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ORIGINAL ARTICLE

Theoretical investigation of the interactions in binding pocket of Reverse Transcriptase

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Abstract Interactions in proteins have been studied using several chemical information techniques including quantum chemical methods that are applied to truncated systems composed of the ligand molecule and the surrounding amino acids of the receptor. In this work we adopt an approach to study these interactions accounting for as many as possible explicit solvent molecules and without the need of a fragmented calculation. Furthermore, we embed our quantum chemical calculations within a molecular dynamics framework that enables a fundamentally fast system for quantum molecular dynamic simulations (QCMD). Central to this new system for QCMD is the tight binding QC system, newly developed in our laboratories, and which combined with the MD paradigm results in an ultra accelerated QCMD method for protein–ligand interaction evaluations. We have applied our newly developed method to the Nevirapine (NVP)–Reverse Transcriptase (RT) system. We show how the proposed method leads us to new findings. The advanced QCMD was applied to a system of RT with NVP and it has led to the knowledge of specific groups and atoms that interact with surrounding amino acids of RT and help in drug binding. The information derived from this calculation may be used in designing drugs for NVP resistant virus strains that have binding capability like NVP.

1. Introduction

HIV-1 Reverse Transcriptase (HIV-1 RT) is an important and extensively studied antiviral target for the chemotherapy of AIDS because of its key role in virus replication. The inhibitors of HIV-1 RT can be divided into two main classes, nucleoside RT inhibitors (NRTIs) and non-nucleoside RT inhibitors (NNRTIs) (Rizzo et al., 2001; Mitsuya et al., 1990; Katz and Skala, 1994; Wang et al., 2001). The NNRTIs analogs such as Nevirapine, TIBO, HEPT, and Efavirenz are non-competitive inhibitors that lock the polymerase active site in an inactive conformation (Archer et al., 2001; De Clercq, 1996; Jonckheere et al., 2000). Although NNRTIs are highly specific and less toxic than nucleoside inhibitors, their therapeutic effectiveness is limited by relatively rapid emergence of drug-resistant HIV-1 strains. NNRTIs include structurally unrelated subclasses of compounds that bind to a common allosteric site, adjacent to

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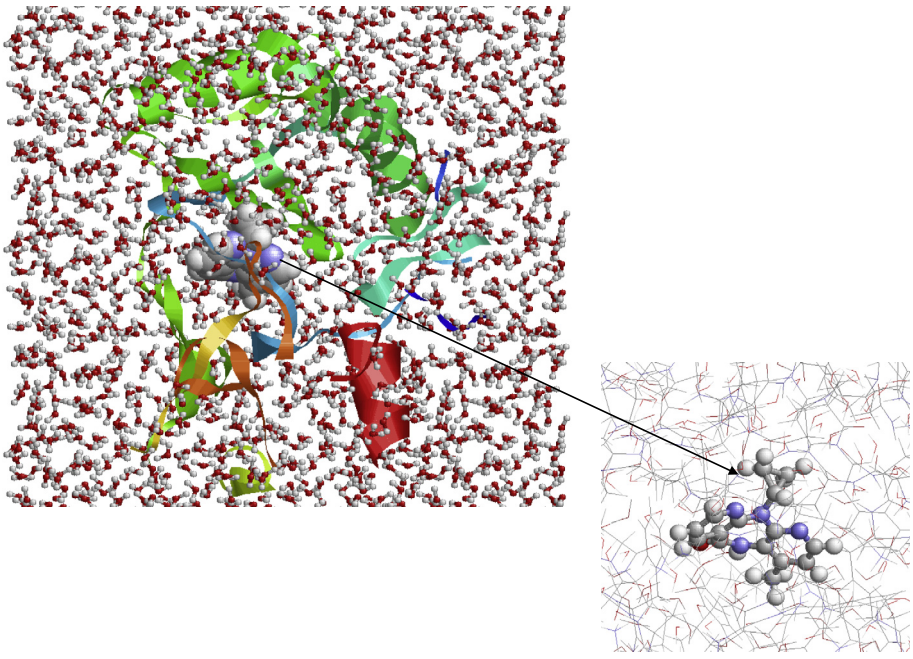

Figure 1 Nevirapine (shown as space fill model) and protein part falling under 10 Å radii from Nevirapine with water molecules.

the NRTI binding site, by a similar three-dimensional arrangement (Archer et al., 2001; De Clercq, 1994; Hannongbua et al., 2001). Nevirapine, a first generation NNRTI, has been approved for clinical use for the therapy of AIDS. Mutations of amino acid residues in the binding pocket of RT reduce sensitivity significantly, and, therefore, new potent drugs have been widely developed.

However, despite intensive experimental investigations, the detailed origin of enzyme–inhibitor interaction, a question of crucial importance, remains to be unclear. A better understanding is vital for the analysis of activities of mutant or designed proteins, and for the design of inhibitors as pharmaceutical lead compounds. Therefore, theoretical investigation has been an alternative method for studies of the enzyme–inhibitor interaction in detail. However, such investigation of larger molecular system is limited by the computational effort required and the accuracy of the method used. Recently, accurate molecular modeling for larger molecules, such as those in molecular biology, became more feasible due to new developments in computational chemistry (Maseras and Morokuma, 1995; Humbel et al., 1996; Svensson et al., 1996).

HIV-1 Reverse Transcriptase (RT) is an important target for drugs used in the treatment of AIDS. Drugs known as non-nucleoside RT inhibitors (NNRTI) appear to alter the structural and dynamical properties of RT, which in turn inhibit RT's ability to transcribe. Molecular dynamics (MD), principal component analysis (PCA), and binding free energy simulations are employed to explore the dynamics of RT and its interaction with the bound NNRTI Nevirapine, for both wild-type and mutant (V106A, Y181C, Y188C) RT. These three mutations commonly arise in the presence of Nevirapine and result in resistance to the drug. The mutations cause a loss of van der Waals interactions between the drug and the binding pocket. This suggests that a good inhibitor should efficiently enter and maximally occupy the binding pocket, thereby interacting effectively with the amino acids around the binding pocket (Zhou et al., 2005).

2. Method

2.1. Periodic density functional theory method

Periodic DFT calculations were performed by using the DMol^3 software (DMol^3, version4.0, Accelrys, 1999). In order to reduce the computational cost, all core electrons were represented by effective core pseudopotentials. In this study, double numerical sets with polarization base were employed. Vosk–Wilk–Nusair (VWN) (Vosko et al., 1980) local correlation functional was used to optimize geometries. Generalized gradient approximation (GGA) in terms of Perdew–Wang exchange and correlation functional (Perdew et al., 1992) was used to evaluate energies. The orbital population and bond populations were obtained using truncated models by the DFT method that employs Cambridge serial total energy package (CASTEP). In CASTEP calculations, we used GGA in terms of Perdew–Burke–Ernzerhof functional (PBE) (Perdew et al., 1996). The crystal lattice size used for DFT calculations on truncated Nevirapine-Tyr188 acid complex was 20 Å × 20 Å × 20 Å.

Table 1 Comparison of orbital population of Nevirapine and Tyrosine 188 system from DFT calculation and colors.

	Castep		Colors	
	%s	%p	%s	%p
Hydrogen	100	0	100	0
Carbon	28.36	71.64	30.06	69.94
Nitrogen	27.21	72.79	24.93	75.07
Oxygen	26.98	73.02	23.21	76.79