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Delphine Firley, Blandine Courcot, Anne Spasojevic - de Biré, Jean-Michel Gillet, B. Fraisse, et al.. Experimental and theoretical electron density and electrostatic properties as a tool for understanding activity of HIV-1 integrase inhibitor precursors. Gordon Conference, Electron distribution & chemical bonding, Jul 2004, South Hadley, United States. hal-02304568

HAL Id: hal-02304568

<https://hal.science/hal-02304568v1>

Submitted on 24 Sep 2020

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

D. Firley^a, B. Courcot^a, A. Spasojevic-de Biré^a, J.M. Gillet^a, B. Fraisse^a, F. Zouhiri^b, D. Desmaele^b, J. d'Angelo^b, P. Becker^a and N.E. Ghermani^{a,c}

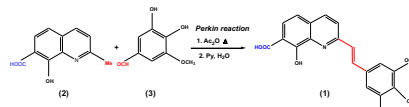
^aLaboratoire Structures Propriétés et Modélisation des Solides (SPMS), UMR 8580 CNRS, Ecole Centrale Paris, Grande Voie des Vignes, 92295 Châtenay-Malabry Cedex, France
^bBiomolécules: conception, isolement, synthèse (BIOCIS), UMR CNRS 8076, Faculté de Pharmacie de l'Université Paris XI, 5 rue JB Clément, 92296 Châtenay-Malabry Cedex, France
^cLaboratoire de Physique Pharmaceutique, UMR CNRS 8612, Faculté de Pharmacie de l'Université XI, 5 rue JB Clément, 92296 Châtenay-Malabry Cedex, France

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).

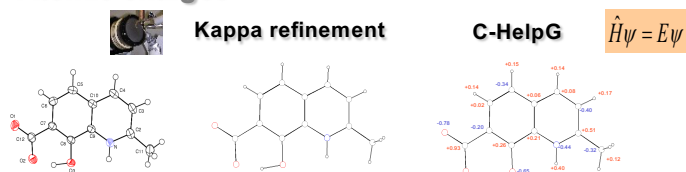
Study's Steps

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

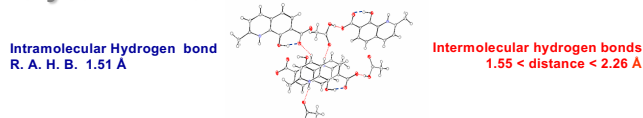


8-hydroxy-7-quinolinic acid

Atomic charges

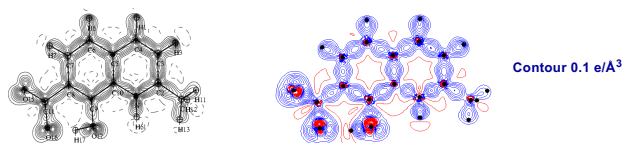


Crystal environment



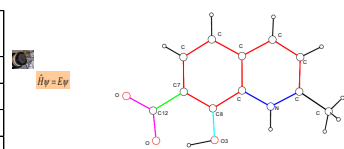
Deformation density

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

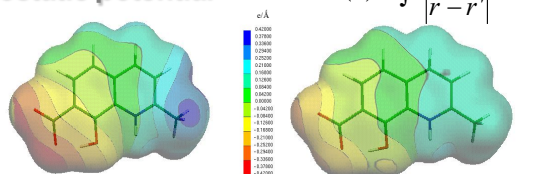


Topological property

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

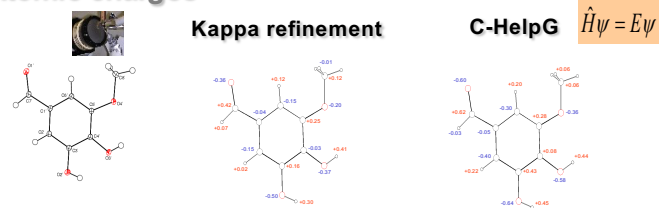


Electrostatic potential

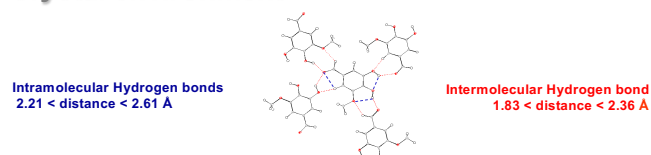


3', 4', 5'-methoxy-dihydroxy benzaldehyde

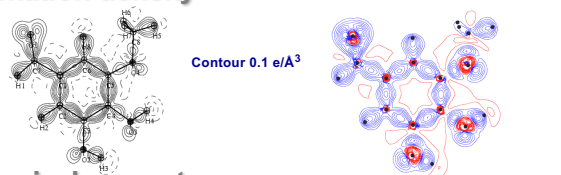
Atomic charges



Crystal environment

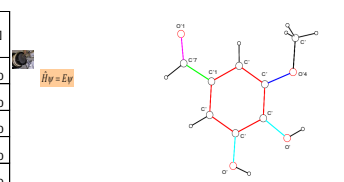


Deformation density

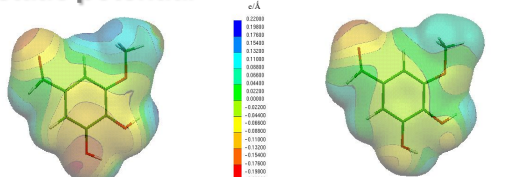


Topological property

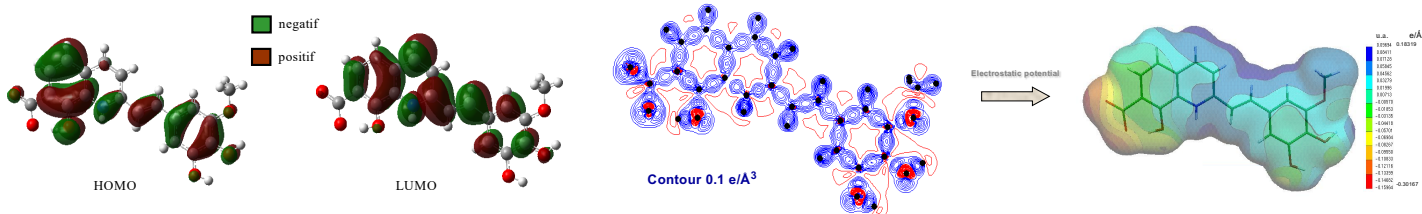
Type de liaison	ρ_{BCP} [e.Å ⁻³]	ϵ	$H(\vec{r})$ [u.a]
C7 — O1	2.77	0.08	-0.72
< C' — C' >	2.06	2.00	0.00
< cycle >	2.06	0.28	0.00
C1' — C7	1.85	0.19	-0.38
C' — O4	1.91	0.11	-0.38
C — O	2.04	2.00	0.00
	2.22	0.14	0.00
		0.00	-0.00



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