J Mol Model (2006) 12: 362–365
DOI 10.1007/s00894-005-0054-2

ORIGINAL PAPER

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HIV-1 GP120 V3 conformational and informational entropies

Received: 21 September 2005 / Accepted: 27 September 2005 / Published online: 29 November 2005

Abstract In an attempt to analyze structure, function and evolution of HIV-1 GP120 V3, interactions among the Hartree–Fock energy, the conformational entropy and the Shannon entropy were determined for the 1NJ0 set of antibody-bound V3 loop conformers. The Hartree–Fock energy of each conformer was determined at the MINI level with GAMESS. The conformational entropy was determined per conformer and per residue from the mass-weighted covariance matrices. The Shannon entropy per residue was determined from sequence-substitution frequencies. Correlations were determined by linear regression analysis. There was a negative correlation between the Hartree–Fock energy and the conformational entropy (R=−0.4840, p=0.0078, df =28) that enhanced the negative Helmholtz-free-energy change for the binding of the GP120 ligand to target CD4. The Shannon entropy of V3 was a function of the conformational entropy variance (R= 0.7225, p=0.00157, df=15) and of the V3 Hartree–Fock energy. Biological implications of this work are that (1) conformational entropy interacts with V3 Hartree–Fock energy to enhance GP120 binding to CD4 cell receptors and that (2) the Hartree–Fock energy of V3 interacts with the evolutionary system to participate in the regulation of V3 diversity.

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Keywords HIV-1 · V3 loop · GP120 · HF-SCF · Entropy · Energy · Conformational entropy · Informational entropy · Shannon entropy · Entropy variance · Molecular evolution

Introduction

The GP120 V3 loop plays crucial roles in the ability of HIV-1 to cause disease [1]. It is important, therefore, to understand the rules that govern V3-loop structure and function in order to develop effective anti-HIV-treatment and prevention strategies. In an attempt to elucidate some of those rules, we present here an analysis of interactions among the Hartree–Fock energy, the conformational entropy and the Shannon entropy that characterize a set of HIV-1 GP120 V3 loop conformers.

Materials and methods

All-atom, including hydrogen, atomic coordinates for 29 MN-strain HIV-1 GP120 V3 loop conformers (PDB 1NJ0) bound to the antigen-binding site of the human antibody Fv fragment 447-52D at 308 K were obtained from the Protein Data Bank [2, 3]. The total energy (E) of each 1NJ0 V3 conformer was determined *in vacuo* from the atomic coordinates of all 29 1NJ0 V3 conformers by the restricted Hartree–Fock self-consistent field (HF) method using the US version of GAMESS [4] with the MINI basis set, as previously reported [5].

For a five-conformer subset spanning the HF energy space of the 1NJ0 conformers, E was determined with the 3-21G** basis set and also with the MINI basis set by the self-consistent reaction field (SCRF) method of Kirkwood [6] and Onsager [7] with water as solvent. For the SCRF computations, the radius of the spherical cavity was set at 18 Å and the dielectric constant to 80.

A maximum value for the conformational entropy was determined from the atomic coordinates of each 1NJ0 conformer by the mass-weighted covariance matrix equation of Schlitter [8] using Matlab (The Mathworks, Natick,

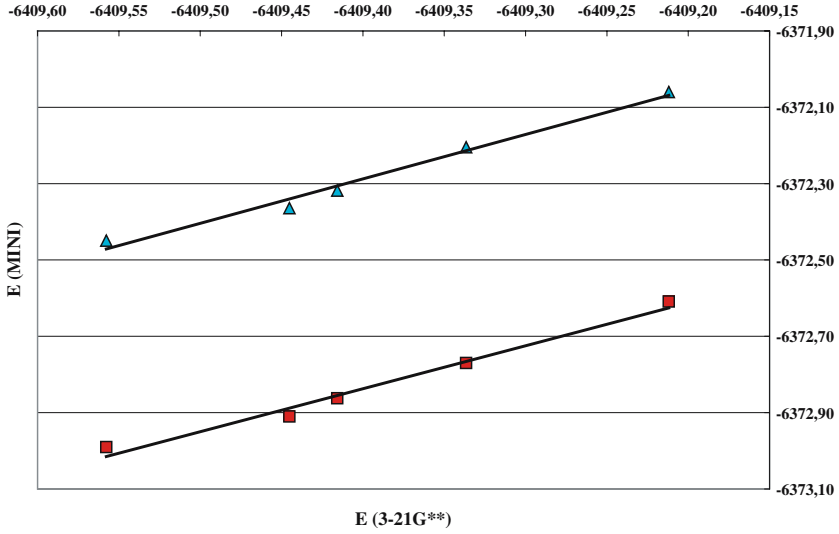


Fig. 1 Hartree–Fock Energy of HIV-1 1NJ0 V3 Conformers. Energy (E) obtained *in vacuo* with the extended 3-21G** basis set is on the abscissa. Energy obtained with the minimum MINI basis set *in vacuo* (*triangles*) and in solvent water (*rectangles*) is on the ordinate

MA). The conformational entropy (S^j_{conf}) was determined for each j^{th} amino acid residue of each V3 conformer. The conformational entropy (S_{conf}) was also determined per V3 conformer so as to allow for correlations between amino-acid residues [9]. Prior to the computation of the conformational entropies, both per residue and per conformer, the coordinates of all conformers were first superimposed on those of the conformer of highest energy by the singular-value decomposition method of Arun et al. [10] in order to minimize translational and rotational effects.

A Shannon entropy (S^j_{shannon}) for each j^{th} residue of the 16-residue V3 loop sequence was determined from HIV-1 subtype B V3 consensus sequence data [11] as:

$$S^j_{\text{shannon}} = -\sum \mathrm{p}_k log_2 \mathrm{p}_k \quad (1)$$

where p is the probability of occurrence of the k^{th} amino acid at the j^{th} position and the summation is taken from k=1 to 20 [12].

The statistical variance of the conformational entropy (varS^j_{conf}) was calculated for each j^{th} amino acid of the set of 29 1NJ0 V3 conformers. The calculations of the variances and the linear regression analyses were performed with Excel (Microsoft).

Results

The correlation between the HF energy of the V3 conformers at the MINI level and with the 3-21G** basis set is shown in Fig. 1. (R=0.992, p<0.001 and df=4 both *in vacuo* and in solvent water).

A plot of the S_{conf} per V3 conformer as a function of E is shown in Fig. 2 (R=−0.4840, p=0.0078 and df=28). The linear regression equation for the data in Fig. 2 is:

$$-S_{\text{conf}} = 0.0278E + 176.0 \quad (2)$$

A plot of S^j_{shannon} as a function of varS^j_{conf} is shown in Fig. 3a (R=0.7225, p=0.00157 and df=15). The distribution

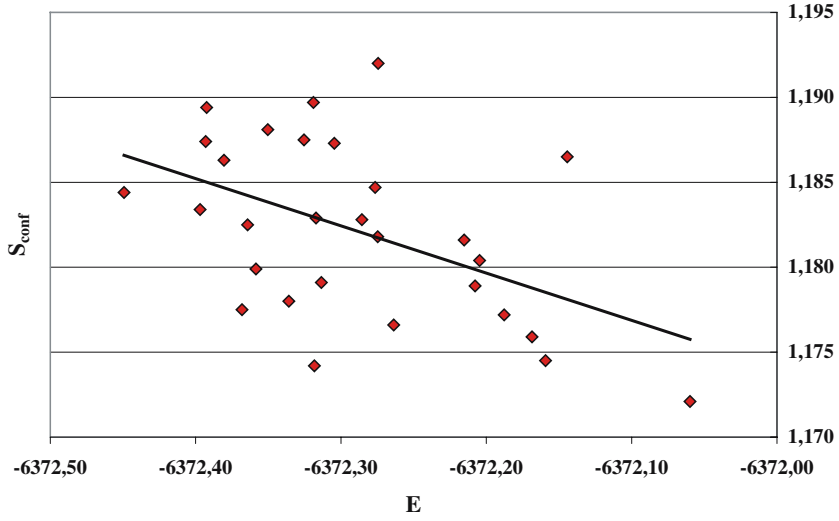
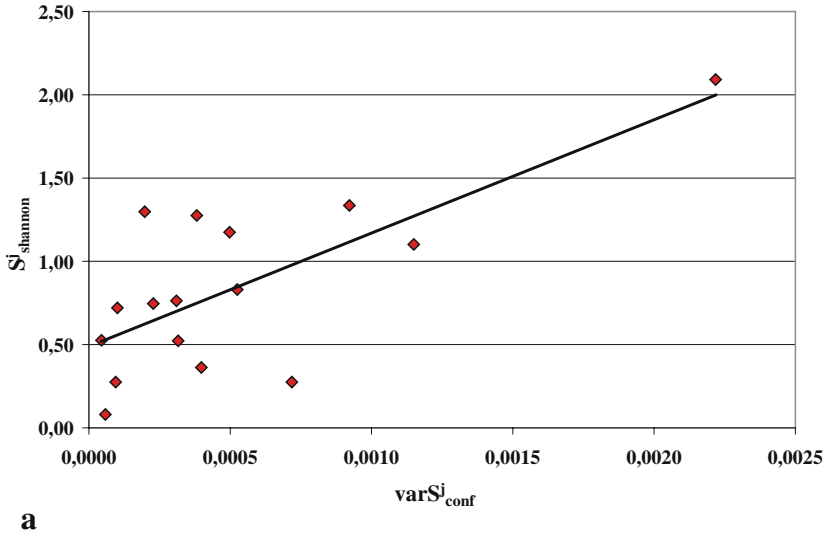


Fig. 2 Correlation between conformational entropy and Hartree–Fock Energy in 1NJ0 V3 Conformers. The conformational entropy (S_{conf}) per V3 conformer is on the ordinate and the energy (E) is on the abscissa. E is in atomic units (a.u.). S_{conf} is in a.u./K



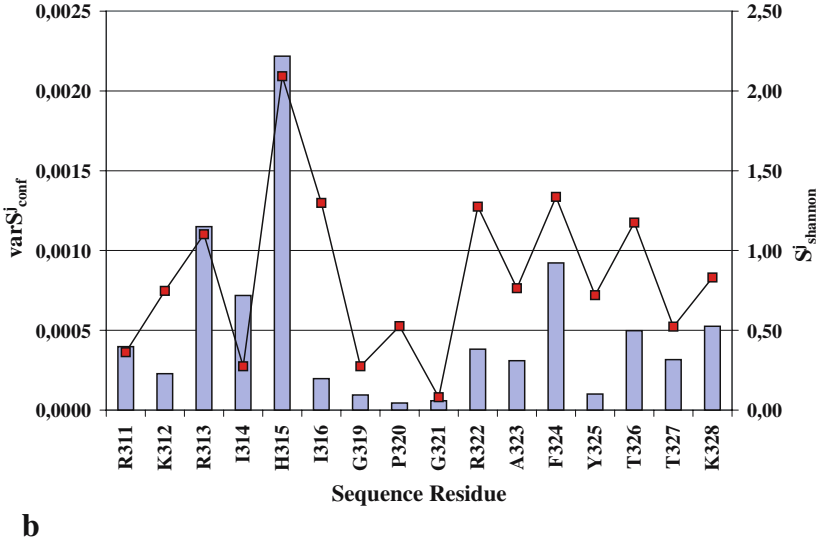


Fig. 3 Correlation between the shannon entropy and the variance of the conformation entropy per amino acid residue of the 1NJ0 V3 conformers. **a** Shannon entropy ($S^j_{shannon}$) per *j*-th amino acid residue is on the ordinate and the variance of conformational entropy (varS^j_{conf})) per *j*-th amino acid residue is on the abscissa. **b** Shannon entropy ($S^j_{shannon}$) and the variance of the conformational entropy (varS^j_{conf}) are shown for each individual *j*-th amino acid residue of the 1NJ0 V3 peptide. The *lines* depict $S^j_{shannon}$ and the *bars* depict varS^j_{conf}. $S^j_{shannon}$ is in bits per amino acid residue. varS^j_{conf} is in a.u./K

of $S^j_{shannon}$ and of varS^j_{conf} among the 16 amino acid residues of V3 1NJ0 peptide is shown in Fig. 3b.

Discussion

We report here the detection of interactions among the Hartree–Fock energy, the conformational entropy and the Shannon entropy in the 1NJ0 set of antibody-bound V3 loop conformers. For this analysis, the Hartree–Fock energy of all 29 V3 conformers was determined *in vacuo* with the MINI minimal basis set. The use of the minimal basis set and gas phase conditions for this analysis is justified by the data in Fig. 1, which show close correlation between the energies of V3 loop conformers at the MINI level and with an extended basis set *in vacuo* and between energy *in vacuo* and energy in water. Thus, use of an extended basis set and solvent corrections would affect the absolute energy values obtained, but the relative energy values and the relative ordering of the V3 conformers would remain unchanged. We have previously reported that the HF energy of these V3 conformers follows a Boltzmann distribution [5].

In V3-loop conformers that are constrained [13] in a β-hairpin conformation by anti-V3 antibody, (1) there is correlation between the Hartree–Fock energy and the conformational entropy and (2) this correlation is negative (Fig. 2). Furthermore, the negative correlation shown in Fig. 2 is contrary to the usual dq/T thermodynamic relationship, in which a reversible increase in thermal energy is synonymous with an increase in entropy [14].

Hsu et al. [15] reported an increase of 91.4×10^{-6} a.u. K^{-1} (0.24 kJK^{-1} mol^{-1}) in V3 S_{conf} as a result of the binding of GP120 to the CD4 receptor. According to the slope ($\Delta S_{conf}/\Delta E$) of Eq. 2, this ΔS_{conf} would be accompanied by a decrease in E, i.e., $\Delta E=-3288\times10^{-6}$ a.u. An equation for the V3 Helmholtz-free-energy [16] change (ΔA) for the binding of GP120 to CD4 can therefore be written as:

$$\Delta A = -3288x10^{-6}\text{a.u.} - T\left(91.4x10^{-6}\text{a.u.}\right)K^{-1} \qquad (3)$$

From Eq. 3 it is seen that $\Delta A<0$ for $T>36.97$ K. If an additional entropic term, e.g., $T(3288\times10^{-6}$ a.u.)/K) were added to Eq. 3 in order to allow for thermodynamic entropy, ΔA becomes negative for GP120 binding to CD4 at all temperatures. Thus, the negative correlation between ΔS_{conf} and Hartree–Fock ΔE synergistically facilitates negative free-energy changes in the V3 loop associated with the binding of GP120 to its CD4 cellular receptor.

In order further to investigate the biological significance of V3 S_{conf}, we sought to determine whether V3 S_{conf} correlates with the genetic diversity of the V3 peptide. A correlation between V3 conformational entropy per residue (S^j_{conf}) and the V3 Shannon entropy per residue ($S^j_{shannon}$) was sought, but not found (data not shown). This is, perhaps, not unexpected because S^j_{conf} and $S^j_{shannon}$ are not mathematically isomorphic [17]. However, in spite of this lack of isomorphism, we did detect (Fig. 3) a correlation between $S^j_{shannon}$ and the variance of the V3 conformational entropy per residue (varS^j_{conf}). The data in Fig. 3 suggest that the structural information in the V3 loop becomes imprinted upon the evolutionary system that generates HIV-1 genetic diversity.

Mutations occur relatively infrequently in the G319 P320 G321 sequence of low varS^j_{conf} in the central portion of the V3 loop (Fig. 3b). To our knowledge, no case of a single amino-acid substitution has yet been reported in this 1NJ0 V3 sequence. Conservation of the G319 P320 G321 sequence of V3 may be important for protein folding and for flexibility of the GP120 peptide chain. [18, 19] An increase in the absolute value of a negative ΔA in Eq. 3 produced by specific mutations would confer a selective advantage to those mutated HIV-1 virions by enhanced binding of GP120 to cell CD4 receptors.

The data in this paper are based on the conformational entropy per conformer (Fig. 2) and the conformational entropy per amino-acid residue (Fig. 3). These entropies are related by correlated distributions of atomic coordinates in the intact conformer [9]. This relationship yields Eq. 4:

$$S^j_{shannon} = S^j_{shannon}(E) \tag{4}$$

which states that the Shannon entropy per amino-acid residue of the V3 loop is a function of the V3 conformer Hartree–Fock energy. A biological implication of Eq. 4 is that changes in the Hartree–Fock energy of HIV-1 GP120 V3 interact with the evolutionary system to drive and regulate the generation of V3 diversity.

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