Molecular Modeling for Generation of Structural and Molecular Electronic Descriptors for QSAR Using Quantum Mechanical Semiempirical and *ab initio* Methods

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1 Introduction

The major thrust of scientific research is to understand and explain the biological functions of biological systems in molecular terms. The development of techniques of molecular modeling has opened the prospects for understanding the function, reactivity and properties of biological systems in terms of molecular structure. QSARs quantify the connection between the structure and properties of molecules and allow the prediction of properties from structural and electronic parameters. The QSAR studies employ electronic, hydrophobic, structural and topological parameters of the compounds. In particular, electronic parameters are considered important in the establishment of QSAR models and are helpful to quantify different types of intermolecular and intramolecular interactions, as these interactions are usually responsible for properties of biological systems. The hydroxy substituted quinones and their derivatives are of considerable practical importance in the field of biology and pharmacology, as prominent family of pharmaceutically active and biologically relevant chromophores. Hydroxy naphthoquinone derivatives, in particular, have shown inhibitory effect on DNA topoisomerase-I and antiproliferative activity and cytotoxic activity [1, 5, 6]. We have generated the molecular electronic descriptors like the energies of HOMO and LUMO, dipole moment μ ionization potentials, heat of formation, total energy E_T, electronic energy E_{el}, electronic transition energies and IHB strengths for the hydroxy derivatives of series of quinones by optimizing their geometries using the semiempirical and ab initio molecular modeling methods.

2 Method and Results

2.1 Method

The model starts with the computation of the energy minimum geometries of the individual molecular systems by minimizing the energy with respect to all geometrical co-ordinates, without imposing any geometrical constraint using the semiempirical quantum mechanical AM1 or the ZINDO/1 method. The optimized geometries so obtained are then used as initial input structure for geometry optimizations using the ab initio calculations at HF level employing basis sets selected depending on the accuracy required. The strengths of the IHBs are calculated by performing the optimization of

the geometry for various conformers of the molecular systems using the semiempirical AM1 and the ZINDO/1 methods, the same can also made at the ab initio level at the cost of larger computational time [2, 3, 4].

2.2 Results

Table 1 shows the calculated electronic and geometrical descriptors obtained for the pharmaceutically important series of hydroxy derivatives of 1,4-naphthoquinone (NQ), viz., 2-hydroxy-1,4-NQ, 5-hydroxy-1,4-NQ, and 5,8-dihydroxy-1,4NQ. In Fig. 1, HOMO-1, HOMO and LUMO MOs are displayed.

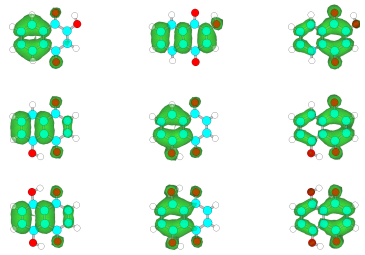

Figure 1: MOs of the Hydroxy NQs.

Table 1: Electronic and Structural Descriptors.

Descriptor	2HNQ		5HNQ		DHNQ	
	ZINDO/1	ab initio	ZINDO/1	ab initio	ZINDO/1	ab initio
HOMO (eV)	-8.23	-9.43	-8.82	-9.03	-8.51	-8.50
LUMO (eV)	2.84	-1.73	-2.58	-1.85	-2.83	-0.35
μ(D)	4.52	1.57	-60034	0.58	1.81	0.81
E_T(kcal/mol)	-75091	3.96	-60265	-67717	-62658	
E_{el}(kcal/mol)	-303022	-60226	-231244	-231549	-276895	-256574
H→L energy (eV)	3.06	-230063	2.85	3.57	2.51	3.26
IHB str. (kcal/mol)	6.78	3.82	24.55	-	22.96	-
O ——— O (Å)	2.325	-	2.312	-	2.331	-
O ——— H (Å)	1.460	-	1.280	-	1.276	-

3 Conclusions

The electronic and geometrical descriptors for the ligands are calculated using the quantum mechanical semi empirical and ab initio methods that can be directly used for QSAR studies of the ligand-protein interactions.

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