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Experimental and theoretical electron density and electrostatic properties as a tool for understanding activity of HIV-1 integrase inhibitor precursors

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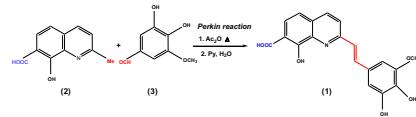
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Introduction

Styrylquinoline derivatives are potent inhibitors of the HIV-1 virus integrase activity⁽¹⁾. The biologically tested molecules contain one aromatic part connected to the quinoline group through different chemical spacers. The most promising molecule in the inhibition of the HIV-1 integrase is the (E)-8-hydroxy-2[2-(4,5-dihydroxy-3-methoxyphenyl)-ethenyl]-7-quinoliniccarboxylic acid (**1**) where the spacer is a C=C double bond. The crystallization of this molecule is particularly difficult giving rise to very small needle-shape crystals which are instable in time. In order to recover the molecular property, we have synthesized and crystallized the two precursors of this molecule: the 3', 4', 5'-methoxy-dihydroxy benzaldehyde aromatic part (**2**) and the 8-hydroxy-7-quinolinic acid (**3**).

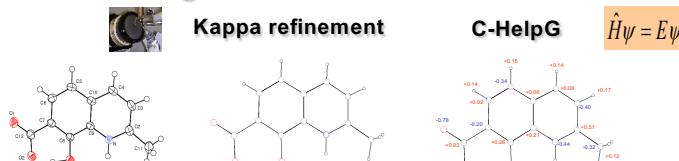
Study's Steps

1. High resolution X-ray diffraction data Collecte at 100K on a Smart CCD diffractometer
2. Data refinement by the Hansen-Coppens⁽²⁾ multipole model
3. Characterization of the chemical bonds and the electrophilic/nucleophilic characters of the two precursors: electron density topological properties and the electrostatic potential
4. Comparaison between the experimental results and the *ab initio* quantum mechanic calculations for (**2**) and (**3**) isolated molecules
5. Theoretical calculations for (**1**) molecule



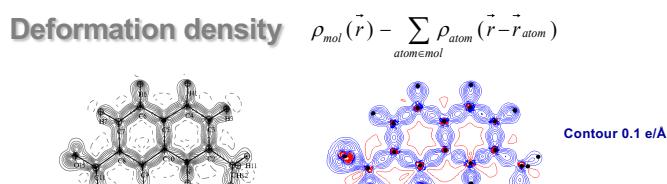
8-hydroxy-7-quinolinic acid

Atomic charges

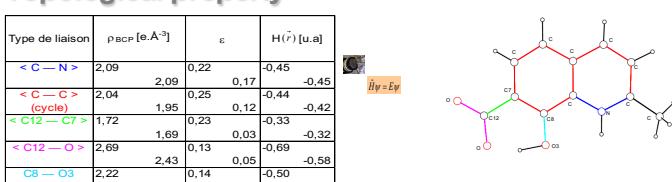


Crystal environment

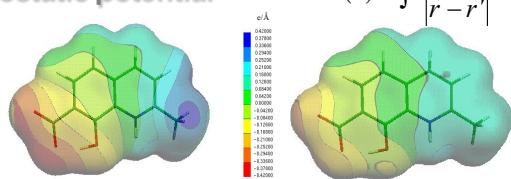
Intramolecular Hydrogen bond R. A. H. B. 1.51 Å
 Intermolecular hydrogen bonds 1.55 < distance < 2.26 Å



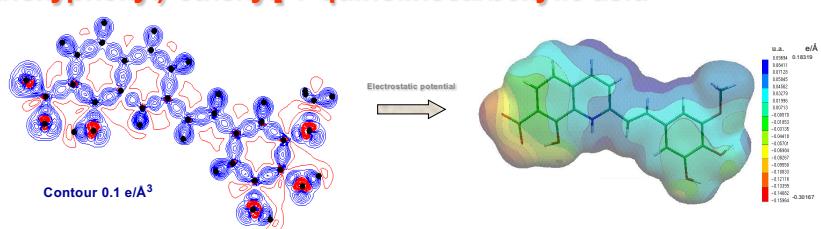
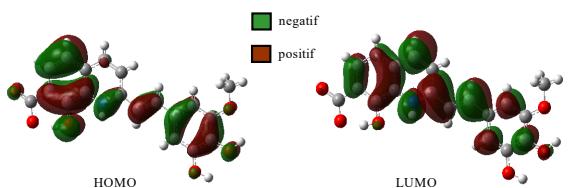
Topological property



Electrostatic potential



(E)-8-hydroxy-2[2-(4,5-dihydroxy-3-methoxyphenyl)-ethenyl]-7-quinoliniccarboxylic acid



⁽¹⁾ Mekouar, K., Mouscadet, J.F., Desmaele, D., Subra, F., Leh, H., Savouré, D., Auclair, C. & d'Angelo, J. (1998). *J. Med. Chem.* **41**, 2846-2857.

⁽²⁾ Hansen, N. and Coppens, P. (1978). *Acta Crystallogr.* **A34**, 909