Thermodynamics of Synthesis of New Phenoxazine Derivatives

V. José Cotuá[1,*], Sandra Cotes[2], Fernando Castro[1] and Pedro Castro[1]

[1]*Grupo de Investigación Max Planck, Universidad del Atlántico, Facultad de Química y Farmacia, Km 7 Antigua Vía a Puerto Colombia, Barranquilla, Colombia*

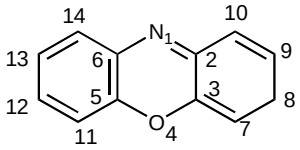
[2]*Universidad del Norte, Departamento de Química y Biología, Km 5 Antigua Vía a Puerto Colombia, Barranquilla, Colombia*

Abstract: This article describes a semi-empirical study on the thermodynamics involved in the synthesis of three novel *ortho*, *meta* and *para,* potentially intercalating phenoxazine **1** derivatives *o*-(**6**), *m*-(**7**) and *p*-(**8**)**.** Quantum chemical calculations at the semi-empirical PM3 method were used in order to evaluate conformational states of the molecules, as well as to predict thermodynamic properties and equilibrium constants. The more favourable product was found to be the compound with the methoxy group in *ortho*-position. The methoxy group in *para*-position hinders the reaction by steric factor, which is reflected from the small constant, *Kp*.

Keywords: Phenoxazine, PM3 calculation, conformational structures, equilibrium constant, thermodynamics.

INTRODUCTION

Substituted phenoxazine amine in position 10 and 14 have been used in organic synthesis for the production of biologically interesting heterocycles, e.g. 3H-phenoxazine **1**. Many molecules with antiviral, antibiotic and anticarcinogenic effects have a phenoxazine ring in common [1-3]. It has been shown that the tricyclic ring system intercalates between adjacent G-C base pairs inhibiting transcription of RNA polymerase.



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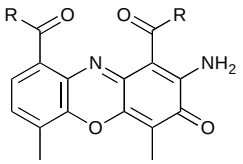

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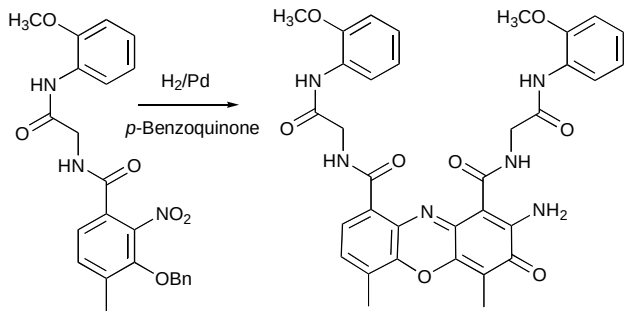
The search for phenoxazine-based compounds with different collateral peptide chains is a challenging research area, in which diminution of toxicity is the main concern. Several synthetic routes to phenoxazines have been reported [4-7], however, the yields are frequently low and methods are often not applicable for the preparation of a wide variety of derivatives. Here, the synthesis of three phenoxazine derivatives with the general structure of **2** with side chains bearing glycine-anisidine substituents were studied and the thermodynamics of the reaction calculated.

*Address correspondence to this author at the Km 7 Antigua Vía a Puerto Colombia. Barranquilla, Colombia. Grupo de Investigación Max Planck, Universidad del Atlántico. Facultad de Química y Farmacia.;
E-mail: jcotuaval@gmail.com

It is important to emphasize the relevance of anisidine as an electron donor substituent that makes the formation of complexes with DNA possible. As a new group of compounds derived from phenoxazine there is no theorethical study available till now and also there is no satisfactory account for the experimental low yields.

Many phenoxazine derivatives, in addition to their marked pharmacological effects, also display high levels of toxicity. These findings make the search of phenoxazone based compounds with different collateral peptide chains a challenging research area, where diminution of toxicity is the main concern.



o - **3**
m - **4**
p - **5**

o - **6**
m - **7**
p - **8**

Scheme 1: General reaction pathway to phenoxazine derivatives **6**, **7** and **8**.

The synthesis of phenoxazine derivatives **6**, **7** and **8** from 3-(benzyloxy)-N-[2-(2-methoxyaniline)-2-oxoethyl]-4-methyl-2-nitrobenzamides **3**, **4** and **5** follows the general procedure outlined in Scheme **1** according to the literature [8-11].

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COMPUTATIONAL DETAILS

This article describes a semi-empirical [12-13] study on the thermodynamics involved in the synthesis of *o*-**6**, *m*-**7** and *p*-**8**. The semi-empirical PM3 method [14] implementation in Spartan´06 software package was used, and the calculations were performed on a DELL PC using the default convergence criteria. For the calculations in this work, the most stable conformations were determined for the corresponding deprotected amine versions of **3**, **4** and **5**, using the systematic approach and MMFF force field [15], except for *p*-benzoquinone and hydrogen, which have no rotational bonds. Deprotected amine versions are now named **3a**, **4a** and **5a**. Once the molecules were optimised at the PM3 semi-empirical model and no imaginary frequencies were found, the thermodynamics - entropy, enthalpy, heat of formation, electric charge distribution and vibrational transitions, the Gibb's free energy and the equilibrium constants were evaluated [16].

RESULTS AND DISCUSSION

Figure **1** shows the general atomic numbering for structures **3a**, **4a** and **5a**. The optimised structures of **3a**, **4a** and **5a** are depicted in Figure **2**. Geometric parameters for structures **3a**, **4a** and **5a**, such as bond length and bond angles, show no significant variation from the average ones, except for $C_{12}N_2C_9$ and $N_2C_9C_8$ in *m*-**4a** with deviations of 2.2° and 5.0°, respectively.

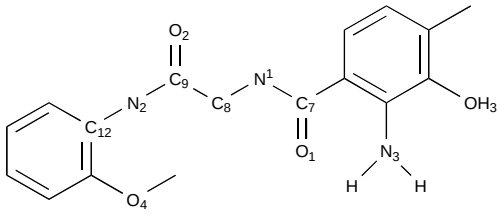

Figure 1: General atomic numbering scheme for **3a**, **4a** and **5a**.

As can be seen in Figure **2**, *m*-**4a** exhibits a chain inversion of direction starting at N2. Also, N1 and the carbonyl group at C7 points to the opposite direction regarding **3a** and **5a**. This particular orientation in *m*-**4a** exposes electron-rich regions to the frontal plane while **3a** and **5a** to the back**.** On the other hand, structure **5a** shows a significant chain extension by the projection of the methoxy group in the *para* position.

Selected Mulliken atomic charges are listed in Table **1**. In view of the similarity among molecules **3a**, **4a** and **5a**, only heteroatoms have been listed in Table **1**.

Table 1: Selected Mulliken Atomic Charges (*e*) of Compounds 3a, 4a and 5a

	3a	4a	5a
O3	-0.207	-0.188	-0.188
N2	0.054	0.048	0.055
C9	0.212	0.215	0.211
O2	-0.367	-0.382	-0.367
C8	-0.111	-0.109	-0.109
N1	-0.024	-0.023	-0.024
O1	-0.372	-0.369	-0.375
N3	0.085	0.085	0.085
O4	-0.238	-0.238	-0.238

Mulliken charges are similar in values across the molecules **3a**, **4a** and **5a**. The atom O1 has the biggest negative charge. N1 has a negative charge while the other two nitrogen atoms N2 and N3 have net positive charges. The dipole moments are 1.33, 1.36 and 1.49 Debye, respectively. Selected vibrational frequencies are listed in Table **2**. The descriptions concerning the assignment have also been indicated in this table.

3a **4a** **5a**

Figure 2: Three-dimensional structures of **3a**, **4a** and **5a**.

Table 2: Selected Vibrational Frequencies in cm^{-1} for 3a, 4a and 5a

3a	4a	5a	Description
1914	1906	1912	C=O str
1617	1606	1613	N-H bending
1439	1403	1409	C=C Ar str
1325	1325	1326	C-N Ar str
1199	1238	1199	C-O str
967	968	966	Disubstituted Ar str

Table 3: Frontier Molecular orbital energies for 3a, 4a and 5a

	E HOMO (eV)	E LUMO (eV)
3a	-8.42	-0.16
4a	-8.50	-0.18
5a	-8.46	-0.13

Considering the frontier molecular orbitals rules related to relative reactivity and taking into account the HOMO-LUMO energy gap for **3a**, **4a** and **5a** (see Table **3**), it can be said that the smaller energy gap of **3a** allowed it to react more efficiently than **4a** and **5a** with both electron rich and electron poor reagents.

Equilibrium constants and reaction yields follow the order *o*-**6** > *m*-**7** > *p*-**8** which are given in Table **4**. The thermodynamic properties of *o*-**6**, *m*-**7** and *p*-**8** synthesis are listed in Table **5**. The equilibrium constants were calculated by the following equation: $\Delta G_T = -RT \ln K_p$

Table 4: Equilibrium Constants and yield of *o*-6, *m*-7 and *p*-8

Product	*Kp*	% Yield
o-**6**	22.28	74
m-**7**	1.23	37
p-**8**	0.11	--

Table **5** reveals that changes in enthalpy and entrophy were negative $\Delta St<0$, $\Delta Ht<0$, indicating that the reactions are exothermic. The free energy change is negative for *o*-**6** and *m*-**7**, which implies an spontaneous process, whereas for *p*-**8**, the free energy is positive, which shows that the process is not spontaneous.

The subsequent calculation of the equilibrium constants at 298.1 K show that the most favourable compound is *o*-(**6**), as shown in Table **4**. The calculated constants are related to the experimental results [17]. In Table **4**, compound *o*-**6** has the greatest equilibrium constant and highest yield, followed by *m*-**7**. In contrast, *p*-**8** has the lowest k_p, and thus could not be synthesised.

Figure **3** shows the general atomic numbering for structures *o*-**6**, *m*-**7** and *p*-**8** and figure **4** the minimun energy conformation. In Table **6** the atom N3 in *m*-**7** has the biggest negative charge, which makes it the

Table 5: Thermodynamic Properties, Total Energy (*E*) and Zero Point Energy (*ZPE*) at 298.15*K*

	E **Kcal.mol^{-1}**	***ZPE*** **Kcal.mol^{-1}**	***S^o*** **Kcal.mol^{-1}K^{-1}**	***H^o*** **Kcal.mol^{-1}**	**ΔS_T Kcal.mol^{-1}K^{-1}**	**ΔH_T Kcal.mol^{-1}**	**ΔG_T Kcal.mol^{-1}**
Compound **3**	-111.07	222.58	0.16	236.62			
Compound **4**	-111.86	222.97	0.17	237.05			
Compound **5**	-111.00	222.88	0.16	236.95			
p- Benzoquinone	-23.74	55.74	0.08	59.37			
Hydroquinone	-64.29	70.12	0.08	74.57			
Hydrogen	-5.07	6.40	0.03	5.88			
o-**6**	-145.39	405.50	0.27	432.76	-0.02	-6.97	-1.83
m-**7**	-146.98	405.94	0.26	433.04	-0.03	-7.88	-0.12
p-**8**	-144.43	405.60	0.26	432.75	-0.03	-7.28	1.30

[a] ΔS_T = (S^oproduct + S^ohydroquinone + 2S^oH$_2$) – (2S^oreactant + S^o*p*-benzoquinone);ΔH_T = (H^o + *E* + *ZPE*) product + (H^o +*E* +*ZPE*) hydroquinone + 2(H^o + *E* + *ZPE*) H$_2$ - (H^o + *E* + *ZPE*) reactant – (H^o +*E* +*ZPE*) *p*-benzoquinone. $\Delta G_T = \Delta H_T - T\Delta S_T$

most likely site of protonation as well as a potential coordination site with metallic ions.

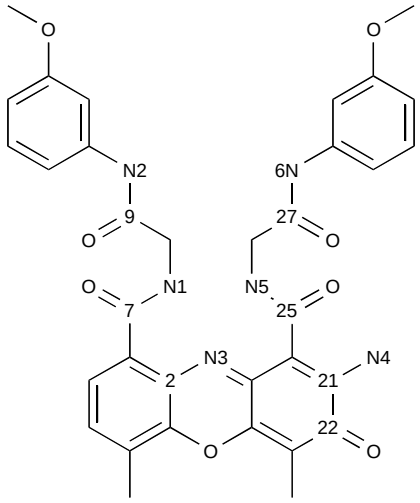

Figure 3: General atomic numbering scheme for structures *o*-**6**, *m*-**7** and *p*-**8**.

On the other hand, althought the C2 in *o*-**6** and *p*-**8** atom have bigger negative charge, the sterically hindered effect prevents it from continuing to react with other atoms. The electron availability in N1, N2, N4, N5 and N6 for protonation or metallic coordination in *o*-**6**, *m*-**7** and *p*-**8** is reduced by the carbonyl group proximity.

Selected IR vibrational frequencies for *o*-**6**, *m*-**7** and *p*-**8** are listed in Table **7**. The descriptions concerning the assignment have also been indicated in this table.

Table 7: Selected Vibrational Frequencies in cm^{-1} for *o*-6, *m*-7 and *p*-8

	C=O	NH	C=C
o-**6**	1884.52 str	3340.90 str	1753.10 str
	1912.36 str	3371.59 str	
	1945.96 str		
m-**7**	1807.65 str	3196.35 str	1782.69 str
	1898.11 str	3301.33 str	
	1942.43 str		
p-**8**	1894.65 str	3185.44 str	1759.05 str
	1915.65 str	3295.47 str	
	1944.99 str		

The dipole moment of molecules *o*-**6**, *m*-**7** and *p*-**8** are 0.57, 5.74 and 3.03, respectively. The carbonyl group presence in the side chains of phenoxazone ring promotes an electron movement in which the methoxy group stabilizes the charges most satisfactorily in *ortho* and *para* positions. On the other hand, in *m*-**7** the electron donating capabilities of the methoxy group are

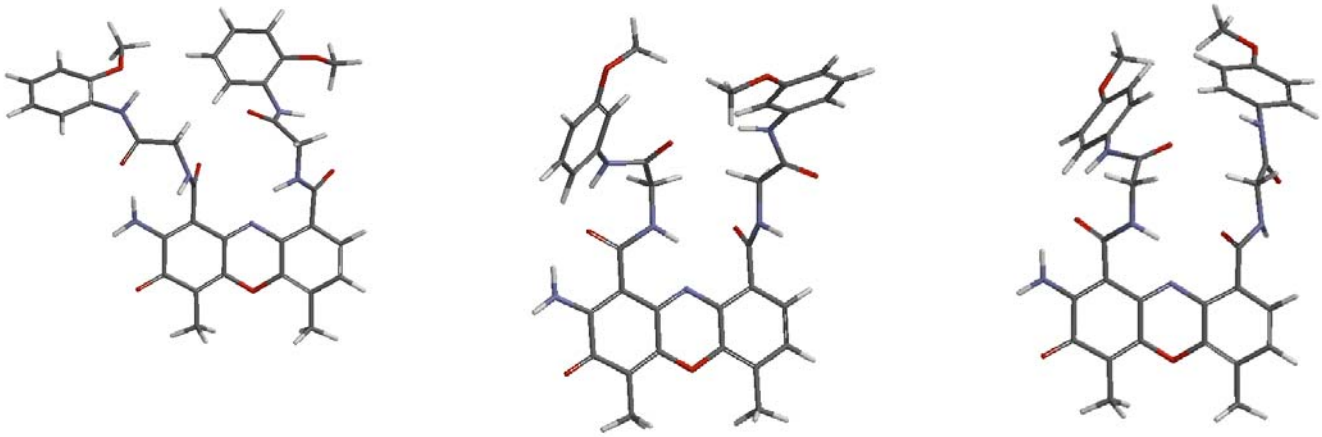

Figure 4: Three-dimensional structures of *o*-**6**, *m*-**7** and *p*-**8**.

Table 6: Selected Mulliken Atomic Charges (*e*) of Compounds *o*-6, *m*-7 and *p*-8

	N1	N2	N3	N4	N5	N6	C9	C2	C21	C22	C25	C7	C27
o-6	-0,027	0,071	-0,053	-0,119	-0,025	0,069	0,215	-0,064	0,364	-0,277	0,325	0.310	0.226
m-7	-0,035	0,044	-0,065	0,181	-0,049	0,017	0,230	-0,058	- 0,043	0,357	0,335	0.296	0.244
p-8	-0,026	0,048	-0,066	0,170	-0,030	0,030	0,232	-0,082	-0,044	0,358	0,326	0.294	0.226

less involved, causing a higher dipole moment. The higher polarity of *m*-**7** could enhance a phosphate interaction with the DNA chains.

CONCLUSION

The computational calculations are consistent with the experimental result, which is reflected in the predicted values of the constants K_p and yields of the respective reactions. Based on the theoretical calculations and the experiment, the formation of the more favourable product was found to be the compound with the methoxy group in the *ortho* position. This may be due to the spatial organisation of the minimum energy conformer (see Figure **1**), which adopts an arrangement, making it more accessible to reactive species. Meanwhile, the *para*-reagent hinders the reaction by the steric factor of the methoxy group in *para*-position, which is reflected by the small K_p value and by the fact that it was not obtained experimentally.

Atomic charge distribution analyses show that the title compounds can use N3 to react with metallic ions. The change of Gibb's free energy is negative for *o*-**6** and *m*-**7**, indicating the process of formation from 3-(benzyloxy)-N-[2-(2-methoxyaniline)-2-oxoethyl]-4-methyl-2-nitrobenzamide at room temperature is spontaneous.

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