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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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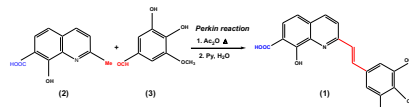
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Introduction

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-quinolinecarboxylic 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).

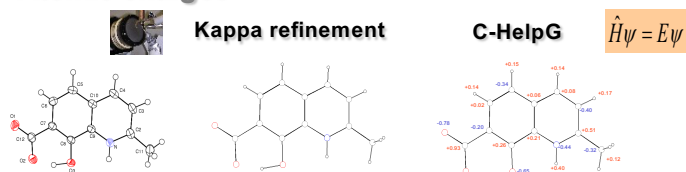
Study's Steps

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

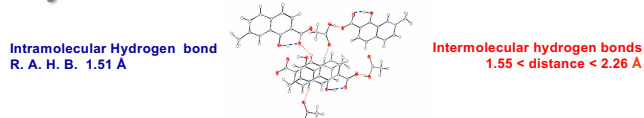


8-hydroxy-7-quinolinic acid

Atomic charges

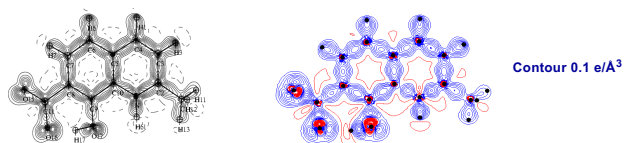


Crystal environment



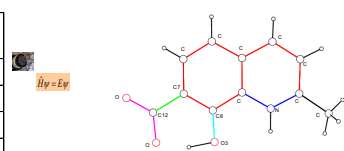
Deformation density

$$\rho_{mol}(\vec{r}) - \sum_{atom \in mol} \rho_{atom}(\vec{r} - \vec{r}_{atom})$$

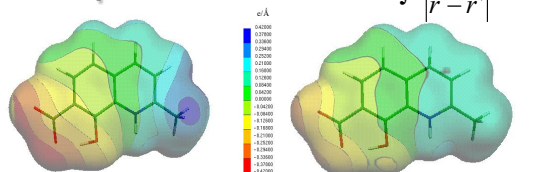


Topological property

Type de liaison	ρ_{BCP} [e.Å ⁻³]	ϵ	$H(\vec{r})$ [u.a]
< C — N >	2.09, 2.09	0.22, 0.17	-0.45, -0.45
< C — C > (cycle)	2.04, 1.95	0.25, 0.12	-0.44, -0.42
< C12 — C7 >	1.72, 1.69	0.23, 0.03	-0.33, -0.32
< C12 — O >	2.69, 2.43	0.13, 0.05	-0.69, -0.58
C8 — O3	2.22, 2.04	0.14, 0.06	-0.50, -0.44

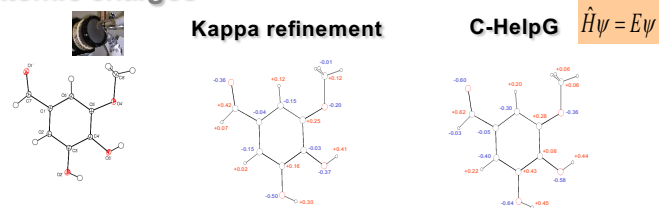


Electrostatic potential

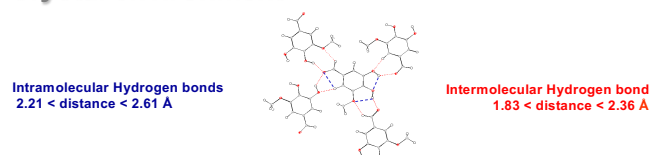


3', 4', 5'-methoxy-dihydroxy benzaldehyde

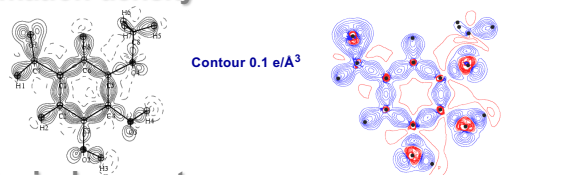
Atomic charges



Crystal environment

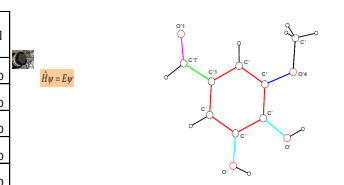


Deformation density

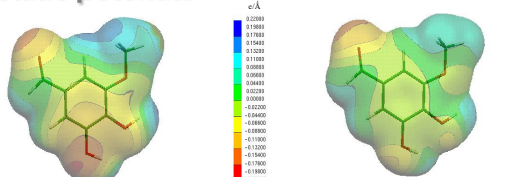


Topological property

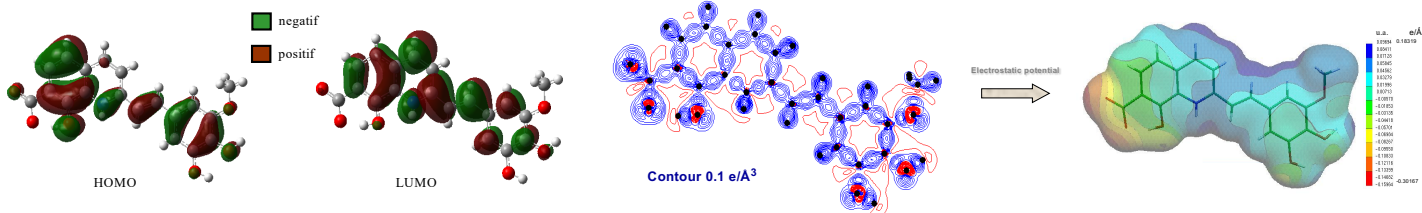
Type de liaison	ρ_{BCP} [e.Å ⁻³]	ϵ	$H(\vec{r})$ [u.a]
C7 — O1	2.77	2.00, 0.08	-0.72, -0.00
< C' — C' > (cycle)	2.06, 2.00	0.28, 0.00	-0.46, -0.00
C'1 — C'7	1.85	0.19, 0.00	-0.38, -0.00
C' — O4	1.91	2.00, 0.11	0.00, -0.38
C — O	2.04, 2.22	0.14, 0.00	0.00, -0.43



Electrostatic potential



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



(1) Mekour, K., Mouscadet, J.F., Desmaële, 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