 8.17 (2H, s), 7.73 (4H, s), 7.32–7.16 (10H, m), 3.88 (2H, t, $J = 7.5$ Hz), 3.02 (2H, t, $J = 7.5$ Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 160.9, 139.8, 138.0, 129.0, 128.4, 128.2, 126.1, 63.3, 37.5. FT-IR (KBr) cm^{-1}: 3,027, 2,930, 2,836, 1,642. ESI-HRMS (ESI): *m/z* 341.1896 ($[M + H]^+$, calc. 341.2012).

2-phenyl-*N*-((*E*)-3-phenylallylidene)ethanamine **8e** Dark-red resinous solid. Yield 90 %. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.17 (2H, s), 7.73 (4H, s), 7.32–7.16 (10H, m), 3.88 (2H, t, $J = 7.5$ Hz), 3.02 (2H, t, $J = 7.5$ Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 163.1, 141.6, 139.8, 135.7, 129.1, 128.9, 128.8, 128.4, 128.1, 127.2,

126.1, 63.0, 37.5. FT-IR (KBr) cm^{-1}: 3,027, 2,929, 2,855, 1,670, 1,601. ESI-HRMS: *m/z* 236.1391 ($[M + H]^+$, calc. 236.1434).

General procedure for the reaction between tyramine 2 and non-enolizable aldehydes

The aldehyde (× mol) was added to a solution of **2** (× mol) in ethanol 96 %. The mixture was refluxed for 24 h; subsequently, the solvent was removed at reduced pressure. The solid obtained was recrystallized from ethanol (96 %).

N-(3-nitrobenzylidene)-2-(4-hydroxyphenyl)ethanamine **9a** Orange solid. Yield 60 %. Mp = 118–121 °C. ^{1}H NMR (400 MHz, DMSO-d6): δ 8.49 (1H, t, $J = 1.8$ Hz), 8.37 (1H, s), 8.27 (1H, dd, $J = 8.2$ Hz and 2.3 Hz), 8.11 (1H, d, $J = 7.7$ Hz), 7.72 (1H, t, $J = 7.9$ Hz), 7.02 (2H, d, $J = 8.4$ Hz), 6.65 (2H, d, $J = 8.4$ Hz), 3.78 (2H, t, $J = 7.3$ Hz), 2.82 (2H, t, $J = 7.3$ Hz). ^{13}C NMR (100 MHz, DMSO-d6): δ 159.4, 155.7, 148.3, 137.8, 134.2, 130.6, 129.9, 125.1, 122.0, 115.2, 62.4, 36.0. FT-IR (KBr) cm^{-1}: 3,087, 2,911, 1,644, 1,612. ESI-HRMS: *m/z* 271.1028 ($[M + H]^+$, calc. 271.1077).

N-(4-hydroxy-3-methoxybenzylidene)-2-(4-hydroxyphenyl)ethanamine **9b** White solid. Yield 87 %. mp = 139–141 °C. ^{1}H NMR (400 MHz, DMSO-d6): δ 9.19 (1H, br s), 8.14 (1H, s), 7.64 (2H, d, $J = 8.8$ Hz), 7.01 (2H, d, $J = 8.4$ Hz), 6.97 (2H, d, $J = 8.8$ Hz), 6.65 (2H, d, $J = 8.4$ Hz), 3.78 (3H, s), 3.68 (2H, t, $J = 7.4$ Hz), 2.77 (2H, t, $J = 7.4$ Hz). ^{13}C NMR (100 MHz, DMSO-d6): δ 161.2, 160.3, 155.5, 130.1, 129.8, 129.5, 129.1, 115.1, 114.1, 62.5, 55.4, 36.3. FT-IR (KBr) cm^{-1}: 3,012, 2,920, 2,678, 2,604, 1,649, 1,605. ESI-HRMS: *m/z* 272.1228 ($[M + H]^+$, calc. 272.1281).

1,4-*bis*(*N*-(2-(4-hydroxyphenyl)ethyl)iminomethyl)benzene **9c** Light-brown solid. Yield 94 %. mp = 168–169 °C. ^{1}H NMR (400 MHz, DMSO-d6): δ 9.21 (2H, br s), 8.25 (2H, s), 7.75 (4H, s), 7.02 (4H, d, $J = 8.4$ Hz), 6.65 (4H, d, $J = 8.4$ Hz), 3.75 (4H, t, $J = 7.3$ Hz), 2.80 (4H, t, $J = 7.3$ Hz). ^{13}C NMR (100 MHz, DMSO-d6): δ 160.7, 155.6, 137.9, 130.0, 129.8, 128.2, 115.1, 62.6, 36.1. FT-IR (KBr) cm^{-1}: 3,486, 3,200–2,500, 1,641. ESI-HRMS: *m/z* 373.1815 ($[M + H]^+$, calc. 373.1911).

2-(4-hydroxyphenyl)-*N*-((*E*)-3-phenylallylidene)ethanamine **9d** Light-brown solid. Yield 46 %. mp = 165–168 °C. ^{1}H NMR (400 MHz, Pyridine-d5): δ 11.33 (1H, br s), 7.98 (1H, d, $J = 8.7$ Hz), 7.52 (2H, d, $J = 7.1$ Hz), 7.35–7.25 (5H, m), 7.21–7.15 (3H, m), 6.94 (1H, d, $J = 16.1$ Hz), 3.84 (2H, t, $J = 7.3$ Hz), 3.02 (2H, t, $J = 7.3$ Hz). ^{13}C NMR (100 MHz, Pyridine-d5): δ 163.2, 157.7, 141.6, 136.8, 131.4, 130.9, 129.6, 129.54, 129.52, 128.0, 116.6, 64.3, 37.5. FT-IR (KBr) cm^{-1}: 3,200–2,200, 1,635, 1,610. ESI-HRMS: *m/z* 252.1331 ($[M + H]^+$, calc. 252.1383).

*Procedure for the reaction between dopamine 3 and trans-cinnamaldehyde **7d***

The aldehyde **7d** (× mol) was added to a solution of **3** (× mol) in methanol. The mixture was refluxed for 24 h; subsequently, the solvent was removed at reduced pressure. The solid obtained was recrystallized from ethanol (96 %).

2-(3,4-dihydroxyphenyl)-*N*-((*E*)-3-phenylallylidene)ethanamine **11d** Light-brown solid. Yield 83 %. mp = 122–123 °C. ^{1}H NMR (400 MHz, CD_3OD): δ 8.39 (1H, d, J = 10.0 Hz), 7.88 (1H, d, J = 15.6 Hz), 7.77 (2H, d, J = 7.2 Hz), 7.59 (1H, t, J = 6.8 Hz), 7.53 (2H, t, J = 7.6 Hz), 7.20 (1H, dd, J = 15.6 Hz and 10.0 Hz), 6.75 (1H, d, J = 8.0 Hz), 6.72 (1H, d, J = 2.0 Hz), 6.58 (1H, dd, J = 8.0 Hz and 2.0 Hz), 3.99 (2H, t, J = 6.8 Hz), 2.97 (2H, t, J = 6.8 Hz). ^{13}C NMR (100 MHz, CD_3OD): δ 159.2, 145.4, 144.3, 133.4, 133.1, 129.6, 129.2, 117.8, 115.7, 115.3, 53.6, 33. FT-IR (KBr) cm^{-1}: 3,335–2,300, 1,663, 1,618. ESI-HRMS: *m/z* 268.1271 ($[M + H]^+$, calc. 268.1332).

Results and discussion

Initially, geometry optimization computational calculations were performed in the Firefly program version 8.0 [12], partially based in the GAMESS computational quantum chemistry software (US), at a DFT-B3LYP/6-31G(d,p) theory level [13]. The combination of this ab initio method and this base set is appropriate for structure prediction in similar molecules [14]. The analysis of frontier molecular orbitals in the aromatic ring for the three model amines showed significant differences (Fig. 1): in **1**, the ring contributes little to the HOMO orbital, while in **2** and **3** (hydroxylated amines), the aromatic rings participate substantially in their

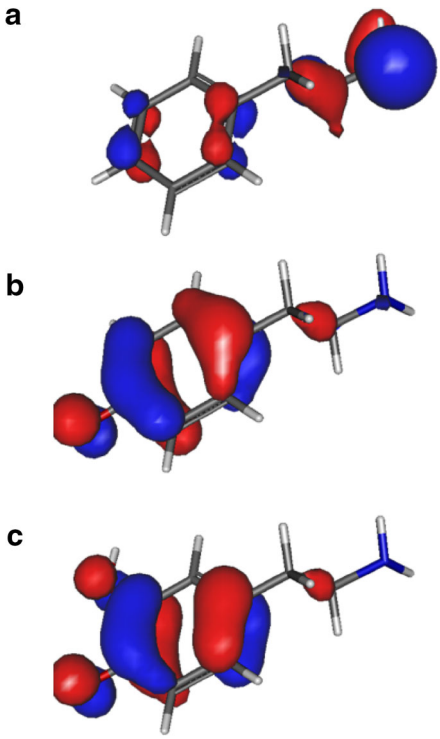


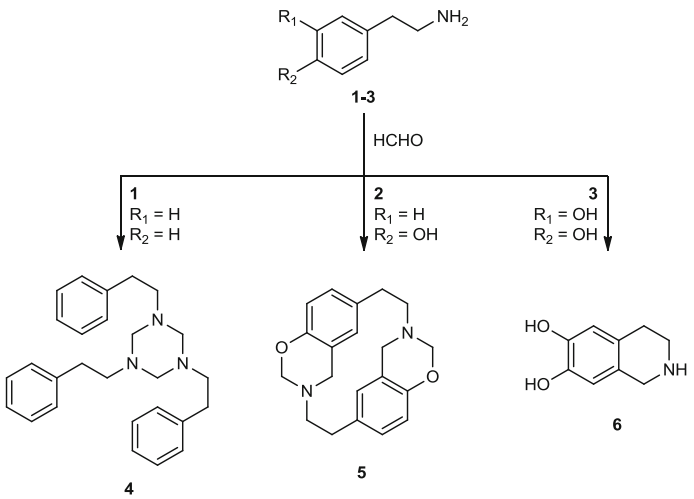
Fig. 1 HOMO of **a** phenethylamine **1**, **b** tyramine **2** and **c** dopamine **3** (DFT-B3LYP/6-31G(d,p), isovalue = 0.05)

respective HOMO orbitals by resonance effects of hydroxyl groups. In addition, the HOMO of **2** and **3** reveal that in **2**, the most activated positions are the *ortho*- to the hydroxyl group (positions C-3 and C-5), while for **3**, the most activated position is C-6.

The electronic differences observed based on the analysis of the molecular orbitals (Fig. 1) for compounds **1–3** correlated fully with the experimental observations for the reaction with formaldehyde. The HOMO orbital of phenylethylamine **1** shows the amine group as the site of greatest nucleophilicity; upon reaction with formaldehyde, the 1,3,5-triphenylhexahydro-1,3,5-triazine **4** was obtained, the product of reacting three moles of phenylethylamine with three moles of formaldehyde [15]. The HOMO orbital of the phenylethylamine **2** shows the carbons *ortho* to the phenolic hydroxyl (C-3 and C-5) as sites of greater nucleophilicity; the reaction with formaldehyde at one of these carbons, through a Mannich-type aromatic condensation, produces azacyclophane-type macrocyclic [11]. The HOMO orbital of the phenylethylamine **3** shows carbon 6 as the position of greatest activation, and against formaldehyde, it produces the respective tetrahydroisoquinoline 6 through a Pictet–Spengler reaction (Scheme 1) [10].

Given the great differences observed for the reaction of phenylethylamines **1–3** with formaldehyde, it became necessary to explore their reactivity against other non-enolizable aldehydes. Chosen for this study were an aldehyde with electron-withdrawing substituents (3-nitrobenzaldehyde **7a**), an aldehyde with electron-donating substituents (vanillin **7b**), a dialdehyde (terephthalaldehyde **7c**) and an α,β-unsaturated aldehyde (*trans*-cinnamaldehyde **7d**).

It is known that dopamine **3** reacts with aromatic aldehydes to produce THIQs through a Pictet–Spengler reaction, as occurred with formaldehyde [10]. In this work, it was observed that when the reaction is performed with aldehydes **7a–c**, the respective THIQs **10a–c** are obtained. This product does not occur when the

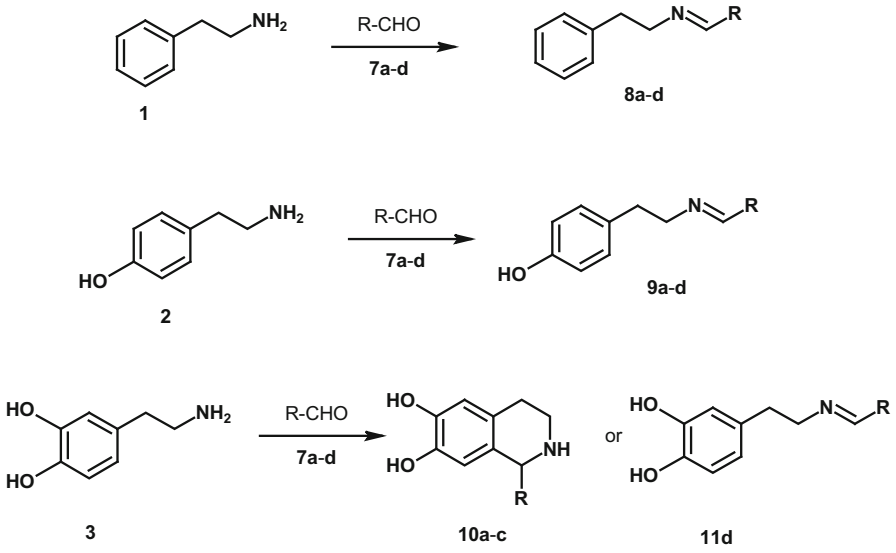


Scheme 1 Reaction of phenylethylamines **1–3** with formaldehyde

reaction is performed with *trans*-cinnamaldehyde **7d**; in this case, it was only possible to obtain with good yields the corresponding intermediate imine **11d** (Scheme 2). Even under strong experimental conditions (reflux in HCl 37 %) it was not possible to obtain the respective THIQ. The formation of the respective THIQ is not favored, most likely due to the conjugation of **11d**, which decreases the carbon electrophilicity and prevents the nucleophilic addition reaction.

The reaction of phenylethylamines **1** and **2** with the aldehydes under study presented the same behavior, and in all cases it was only possible to obtain the corresponding imines (**8a–d** and **9a–d**) (Scheme 2). This behavior allows the conclusion that the nucleophilicity of the aromatic rings in these two phenylethylamines is low and does not favor the aromatic electrophilic substitution required for the formation of THIQs. Likewise, the electrophilicity of the imines (**8a–d** and **9a–d**) is too low to generate aminals or benzoxazinic azacyclophanes through nucleophilic addition reactions, as occurred in the reactions with formaldehyde.

As shown in Table 1, the yields obtained for **1** were higher than those for **2** and **3**. As mentioned above, the analysis of the HOMO orbitals of the three studied amines showed differences in the contribution of the nitrogen atom (Fig. 1). In **1**, the nitrogen atom contributes mainly to the HOMO; the corresponding orbitals in the hydroxylated amines **2** and **3** do not exhibit a contribution from the nitrogen. The decreased contribution of the nitrogen atom to the HOMO orbital as the hydroxylation degree of the ring increases can be related to a lower nucleophilicity character of the amine and explains the decrease in the reaction yields with **2** and **3** compared to the reaction with **1**.



a: R= 3-NO_2-Ph-; **b:** R= 4-OH-3-OMe-Ph-; **c:** R= OHC-Ph-; **d:** R= Ph-CH=CH-

Scheme 2 Reaction of β-phenylethylamines **1–3** with aldehydes **7a–d**

Table 1 Reaction of β-phenylethylamines **1**–**3** with aldehydes **7a**–**d** (products and yields)

R-CHO	Phenethylamine **1** (Yield %)	Tyramine **2** (Yield %)	Dopamine **3** (Yield %)
3-NO2-Ph- (**7a**)	**8a** (98)	**9a** (60)	**10a** (90)[a]
3-OMe-4-OH-Ph- (**7b**)	**8b** (91)	**9b** (80)	**10b** (38)[a]
(1,4)-C6H4- (**7c**)	**8c** (100)	**9c** (94)	**10c** (35)[a]
(E)-Ph-CH=CH- (**7d**)	**8d** (90)	**9d** (46)	**11d** (83)

[a] Data taken from Quevedo et al. [10]

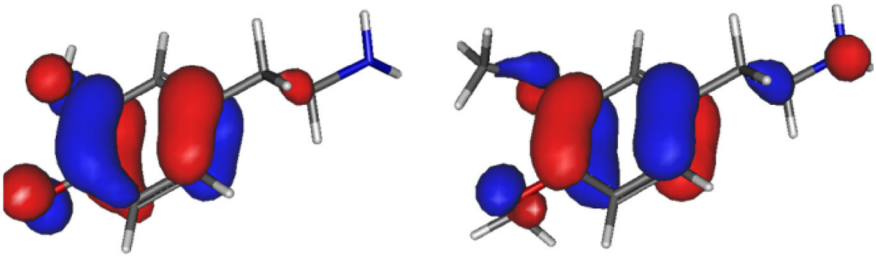


Fig. 2 HOMO of dopamine **3** (*left*) versus 3,4-dimethoxyphenethylamine (*right*) (DFT-B3LYP/6-31G(d,p), isovalue = 0.05)

In an attempt to obtain the corresponding THIQs, the imines **8a** and **11d** were subjected to reflux for long periods of time in methanol, using acetic acid as a catalyst, to simulate the previously reported experimental conditions [10]. No transformations were observed in any of the cases, and the starting amines were always recovered. In imine **8a**, the poor activation of the phenethylamine **1** ring disfavors the aromatic electrophilic substitution required for the cyclization; in imine **11d**, the conjugation of the α,β-unsaturated imine imposes high energy barriers for the nucleophilic addition, even with the high activation of the dopamine ring. In an attempt to force the cyclization of a tyramine amine towards the THIQ, imine **9a** was treated with concentrated HCl (37 %) in reflux; even for strong experimental conditions, as in this case, it was not possible to accomplish the Pictet–Spengler cyclization. These results demonstrate that for the Pictet–Spengler cyclization to occur, it is necessary for the carbon **3** of the phenylethylamine ring to be strongly activating.

To determine if the hydroxyl group is responsible for decreased nucleophilicity of the nitrogen in phenylethylamine, the geometry of 3,4-dimethoxyphenethylamine (*O*-protected dopamine) was optimized. As observed in Fig. 2, the nitrogen atom of the *O*-protected amine present a similar contribution to the values observed in **1**. The analysis of the HOMO orbitals allows the conclusion that the low nucleophilicity of the nitrogen in **2** and **3** and the low yields obtained in the reactions of these amines with non-enolizable aldehydes are due to the presence of hydroxyl groups in the aromatic ring: hydroxyl groups that, by inductive effect, decrease electronic density at the nitrogen and by resonance effects increase

electronic density on the aromatic ring. The analysis of the HOMO orbitals explains the high yield (90 %) reported for the reaction of dimethoxyphenethylamine with 3-nitrobenzaldehyde [10].

Conclusions

In conclusion, in this work, differences were found in the reactivity of the β-phenylethylamines (phenethylamine **1**, tyramine **2**, and dopamine **3**) against formaldehyde, generating a cyclic aminal, a benzoxazinephane, and a tetrahydroisoquinoline, respectively. The differences in reactivity were explained by comparing the HOMO orbitals for the starting amines, observing changes in the ring activity and in the nucleophilicity of the nitrogen. In the reaction with other less reactive non-enolizable aldehydes, only the most activated amine in the ring (dopamine) generated tetrahydroisoquinolines, while the other two formed Schiff bases. The computational calculations demonstrated that a greater hydroxylation on the ring corresponds to a lower nucleophilicity of the nitrogen due to inductive effects; however, if the phenolic hydroxyls are protected, the inductive effect decreases, and the nitrogen nucleophilicity increases.

Acknowledgments The authors wish to acknowledge the Universidad Nacional de Colombia for funding this study (DIB Research Project No. 18615). C.D.-O. thanks the Vicerrectoría Académica de la Universidad Nacional de Colombia for their fellowship support. Y.Q.-A. thanks COLCIENCIAS for their fellowship support.

References

1. E.D. Cox, J.M. Cook, Chem. Rev. **95**, 1797 (1995)
2. J. Stöckigt, A.P. Antonchick, F. Wu, H. Waldmann, Angew. Chem. Int. Ed. **50**, 8538 (2011)
3. R. Quevedo, C. Perdomo, S. Moreno, J. Chem. (2013). doi:10.1155/2013/125302
4. M.F. Melzig, I. Putscher, P. Henklein, H. Haber, J. Ethnopharmacol. **73**, 153 (2000)
5. T. Ohya, M. Niitsu, Biol. Pharm. Bull. **26**, 1215 (2003)
6. K. Okuda, Y. Kotake, S. Ohta, Bioorg. Med. Chem. Lett. **13**, 2853 (2013)
7. M. Ludwig, C.E. Hoesl, G. Höfner, K.T. Wanner, Eur. J. Med. Chem. **41**, 1003 (2006)
8. R. Quevedo, E. Baquero, M.L. Quiñones, Nat. Prod. Res. **26**, 1094 (2012)
9. R. Quevedo, N. Nuñez-Dallos, M.L. Quiñones, Res. Chem. Intermed. (2014). doi:10.1007/s11164-014-1630-9
10. R. Quevedo, E. Baquero, M. Rodriguez, Tetrahedron Lett. **51**, 1774 (2010)
11. R. Quevedo, B. Moreno-Murillo, Tetrahedron Lett. **50**, 936 (2009)
12. Alex A. Granovsky, Firefly version 8.0. http://classic.chem.msu.su/gran/firefly/index.html
13. M.W. Schmidt, K. Baldridge, J. Boatz, S. Elbert, M. Gordon, J. Jensen, S. Koseki, N. Matsunaga, K. Nguyen, S. Su, T. Windus, M. Dupuis, J. Montgomery Jr, J. Comput. Chem. **14**, 1347 (1993)
14. P.R. Richardson, S.P. Bates, A.C. Jones, J. Phys. Chem. A **108**, 1233 (2004)
15. K. Bujnowski, A. Adamczyk, L. Synoradzki, Org. Prep. Proced. Int. **39**, 153 (2007)