The Intramolecular Hydrogen Bond in Local Anesthetics Analogs A DFT Study

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Introduction

Local anesthetics (LA) are drugs used to prevent or reverse acute pain and treat symptoms of chronic pain. In terms of chemical structure, local anesthetics have three parts: a lipophilic (aromatic) end, a hydrophilic (amine), and a link between both ends containing either aminoester or aminoamide bonds[1]. Sets of substituted N,N-[(dimethylamino)ethyl] benzoate hydrochlorides, structurally related to procaine, have been previously synthesized in our group and their lethal potencies determined. QSAR studies revealed that their toxicity (LD_{50}) is described mainly by a hydrophobic term. A small contribution of an electronic term was also observed [2].

The lateral chain of this set of hydrochlorides leads to conformers that exhibit intramolecular hydrogen bonds, previously studied by us.[3] The purpose of this theoretical study is to give a new insight on the N-H---O bonding situation of N,N-[(dimethylamino)ethyl] benzoate and benzamide hydrochlorides, providing information about the effect of substitution on the aromatic ring at *meta* and *para* positions (H (**1**), OCH_3 (**2**) , Cl (**3**), NO_2 (**4**), N-$(CH_3)_2$ (**5**), and SO_2CH_3 (**6**)) for this set of compounds (Figure 1).

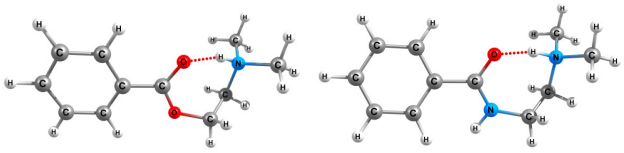

Figura 1. .Optimized structures of N,N-[(dimethylamino)ethyl] benzoate and benzamide hydrochlorides.

Results e Discussion

All calculations (geometry optimizations, stretching frequencies, relative energies, topological analyses (AIM and ELF), NBO, and NPA analyses) were performed in gas-phase by using B3LYP/6-311++G(d,p) level of theory. According to Table 1, the differences in the vibrational frequencies in relation to **1** show a similar pattern for both C=O and N-H stretching modes. The frequency associated to N-H (hydrogen bond donor) stretching is typically red-shifted. For compounds **2** and **5** (*meta* or *para* substituted) this shift occurs due to N-H bond length increase, when compared with **1**. The lowering of N-H stretching frequency is much more pronounced for *para*-substituted benzamides when compared with the corresponding benzoates *para*- or *meta*-substituted. On the other hand, improper blue-shifting hydrogen bonds (characterized by an increase of N-H stretching frequencies) are observed for **3**, **4**, and **6**. Improper blue-shifts are more pronounced in *meta* than in *para* substituted derivatives. In addition, it is slightly more effective for benzamides than for benzoates.

Table 1. Harmonic vibrational frequencies values (cm^{-1}) of compounds **1**-**6**, including *meta* and *para*-substituted derivatives.[a]

Comp.	meta		para	
	C=O	N-H	C=O	N-H
		Benzoate		
1	1688	2955	1688	2955
2	1687 (-1)	2944 (-11)	1678 (-10)	2882 (-73)
3	1695 (7)	2988 (33)	1688 (0)	2963 (8)
4	1703 (15)	3033 (78)	1703 (15)	3031 (76)
5	1681 (-7)	2909 (-46)	1670 (-18)	2778 (-177)
6	1698 (10)	3019 (64)	1698 (10)	3015 (60)
		Benzamide		
1	1658	2690	1658	2690
2	1657 (-1)	2668 (-22)	1655 (-3)	2607 (-83)
3	1660 (2)	2738 (48)	1655 (-3)	2712 (22)
4	1668 (10)	2803 (113)	1669 (11)	2804 (114)
5	1656 (-2)	2609 (-81)	1635 (-23)	2486 (-204)
6	1661 (3)	2767 (77)	1662 (4)	2770 (80)

a: The values in parentheses depict the differences in relation to **1**.

Conclusions

In general, ligands containing electron donors substituents favour red-shifting hydrogen bonds, while electron withdrawing groups favour unusual hydrogen bonds.

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[2] Amaral, A. T.-do *et al.*. *Eur. J. Med. Chem.* **1997**, *32*, 433.
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