Synthesis and theoretical study on 5,6-dimethoxy-2,3-dihydro-7*H*-dibenzo[*de,h*]quinolin-7-one: Possible precursor on the aromatic demethoxylation in oxoisoaporphines

Eduardo Sobarzo-Sánchez · Luis Castedo · Julio R. De la Fuente

Abstract 5,6-Dimethoxy-2,3-dihydro-7*H*-dibenzo[*de,h*]quinolin-7-one has been synthesized by cyclization of phenylethylaminophtalides with polyphosphoric acid and characterized by X-ray diffraction and NMR assignments. A theoretical study by using DFT hybrid method B3LYP and the 6-311 + + G(2d,p) basis set has been carried out. The local reactivity descriptors such as Fukui functions, local softness and local electrophilicity were calculated on the isolated molecule. The results of the calculations were compared with experimental data for understanding the aromatic demethoxylation to afford 5-methoxy-2,3-dihydro-7*H*-dibenzo[*de,h*]quinolin-7-one as final product.

Keywords Oxoisoaporphines · 7*H*-dibenzo[*de,h*]quinolin-7-one · X-ray crystallography · DFT theoretical calculations · Local reactivity indices

Introduction

Alkaloids possessing the 7*H*-dibenzo[*de,h*]quinoline skeleton and bearing different substitution patterns have been isolated from *Menispermum dauricum* DC. (Menispermaceae) [1]. Compounds with the same skeleton, known as oxoisoaporphines or 1-azabenzanthrones, had been synthesized earlier due to their possible photo- and electrochemical properties [2] and as intermediates for the formation of dyes [3]. Some of them have exhibited cytotoxic activities against a small panel of cancer cell lines [4]. However, these compounds had been synthesized previously by a cyclization of phenylethylaminophtalides with polyphosphoric acid (PPA) affording 2,3-dihydrooxoisoaporphines, being only partially characterized through their spectral data and chemical procedures [5]. Otherwise, the 2,3-dihydrooxoisoaporphine non substitution was synthetized through a different way by heating 1-(2-carboxyphenyl)-3,4-dihydroisoquinoline hydrochloride in sulfuric acid [6]. Although in the synthesis of 5,6-dimethoxy-2,3-dihydrooxoisoaporphine starting from the homoveratrylamine (HV) **1** and phthalaldehydic acid (PA) **2**, the global yield of reaction is quite low, an important proportion of 5-methoxy-2,3-dihydrooxoisoaporphine **3** can be identified as final product. This derivate involves the unusual demetoxylation of the 6-*O*-CH_3 group, fact that has been previously reported in the reduction of 1,2,9,10-tetramethoxyoxoaporphine over Adams' catalyst in acid conditions [7]. The facility of elimination of the methoxyl group would involve the participation of a possible intermediate whose reactivity of its methoxyl groups at C(5) and C(6) is highly liable to the PPA.

In order to understand and to correlate the participation of 5,6-dimethoxyoxoisoaporphine **4** as precursor of this unusual aromatic demethoxylation in the mixture of reaction, it seems essential to undertake a detailed comparative study of the isolated molecule and the solid state unit.

In this paper, we describe the synthesis and the chemical reactivity at DFT level of theory of 5,6-dimethoxy-2,3-dihydrooxoisoaporphine by using local reactivity indices on the isolated structure to understand the synthesis of some alkaloids in which the number of oxy groups varies.

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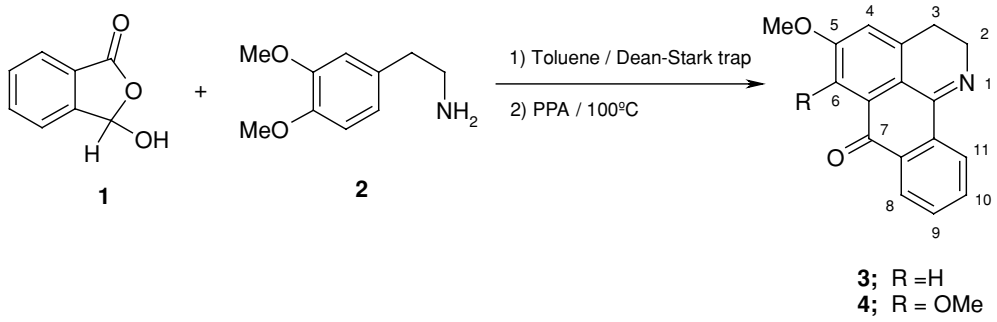


Scheme 1 Synthesis of 2,3-dihydrooxoisoaporfine derivatives with their IUPAC numbering atoms

Experimental

Preparation

5,6-Dimethoxy-2,3-dihydrooxoisoaporphine **4** was prepared as shown in Scheme 1. Meeting points: Kofler Reichert-Jung Galen III apparatus, uncorrected. ^{1}H and ^{13}C spectra: Bruker AMX-300, TMS as internal standard (δ (ppm), J (Hz)). IR spectra: Perkin-Elmer Paragon 1000 FT-IR spectrometer (KBr disk, υ (cm^{-1})). Mass spectra: Hewlett Packard 5988A spectrometer. Microanalyses: Fisons EA 1108 instrument. Flash chromatography (FC): Merck silica gel 60 (230–400 mesh). Analytical thin-layer chromatography (TLC): Merck 60 F254 precoated silica gel plates (0.25 mm).

Synthesis of 5,6-dimethoxy-2,3-dihydro-7*H*-dibenzo[*de*,*h*]quinolin-7-one (4)

A solution of phthalaldehydic acid **2** in toluene was treated with homoveratrylamine **1** and refluxed with stirring under a Dean-Stark trap for 2 h. The resulting mixture was treated with polyphosphoric acid and kept at 100°C for 10 min. The red mixtures were taken up in water, neutralized with NH_4OH and extracted with $CHCl_3$. The chloroform extracts were then dried over anhydrous Na_2SO_4, concentrated, and the residues subjected to silica gel flash chromatography, eluting with hexane-ethyl acetate 95:5 (v/v) to give 5-methoxy-2,3-dihydro-7*H*-dibenzo[*de*,*h*]quinolin-7-one **3** (yield 30%) [8] and 5,6-dimethoxy-2,3-dihydro-7*H*-dibenzo[*de*,*h*]quinolin-7-one **4** as yellow needles (yield 4%).

Experimental data for **4**: M.p. 154–155°C. Found: C, 73.47; H, 5.15; N, 4.57%. Calc. for $C_{18}H_{15}NO_3$: C, 73.71; H, 5.15; N, 4.78%.

^{1}H-NMR ($CDCl_3$): δ 2.86 (t, J = 8.1 Hz, 2H, H-3), 3.96 (s, 3H, O-5-CH_3), 3.98 (s, 3H, 6-OCH_3), 4.07 (t, J = 7.7 Hz, 2H, H-2), 7.01 (s, 1H, H-4), 7.59 (ddd, J (8.9) = J (9.10) = 7.3 Hz, J (9.11) = 1.1 Hz, 1H, H-9), 7.66 (ddd, J (9.10) = J (10.11) = 7,3 Hz, J (10.8) = 1.3 Hz, 1H, H-10), 8.22 (d, J (8.9) = 7,6 Hz, 1H, H-8), 8.31 (d, J (11.10) = 7,1 Hz, 1H, H-11), ^{13}C-NMR ($CDCl_3$): δ 26.07 (C-3), 47.98 (C-2), 56.64 (O-5-CH_3), 61.79 (6-OCH_3), 116.30 (C-4), 120.20 (C-3b), 124.30 (C-6a), 124.60 (C-11), 127.20 (C-8), 131.0 (C-9), 133.40 (C-10), 133.60 (C-3a), 133.80 (C-7a), 135.60 (C-11a), 148.80 (C-6), 156.0 (C-11b), 156.60 (C-5), 184.10 (C-7), IR (KBr disk) υ max: 1659 cm^{-1}. EI-MS (m/z) relative intensity: 293.9 ((M + 1)$^{+}$, 100).

Structure determination

A yellow prismatic crystal of $C_{18}H_{15}NO_3$ was mounted on a glass fiber in an Enraf-Nonius Turbo CAD4 four-circle diffractometer with graphite monochromated Cu K_α radiation (λ = 1.5418 Å) at the temperature 293(2) K. Cell constants and an orientation matrix for data collection were obtained by least-squares refinement of the diffraction data for a total of 12,817 reflections collected with 2353 unique ones (R_{int} = 0.062). The technique used was ω-scan with θ limits $2.45 < \theta < 65.16°$. An empirical absorption correction was also made with SIR-97 program [9]. The structure was solved by direct method and refined by full-matrix least-squares procedure on F^2_{obs} by using the SHELXL-97 software package [10]. All non-H atoms were anisotropically refined. The hydrogen atoms were located on a difference Fourier map and refined geometrically. Atomic scattering factors were taken from *International Tables for X-ray Crystallography* [11]. Molecular graphics were generated with ORTEP-3 [12]. The experimental crystallographic data are given in Table 1. Non-hydrogen atomic coordinates and equivalent isotropic thermal parameters are listed in Table 2.

CCDC 600038 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12,

Table 1 Crystal data and structure refinement for **4**

Empirical formula	$C_{18}H_{15}NO_3$
Formula weight	293.31
Temperature (K)	293 (2)
Wavelength (Å)	1.54180
Crystal system	Monoclinic
Space group	*P*21/*c*
Unit cell dimensions	
a (Å)	5.0896(19)
α (°)	90
b (Å)	15.120(12)
β (°)	92.52(3)
c (Å)	18.063(12)
γ (°)	90
Volume (Å^3)	1388.7 (15)
Z	4
Density (calculated) (mg/m^3)	1.403
Absorption coefficient (mm^{-1})	0.781
F (0 0 0)	616
Crystal size (mm^3)	0.90 × 0.08 × 0.02
θ range for data collection (°)	2.45–65.16
Index ranges	$-5 \le h < 5$, $0 \le k \le 17$, $0 \le l \le 21$
Reflections collected	12817
Independent reflections	2353 [$R_{int} = 0.062$]
Completeness to $\theta = 65.16°$	99.8%
Max. and min. transmission	0.9845 and 0.5398
Data/restraints/parameters	2353/0/244
Goodness-of-fit on F^2	1.100
Final *R* indices [$I > 2\sigma(I)$]	$R_1 = 0.0804$, $wR_2 = 0.2319$
R indices (all data)	$R_1 = 0.0973$, $wR_2 = 0.2612$
Extinction coefficient	0.008 (2)
Largest diff. peak and hole (eÅ^{-3})	0.494 and −0.307

The theoretical model

Density-functional theory (DFT) is a new tool for describing the ground states of molecular systems. Chemical concepts like electronic potential (μ), absolute hardness (η), chemical softness (S) and electrophilicity (ω) are well defined quantities that conveniently rationalize molecular reactivity and chemical bonding [13]. The electronic chemical potential μ is the natural descriptor of the direction of charge transfer during a chemical interaction [14]. The descriptor η is related with the resistance of the system to charge transfer. A good approximation based on Koopmans theorem allows μ and η to be calculated in terms of the electron energies of the frontier molecular orbitals HOMO and LUMO according to Eqs. (1) and (2) [14]:

$$\mu \approx \frac{(\varepsilon_L + \varepsilon_H)}{2}, \quad (1)$$

$$\eta \approx \varepsilon_L - \varepsilon_H, \quad (2)$$

Table 2 Bond lengths (Å) and bond angles (°), and dihedral angles (°) involving non-hydrogen atoms of **4**

Bond lengths (Å)	X-ray	B3LYP/6-31G
N(1)–C(6)	1.285(4)	1.300
C(2)–C(3)	1.453(5)	1.535
C(4)–C(7)	1.391(4)	1.397
C(5)–C(6)	1.471(4)	1.479
C(7)–C(8)	1.380(4)	1.396
C(8)–O(21)	1.364(3)	1.383
C(8)–C(9)	1.408(4)	1.414
C(9)–O(19)	1.365(3)	1.382
C(9)–C(10)	1.404(4)	1.408
C(10)–C(11)	1.493(4)	1.488
C(11)–O(18)	1.215(4)	1.254
C(11)–C(12)	1.490(4)	1.485
C(12)–C(13)	1.382(4)	1.410
O(19)–C(20)	1.425(4)	1.469
Bond angles (°)		
C(7)–C(4)–C(3)	121.6(3)	121.7
C(4)–C(5)–C(6)	117.7(2)	118.2
C(5)–C(6)–C(13)	118.0(2)	118.3
O(21)–C(8)–C(7)	124.3(3)	124.1
O(21)–C(8)–C(9)	115.0(2)	115.4
O(19)–C(9)–C(10)	123.7(2)	122.1
O(19)–C(9)–C(8)	117.0(2)	117.8
C(10)–C(9)–C(8)	119.3(2)	119.6
C(12)–C(11)–C(10)	117.3(2)	118.0
C(13)–C(12)–C(11)	122.5(2)	122.8
C(14)–C(12)–C(11)	118.0(3)	118.3
C(12)–C(13)–C(17)	119.9(3)	119.3
C(12)–C(13)–C(6)	120.3(3)	120.1
C(9)–O(19)–C(20)	115.2(2)	118.3
C(8)–O(21)–C(22)	116.8(3)	118.9
Dihedral angles (°)		
C(6)–N(1)–C(2)–C(3)	32.3(5)	–30.0
N(1)–C(2)–C(3)–C(4)	–43.8(5)	45.5
C(2)–C(3)–C(4)–C(7)	–154.0(3)	148.5
C(2)–C(3)–C(4)–C(5)	30.2(4)	–34.8
C(3)–C(4)–C(5)–C(10)	174.8(3)	–173.7
C(2)–N(1)–C(6)–C(13)	170.7(3)	–175.1
C(4)–C(7)–C(8)–O(21)	–178.5(2)	178.2
C(7)–C(8)–C(9)–O(19)	176.0(2)	173.2
O(21)–C(8)–C(9)–C(10)	179.1(2)	178.4
C(6)–C(5)–C(10)–C(9)	–179.0(2)	172.0
C(5)–C(10)–C(11)–O(18)	175.1(3)	–167.8
O(18)–C(11)–C(12)–C(13)	–174.1(3)	172.7
C(11)–C(12)–C(13)–C(17)	177.1(2)	–179.3
C(14)–C(12)–C(13)–C(6)	175.3(2)	–179.4
N(1)–C(6)–C(13)–C(12)	–170.9(2)	172.2
C(11)–C(12)–C(14)–C(15)	–177.3(3)	179.4
C(6)–C(13)–C(17)–C(16)	–177.0(3)	179.3
C(10)–C(9)–O(19)–C(20)	–85.6(3)	–101.1
C(8)–C(9)–O(19)–C(20)	96.8(3)	84.9
C(7)–C(8)–O(21)–C(22)	–1.7(4)	–3.4
C(9)–C(8)–O(21)–C(22)	177.5(2)	177.2

where ε_L and ε_H are the energies of the LUMO and HOMO levels, respectively.

The chemical softness, S, related with the electronic polarizability of the system, it can be describe as an approximation [14]:

$$S \approx \frac{1}{(\varepsilon_L - \varepsilon_H)} \tag{3}$$

Recently, the global electrophilicity power ω of an atom or molecule has been introduced by Parr et al. [13c] through the simple expression:

$$\omega = \frac{\mu^2}{2\eta} \tag{4}$$

The global electrophilicity ω measures the energy stabilization when the system acquires an amount of electronic charge from the environment. Another local reactivity descriptor related with specific reactions on some organic systems is the Fukui function $f_{(r)}$ [14]. These indices indicate how the incoming or outgoing number of electrons is redistributed in the various regions of the molecule. The condensed forms of this function, for a nucleophilic and electrophilic attack respectively, on atom k, are as proposed by Yang and Mortier [15]:

$$f_k^+ = q_k(N+1) - q_k(N) \tag{5}$$

$$f_k^- = q_k(N) - q_k(N-1) \tag{6}$$

Here $q_k(N)$ represents the electronic population on atom k, for the N electron system considered. As local softness is related to the Fukui function via $s(r) = Sf(r)$ the condensed local softness is related to the condensed Fukui function [16] through.

$$s_k^{\pm} = f_k^{\pm} S \tag{7}$$

$$\omega_k = f_k^+ \omega \tag{8}$$

where f_k is the Fukui function at the site k in the direction of increasing $(+)$ and decreasing $(-)$ number of electrons. Thus, these two regional reactivity indices, the regional softness S_k and the regional electrophilicity ω_k, are distributed following the Fukui function as nucleophilic and electrophilic attacks at site k, respectively.

On the other hand, the proton affinity (PA) is described using the Eq. (9) as the relationship between the enthalpy of formation of BH^+ and its neutral counterpart, B. This is the negative of the enthalpy change of the hypothetical protonation reaction:

$$PA = \Delta H_f(H^+) + \Delta H_f(B) - \Delta H_f(BH^+) \tag{9}$$

where $\Delta H_f(H^+)$ is equal to 353.6 kcal/mol, the experimentally determined value of the heat of formation of a free proton [17], $\Delta H_f(B)$ is the calculated heat of formation of the free base form of the alkaloid, and $\Delta H_f(BH^+)$ is the calculated heat of formation of the protonated alkaloid either at the atom of nitrogen or the atom of oxygen, from carbonyl or methoxyl group.

Computational details

The structure included in this study was fully optimized at the B3LYP/6-31G level of theory by using the Gaussian 03 package of programs [8]. A single point calculation at the B3LYP/6-311 + + G(2d,p) level of theory was carried out to afford the molecular electronic properties such as molecular orbital energies and local reactivity indices. The calculation of the electronic chemical potential and the chemical hardness were obtained from the expressions $\mu \approx (\varepsilon_L + \varepsilon_H)/2$ and $\eta \approx \varepsilon_L - \varepsilon_H$, in terms of the one electron energies of the HOMO and LUMO frontier molecular orbitals, ε_H and ε_H, respectively [14]. With these quantities at hand, the chemical softness S and the global electrophilicity power ω were obtained using Eqs. (3) and (4), respectively. The local softness and local electrophilicity values are obtained from the

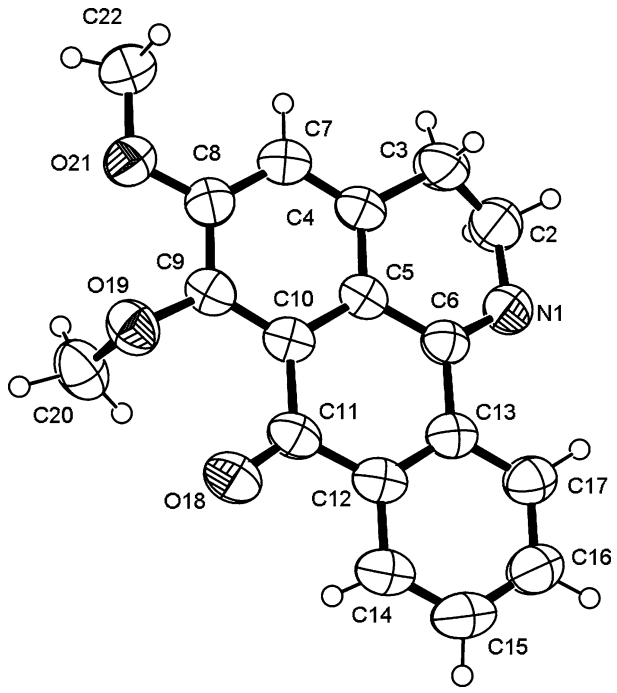


Fig. 1 ORTEP drawing of the molecular structure of **4** indicating atom numbering. Thermal ellipsoids represent 50% probabilities

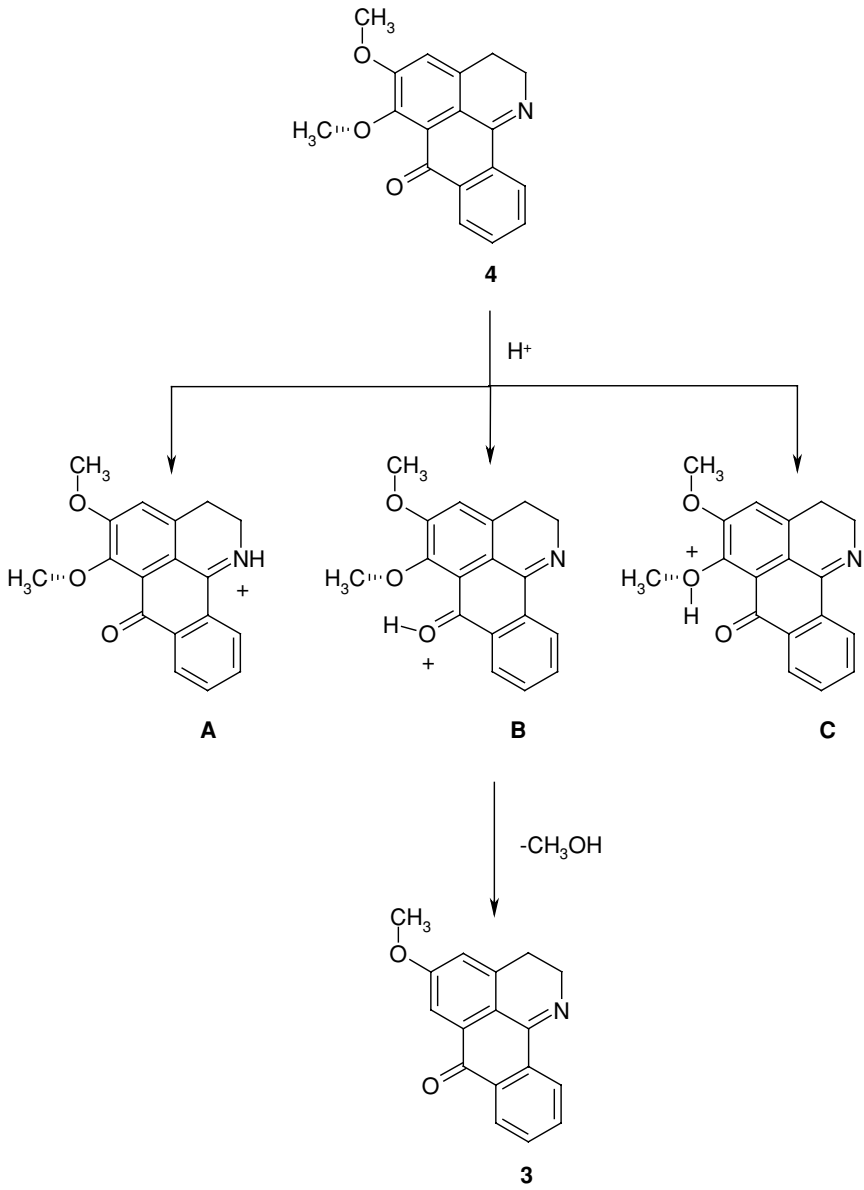
chemical softness and the global electrophilicity indices and the corresponding Fukui function using Eqs. (7) and (8), respectively.

In order to determinate the most stable protonated form for **4** in the aromatic demethoxylation to afford as final product **3**, we have carried out calculations of proton affinity (PA) obtained by using the PM3 semiempirical parameterized method as implemented in version of the HyperChem 7.5 for Windows program [18], through Eq. (9) on the neutral form, and three possible protonated forms: **A**, **B** and **C**. PM3 has proved to be effective in studies on molecules containing heteroatoms for obtaining properties such as electron affinity (EA), proton affinity (PA) and heat of formation ΔH_f [19].

Once the most stable form to be identified, its geometry and molecular electronic properties will be performed at B3LYP/6-311 + + G(2d,p)//B3LYP/6-31G level of theory by using the Gaussian 03 package of programs to compare them regarding the neutral form.

Results and discussion

The ORTEP diagram of the molecule **4** indicating atom numbering scheme with thermal ellipsoids at 50% probability is illustrated in Fig. 1. Selected bond lengths, bond angles and dihedral angles of the crystal structure, together with a comparison of theoretical calculations at B3LYP/6-31G level of theory of the isolated molecule are listed in Table 2. The 5,6-dimethoxy-2,3-dihydrooxoisoaporphine molecule is largely



Scheme 2 Possible intermediates in acid conditions to afford 5-methoxy-2,3-dihydrooxoisoaporphine **3**

planar with two methylene carbons C(2) and C(3), forming a dihedral angle C(6)–N(1)–C(2)–C(3) of 32.3(5)°. The 5-methoxyl group carbon is coplanar with the aromatic ring with a C(8)–O(21)–C(22) of 116.8(3)°. However, the bond angle C(9)–O(19)–C(20) of 115.2(2)° is outside the plane of the aromatic ring with a dihedral angle C(8)–C(9)–O(19)–C(20) of 96.8(3)°. This value is slightly larger than the theoretical calculation by DFT in contrast to the torsion angle of the 5-methoxy group, whose angle C(9)–C(8)–O(21)–C(22) of 117.5(2), is in well agreement with the reported values at B3LYP level of theory. This suggests us that a difference exists between the calculated phase gas and the experimental solid state. The bond lengths for the carbonyl group C(11)–O(18) of 1.215(4) and of the methoxyl groups in the positions 5 and 6, annelated to the aromatic ring C(8)–O(21) and C(9)–O(19) of 1.364(3) and 1.365(3) Å respectively, are in agreement with the reported values for these compounds [20].

In agreement with the information obtained by PM3 semiempirical calculations on all three possible protonated structures present in the reaction (Scheme 2); **A**, **B** and **C**, the calculated proton affinity was: 205.6, 200.2 and 175.6 kcal/mol, respectively. Thus, we observe that the protonated form on the atom of nitrogen is undoubtedly the most stable, though the difference of energy with the protonated form on the atom of oxygen of the carbonyl group **B** is small, only 5 kcal/mol. Therefore, it is logical to think that there would be a balance among these two intermediate structures during the reaction of aromatic demethoxylation at **4**. Even more, when comparing them with the proton affinity of the possible intermediate **C**, we conclude that the protonation of the methoxyl group at O(19) is quite unlikely, in spite of the fact that this group that is outside the aromatic plane, it could be protonated by the lonely electron pairs of the atom of oxygen.

The local reactivity indices calculated on the structure of 5,6-dimethoxy-2,3-dihydrooxoisoaporphine **4** at the B3LYP/6-311 + + G(2d,p) level of theory are described in Table 3. Our results show us that the molecular structure of this alkaloid presents diverse local moieties that can be affected by a nucleophilic attack. For the neutral form **4**, it is noteworthy to mention that the β-atom to carbonyl group C(9) has a ω_k value of 0.188 eV that indicate a major trend to accept electrons from a nucleophile. This fact is confirmed with the local nucleophilic softness s_k^+ whose value of 0.516 a.u. to ratify an orientation towards a possible nucleophilic addition on this atom. Since the experimental conditions of aromatic demethoxylation are carried out in acid conditions, this fact takes us to think that there the possibility of a previous protonation should exist on some atom with high electronic density. In this sense, the atom of oxygen at O(19) would be very favored due to that the 6-*O*-CH_3 group is located outside the plane of the aromatic ring. Therefore, the basicity of its oxygen would be increased due to that the lonely electron pairs are not delocalized on the unsaturated system. Nevertheless, the local electrophilic softness s_k^- and the condensed form of Fukui's function to an electrophilic attack f_k^- of 0.083 a.u. and 0.011 respectively, do not

Table 3 Local reactivity indices of 5,6-dimethoxy-2,3-dihydrooxoisoaporphine[a] **4** and the protonated form **B**

Site$_{(k)}$	$f_{(k)}^+$		$f_{(k)}^-$		$s_{(k)}^+$ (a.u.)		$s_{(k)}^-$ (a.u.)		$\omega_{(k)}$ (eV)	
	NF	PF	NF	PF	NF	PF	NF	PF	NF	PF
C(4)	0.020	0.009	0.030	0.033	0.155	0.090	0.229	0.333	0.056	0.114
C(5)	0.036	0.023	0.032	0.049	0.275	0.232	0.247	0.495	0.100	0.292
C(6)	0.016	0	0.012	0.022	0.124	0	0.091	0.222	0.045	0
C(7)	0.046	0.056	0.039	0.042	0.346	0.566	0.300	0.424	0.126	0.712
C(8)	0.029	0.017	0.037	0.008	0.222	0.171	0.283	0.080	0.081	0.216
C(9)	0.068	0.017	0.038	0.034	0.516	0.171	0.291	0.343	0.188	0.216
C(10)	0.039	0.013	0.020	0.015	0.296	0.131	0.154	0.151	0.107	0.165
C(11)	0.005	0.075	0.118	0	0.041	0.758	0.889	0	0.015	0.954
C(12)	0.018	0.005	0.052	0.009	0.137	0.050	0.393	0.090	0.049	0.063
C(13)	0.013	0.019	0.026	0.015	0.009	0.192	0.199	0.151	0.003	0.241
C(14)	0.020	0.019	0.042	0.014	0.153	0.192	0.317	0.141	0.056	0.241
C(15)	0.016	0.024	0.007	0.029	0.122	0.242	0.054	0.293	0.044	0.305
C(16)	0.021	0.065	0.058	0.014	0.165	0.657	0.437	0.141	0.060	0.827
C(17)	0.001	0.010	0.024	0.005	0.010	0.101	0.183	0.050	0.003	0.127
N(1)	0.099	0.092	0.090	0.086	0.745	0.930	0.678	0.869	0.271	1.171
O(18)	0.050	0.093	0.127	0.035	0.378	0.940	0.963	0.353	0.137	1.183
O(19)	0.041	0.009	0.011	0.060	0.314	0.090	0.083	0.606	0.114	0.114
O(21)	0.063	0.016	0.010	0.076	0.477	0.161	0.075	0.768	0.174	0.203

Note. NF; neutral form; PF; protonated form.

[a]All local reactivity descriptors were obtained at the B3LYP/6-311 + + G(2d,p) level of theory.

indicate that O(19) should be more liable to be protonated. By contrast, the oxygen of the carbonyl group O(18) have a s_k^- value of 0.963 a.u. that indicate us a major trend of approach of a proton on this heteroatom.

Taking into account this fact, and since the data of PA indicate that **A** and **B** are the possible protonated forms to be considered in the reaction of aromatic demethoxylation, we have selected in the theoretical study of local reactivity to the protonated form (PF) **B** at O(18) to help us to understand the possible obtaining under acid conditions of **3** and MeOH as secondary product. Thus, as can be seen in Table 3, the values of local nucleophilic softness $s_{(k)}^+$ and regional electrophilicity $\omega_{(k)}$ for **B** change onto a possible nucleophilic addition and final expulsion of the methoxyl group at C(9). In this sense, the PF has a $\omega_{(k)}$ and $s_{(k)}^+$ values for the β-atom to carbonyl group C(9) of 0.216 eV and 0.171 a.u., respectively that are lower than the neutral form. In spite of this fact, the major trend of accept a proton of the atom of oxygen at O(19), reflected in its s_k^- value of 0.606 a.u., it suggests us a possible coordination of the proton between O(18)–O(19) through the reaction to afford MeOH. Although the driving force for the reaction of aromatic demethoxylation would be governed by the participation of the protonated carbonyl group as better electron-withdrawing for a possible aromatic substitution at C(9), there are not enough experimental nor theoretical data as to postulate a mechanism that to explain is unusual synthetic reaction on the studied 2,3-dihydrooxoisoaporphine.

Concluding remarks

The calculations DFT applied on the reactivity of **4** were compared with the synthesis and crystalline structure data of the alkaloid. The descriptors of local reactivity: Fukui function index, local electrophilicity and softness, demonstrated to be of great usefulness to predict a possible explanation for this unusual aromatic demethoxylation and the reactive moieties on the framework molecular of this type of compound.

A further study about the applicability of this type of theoretical methods in the synthesis of natural products continues at the present time.

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