Study on the regiosselectivity of the *N*-ethylation reaction of *N*-benzyl-4-oxo-1,4-dihydroquinoline-3-carboxamide

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Introduction

N-1-substituted-4-oxo-1,4-dihydroquinolines are the basic structures for some of the most important antibiotics currently in use against bacterial infections. Moreover, its bioactivity has been successfully extended to antiviral, antiplasmoidal, anticancer and trypanocidal. In many cases, the presence of a hydrogen bond donor group at C-3 of the oxo-1,4-dihydroquinoline core, such as a carboxamide group, seems to be important for achieving a bioactive profile.[1] Experimentally, the *N*-ethylation reaction of the *N*-benzyl-4-oxo-1,4-dihydroquinoline-3-carboxamide (**1**) occurs in a regiosselective way, on the *N*-1, (quinolone core) with no modification of the carboxamide group at C-3, and involves the previous deprotonation of the reagent, followed by an S_N2 reaction with the ethylating agent (Figure 1).[2]

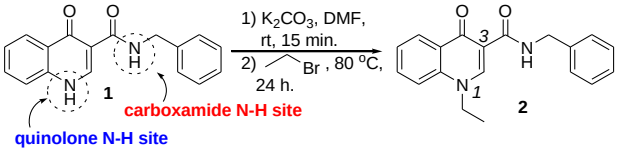

Figure 1. *N*-ethylation reaction of *N*-benzyl-4-oxo-1,4-dihydroquinoline-3-carboxamide (**1**).

In this work, we theoretically investigated the chemical regiosselectivity of the ethylation reaction of 4-oxoquinoline **1** in terms of its acid/base behavior and possible reaction pathways.

Results and Discussion

The acidity of both carboxamide and oxoquinoline N-H sites were compared in gas and condensed phases using water and dimethyl sulfoxide (DMSO). The solvent effects were included according to the Polarized Continuum Model[3] (Table 1).

Table 1: Acidity of both 4-oxoquinoline and carboxamide N-H in different media (kcal.mol^{-1}).

	Gas Phase		H_2O		DMSO	
	ΔH	*ΔG*	*ΔH*	*ΔG*	*ΔH*	*ΔG*
Oxoquinoline	321.2	316.1	182.8	174.8	184.0	175.3
Carboxamide	362.8	358.4	205.8	197.6	207.4	199.1

The results from Table 1 show that the deprotonation of both oxoquinoline and carboxamide are endothermic and favors the reagents. The hydrogen of the oxoquinoline site is more acidic than that of the carboxamide by *ca.* 23.0 kcal.mol^{-1}. Even implicitly, the presence of the solvent drastically decreases the energy required for deprotonation. For water as solvent, this energy is *ca.* 1.5 kcal.mol^{-1} smaller than for DMSO. Following, the pathways for the S_N2 *N*-alkylation reaction of both the deprotonated species (oxoquinoline and carboxamide) using bromoethane were obtained (Table 2).

Table 2: Activation energies and enthalpies of both quinolone and carboxamide *N*-alkylation reaction in different media (kcal.mol^{-1}).

	Gas Phase		H_2O		DMSO	
	E_a	*ΔH*	E_a	*ΔH*	E_a	*ΔH*
Oxouinoline	14.6	-7.3	11.0	-25.4	11.4	-24.7
Carboxamide	9.8	-19.9	9.5	-31.8	9.5	-31.7

The comparison of the two possible reaction pathways shows that, although the *N*-ethylation of the carboxamide site presents lower activation energy, the reaction on the oxoquinoline-*N*-1 site gives much more stable products. The inclusion of the solvent stabilizes the oxoquinoline transition state more than the carboxamide one and again the difference between the solvents is negligible. All the calculations were performed with DFT-B3LYP[4] exchange-correlation functional and 6-31+G(d) basis set function as implemented in Gaussian 09.

Conclusions

The regiosselectivity experimentally observed could be explained through the higher acidity of such site and the higher stability of the respective *N*-1-ethylated product formed when compared with those of the carboxamide.

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