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Molecular Modelling Analysis of the Metabolism of Rasagiline

Fazlul Huq
Discipline of Biomedical Science, School of Medical Sciences,
Faculty of Medicine, Cumberland Campus, C42, The University of Sydney,
Lidcombe, NSW, Australia

Abstract: Rasagiline (RSG) is a second-generation, selective and irreversible inhibitor of monoamine oxidase type B (MAO-B) developed for the treatment of Parkinson's diseases. Molecular modelling analyses based on molecular mechanics, semi-empirical (PM3) and DFT (at B3LYP/6-31G* level) calculations show that both RSG and its metabolite ADN have large LUMO-HOMO energy differences so that they would be kinetically inert. The molecular surfaces RSG and ADN are found to possess neutral, electron-deficient and negatively charged regions so that they may be subject to lyophilic, nucleophilic and electrophilic attacks. However, because of kinetic inertness of the molecules, the rates of the reactions including any adverse reactions with glutathione and nucleobases in DNA are expected to be low. This may explain why RSG and ADN have little side effects.

Key words: Rasagiline, Parkinson's disease, neuroprotection, aminoindan, molecular modelling

INTRODUCTION

Rasagiline (RSG; N-propargyl-1-R-aminoindan) is a second-generation, selective and irreversible inhibitor of monoamine oxidase type B (MAO-B) developed for the treatment of Parkinson's Diseases (PD) (Bonneh-Barkay *et al*., 2005) that is characterized by progressive degeneration of melanin-containing dopaminergic neurons within substantia nigra pars compacta (SNpc) and profound depletion of nigrostriatal dopamine. RSG exerts symptomatic anti-Parkinsonian effect by blocking the oxidative metabolism of dopamine (DA), thus prolonging physiological activity of dopamine in control of movement (Rabey *et al*., 2000). MAO-B is found within glial cells in the human brain and is the predominant isoform responsible for the breakdown of dopamine to 3,4-dihydroxyphenylacetic acid and hoovanillic acid (HVA) (Chen and Swope, 2005).

In addition to inhibition of DA catabolism, RSG has been found to possess neuroprotective properties in a variety of *in vitro* and *in vivo* animal models, an effect which is independent of MAO inhibition (Boulton *et al*., 1997) evident from the fact that the S-isomer of RSG has over 1000-fold weaker MAO-B inhibitory activity than the R-isomer but similar neuroprotective properties (Huang *et al*., 1999). In addition, the neuroprotective properties of RSG manifest at concentrations below those required for the inhibition of MAO-B in cells under test (Maruyama *et al*., 2002).

Once-daily administration of RSG is found to be efficacious and well tolerated as a monotherapy in patients with early PD and as adjunctive therapy in levodopa-treated patients with motor fluctuations. RSG suppresses apoptotic cell death initiated by mitochondria (Mandel *et al*., 2005), by preventing pro-apoptotic decline in mitochondrial membrane potential. The propargyl chain of RSG is essential for activity as it bonds covalently with flavin containing dinucleotide moiety of the MAO enzyme (Binda *et al*., 2004). RSG is rapidly absorbed from the gastrointestinal tract (Youdin *et al*., 2001) and readily crosses the blood-brain barrier (Gotz *et al*., 1998). In the treatment of PD, RSG is well tolerated although the elderly patients may be prone to cardiovascular and psychiatric side effects.

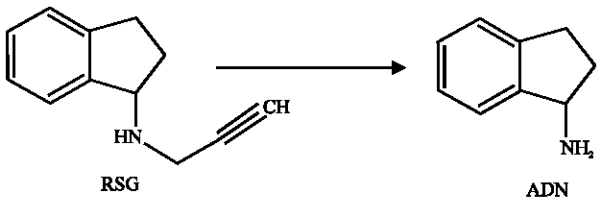

Fig. 1: Metabolic pathway for RSG

RSG undergoes extensive hepatic biotransformation catalysed by CYP1A2, with the main metabolite being 1-R-aminoindan (ADN). ADN is found to be devoid of vasoactive or MAO inhibitory properties. In this study, molecular modelling analyses have been carried out using the program Spartan '02 (Spartan 2002) to investigate the relative stability of RSG and its metabolite ADN with the aim of providing a better understanding on their relative toxicity.

COMPUTATIONAL METHODS

The geometries of RSG and its metabolite (Fig. 1) ADN have been optimised based on molecular mechanics, semi-empirical and DFT calculations, using the molecular modelling program Spartan '02. Molecular mechanics calculations were carried out using MMFF force field. Semi-empirical calculations were carried out using the routine PM3. DFT calculations were carried at B3LYP/6-31G* level. In optimization calculations, a RMS gradient of 0.001 was set as the terminating condition. For the optimised structures, single point calculations were carried out to give heat of formation, enthalpy, entropy, free energy, dipole moment, solvation energy, energies for HOMO and LUMO. The order of calculations: Molecular mechanics followed by semi-empirical followed by DFT ensured that the structure was not embedded in a local minimum. To further check whether the global minimum was reached, some calculations were carried out with improvable structures. It was found that when the stated order was followed, structure corresponding to the global minimum or close to that could ultimately be reached in all cases. Although RMS gradient of 0.001 may not be sufficiently low for vibrational analysis, it is believed to be sufficient for calculations associated with electronic energy levels.

RESULTS AND DISCUSSION

Table 1 gives the total energy, heat of formation as per PM3 calculation, enthalpy, entropy, free energy, surface area, volume, dipole moment and energies of HOMO and LUMO as per both PM3 and DFT calculations for RSG and its metabolite ADN. Figure 2-3 give the regions of negative electrostatic potential (greyish-white envelopes) in (a), HOMOs (where red indicates HOMOs with high electron density) in (b), LUMOs in (c) and density of electrostatic potential on the molecular surface (where red indicates negative, blue indicates positive and green indicates neutral) in (d) as applied to optimised structures of RSG and its metabolite ADN.

The low solvation energy values for RSG and ADN indicate that both the compounds would have low solubility in water. However, this would be increased when they are protonated at the nitrogen center.

The LUMO-HOMO energy differences for RSG and its metabolite ADN from DFT calculations are respectively 6.1 and 6.3 eV, indicating that both the compounds would be kinetically inert with RSG being the more inert one.

Table 1: Calculated thermodynamic and other parameters of RSG and its metabolite ADN

Molecule	Calculation type	Total energy (kcal mol^{-1}/ atomic unit*)	Heat of formation (kcal mol^{-1})	Enthalpy (kcal mol^{-1} K^{-1})	Entropy (kcal mol^{-1} K^{-1})	Free energy (kcal mol^{-1})	Solvation energy (kcal mol^{-1})
RSG	PM3	65.01	67.44	143.10	105.52	111.64	-2.43
	DFT	-519.78		145.08	105.57	113.61	-1.99
ADN	PM3	11.66	16.25	118.15	89.07	91.59	-4.60
	DFT	-404.33		119.53	87.55	93.43	-4.93

Molecule	Calculation type	Area (Å^2)	Volume (Å^3)	Dipole moment (debye)	HOMO (eV)	LUMO (eV)	LUMO-HOMO (eV)
RSG	PM3	219.81	202.32	1.2	-9.32	0.36	9.68
	DFT	221.91	203.16	0.8	-6.05	0.07	6.12
ADN	PM3	170.41	153.12	1.5	-9.36	0.34	9.70
	DFT	170.98	153.60	1.6	-6.15	0.11	6.26

*In atomic units from DFT calculations

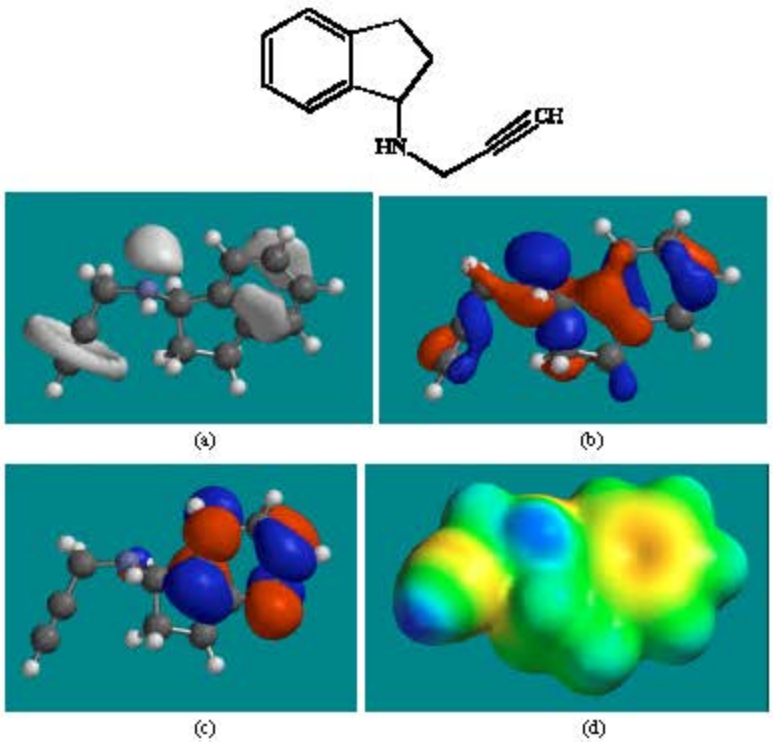

Fig. 2: Structure of RSG giving in: (a) the electrostatic potential (greyish envelope denotes negative electrostatic potential), (b) the HOMOs, (where red indicates HOMOs with high electron density) (c) the LUMOs (where blue indicates LUMOs) and in (d) density of electrostatic potential on the molecular surface (where red indicates negative, blue indicates positive and green indicates neutral)

In the case of RSG, the electrostatic potential is found to be more negative around the carbon-carbon triple bond (possessing cylindrical symmetry), above and below the phenyl ground and around the nitrogen center, indicating that the positions may be subject to electrophilic attack. In the case of ADN, the electrostatic potential is found to be more negative around the nitrogen atom and above and below the phenyl ring, indicating that the positions may be subject to electrophilic attack

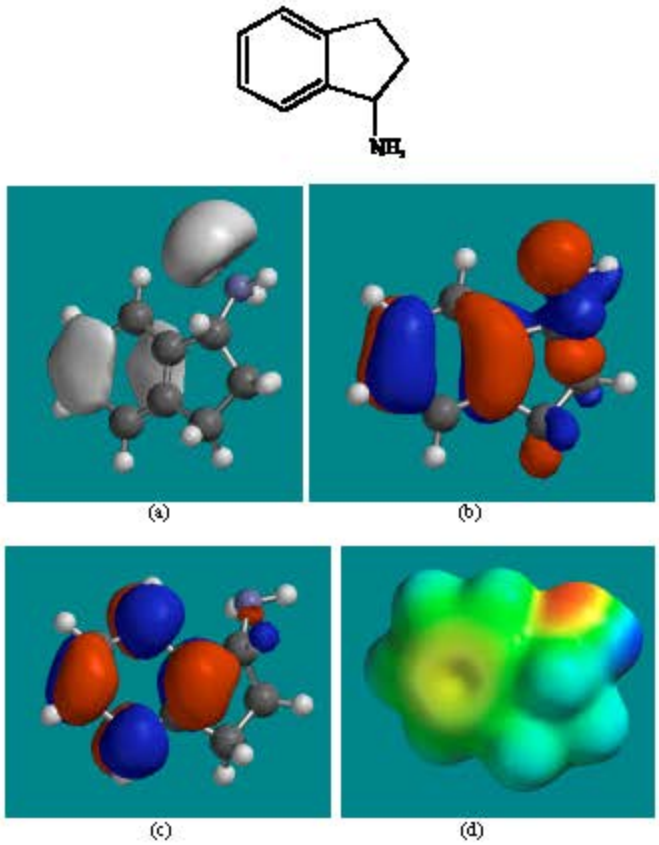

Fig. 3: Structure of ADN giving in: (a) the electrostatic potential (greyish envelope denotes negative electrostatic potential), (b) the HOMOs, (where red indicates HOMOs with high electron density) (c) the LUMOs (where blue indicates LUMOs) and in (d) density of electrostatic potential on the molecular surface (where red indicates negative, blue indicates positive and green indicates neutral)

In the case of RSG, the HOMOs with high electron density are found to be more widely distributed covering essentially all non-hydrogen atoms than the LUMOs which appear on the non-hydrogen atoms of the phenyl ring. In the case of ADN, both the HOMOs with high electron density and the LUMOs appear to cover essentially all the non-hydrogen atoms.

The overlap of HOMO with high electron density and region of negative electrostatic potential at some positions, gives further support to the idea that the positions may be subject to electrophilic attack.

The molecular surface of RSG and ADN are found to possess negative (yellow and red), neutral (green) and electron-deficient (blue) regions so that they may be subject to electrophilic, lyophilic and nucleophilic attacks. Nucleophilic attacks can be due to glutathione and nucleobases in DNA. Reaction with glutathione can induce cellular toxicity by compromising the antioxidant status of the cell whereas that with nucleobases in DNA can cause DNA damage. However, as stated earlier, since RSG and ADN are expected to be kinetically inert, the rate of such adverse reactions may be low unless speeded up enzymatically.

CONCLUSION

Rasagiline is a second-generation, selective and irreversible inhibitor of monoamine oxidase type B developed for the treatment of Parkinson's diseases. Molecular modelling analyses based on semi-empirical and DFT calculations show that both RSG and its metabolite ADN have large LUMO-HOMO energy differences so that they would be kinetically inert. This means that although molecular surfaces of both the compounds have some electron-deficient regions so that they can react with glutathione and nucleobases in DNA, the rates of such adverse reactions may be low, unless speeded up enzymatically.

ABBREVIATIONS

RSG : Rasagiline; N-propargyl-1-R-aminoindan
DFT : Density functional theory
LUMO : Lowest unoccupied molecular orbital
HOMO : Highest occupied molecular orbital

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