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Conformational preferences of non-nucleoside HIV-1 reverse transcriptase inhibitors

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Abstract—The non-nucleoside inhibitors of HIV-1 reverse transcriptase (NNRTI) are a class of compounds that present a common butterfly-like conformation. In the present study, the intramolecular factors that contribute to this conformation were studied. Hydrogen bonds have been analysed by geometric and electrostatic criteria. Only the former allow the elucidation of the relative intensity of hydrogen bonds. The interaction between aromatic rings may contribute to the preferential conformation. For some other NNRTI, it is not possible to explain the butterfly-like conformation on the basis of hydrogen bond and aromatic interactions. © 2001 Elsevier Science Ltd. All rights reserved.

1. Introduction

Since the beginning of anti-AIDS chemotherapy, HIV-1 reverse transcriptase (RT) has been the main target in the attack against this virus and the majority of drugs under clinical use are inhibitors of such enzymes. These inhibitors can be classified into two groups: nucleosides, that are chain terminators blocking the growth of the assembled chain of nucleosides, and the non-nucleosides (NNRTI), which are allosteric and non-competitive inhibitors.[1–4] In contrast to the former group, NNRTI inhibitors present low toxicity. In recent years, the FDA has approved various NNRTI for clinical use in combined therapy.[5] Examples of such compounds are nevirapine,[6,7] delavirdine[8] and efavirenz.[9] Various other compounds of this class are currently being tested in humans.[1]

Although NNRTI present great structural diversity, most of them display a butterfly-like conformation (Fig. 1),[2,10–12] as shown by the crystalline structures of some isolated inhibitors or their RT-complexes.[12–20] Such information, combined with molecular modelling techniques, molecular orbital calculations and QSAR-3D, has allowed the design of some NNRTI pharmacophoric models. Two of these models are stereoelectronic: one of them was developed by Schäfer et al. based on QSAR-3D of nevirapine, TIBO and isoindolinone,[20] while the other, developed by Gussio et al., was based on the minimisation of the energy interaction between a nevirapine derivative and the RT allosteric site together with density functional theory calculations of a series of congeneric derivatives of nevirapine to obtain a model for an active compound.[10] In a report describing the superposition of the crystalline structures of four inhibitors belonging to three different classes and their interaction with the RT allosteric site, various spatial and conformational similarities have been observed.[12] All of these models have many characteristics in common, such as the presence of certain functional groups or the presence of two unsaturated hydrocarbon linkages separated by a well-defined distance (7.5 Å) and an angle of 108–115°. This arrangement originates the so-called butterfly-like conformation.

According to a review recently published by Mager,[21] the analysis of the reported data and molecular modelling studies indicates that a butterfly-like conformation is directly related to the degree of affinity of drugs and to the probability of appearance of viral resistance.

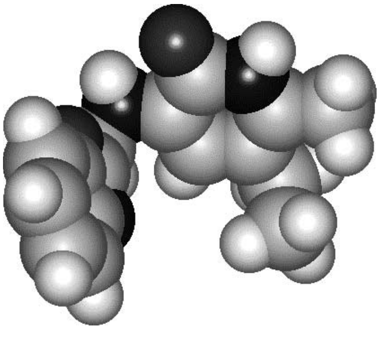

Figure 1. Structure obtained through the DFT method for molecule (**2**).

Keywords: AIDS; intramolecular interactions; hydrogen bonds; pi-interactions; natural bond orbital analysis.

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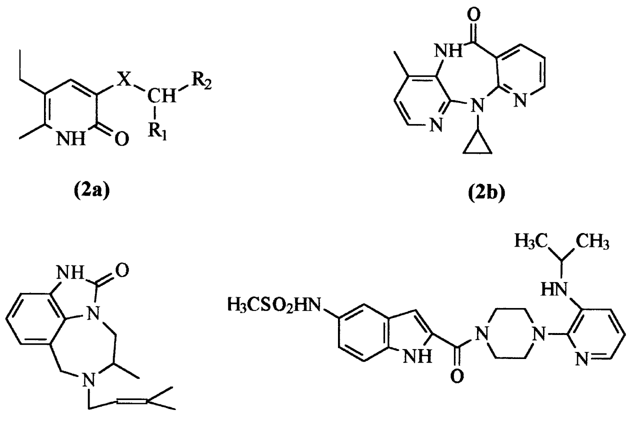

(2a) (2b) (2c) (2d)

Figure 2. Structures of some non-nucleoside inhibitors of HIV-1 reverse transcriptase: the basic skeleton for pyridinones (**2a**), nevirapine (**2b**), TIBO (**2c**) and delavirdine (**2d**).

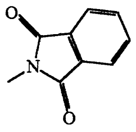
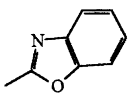
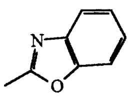
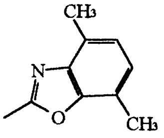
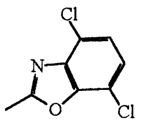
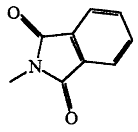
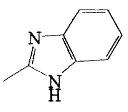
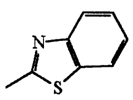
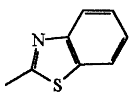
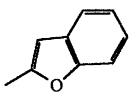
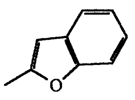
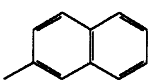
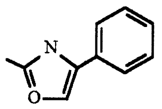
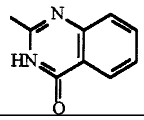
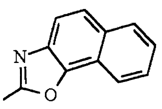
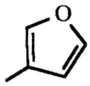
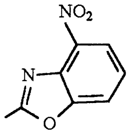
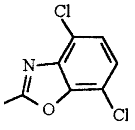
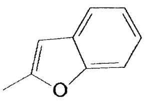
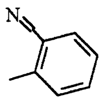
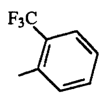
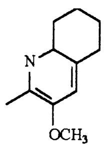
The aim of the present study was to investigate why non-nucleoside inhibitors display the butterfly-like conformation. Studies of intramolecular interactions such as hydrogen bonds and aromatic ring π-interactions were carried out. A series of pyridinones was first studied ((**2a**), Fig. 2, Table 1, items (a), (b) and (c)), followed by the analysis of some of the NNRTI approved for clinical use or testing in humans, i.e. nevirapine (**2b**), TIBO (**2c**) and delavirdine (**2d**) (Fig. 2). After presenting the computational methods utilised, we will describe a study of the geometric factors (distances and the number of ring members) involved in hydrogen bonds and π-interactions using criteria based on crystallographic data. Electrostatic parameters such as charges and dipole moments and hydrogen bond energies will also be discussed.

2. Computational methods

Geometries were designed with the aid of the PCMODEL program, version 6.0,[22] and were then submitted to a pre-optimisation of geometry in the MMX force field, where a conformational search for the dihedral angle variation corresponding to the single bonds was carried out (MLTOR).[22] It is only possible to obtain the global minimum structure with MLTOR because this is a simulated annealing method. Geometries were optimised by the semi-empirical method AM1[23] using the MOPAC6.0 and MOPAC93R2 programs.[24,25] The keywords GNORM=0.0, EF and PRECISE were used to increment the precision of geometry optimisation. Atomic charges generated by electrostatic potentials were calculated by the MNDO method using the Besler, Merz and Kollman algorithm (MNDO/ESP).[26] Some conformational search tests were made using the Monte Carlo method with the MMFF94 force field[27] in SPARTAN 5.1 software.[28]

Calculations based on the density functional theory (DFT)[29] with the 6-31G(d)[30] basis set and Becke's three-parameter hybrid functional with gradient corrections provided by Lee, Yang and Parr (B3LYP)[31] were performed with the GAUSSIAN 94 software.[32] The geometry was optimised without constraints with program default options. This method and basis were used for natural population analysis (NPA)[33–35] and natural bond orbital analysis (NBO).[36]

Table 1. Pyridinones studied in this work

Panel (a) Molecule	(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)
X	CH_2	NH	CH_2	NH	NH	NH	NH	NH
R_1	H	H	H	H	H	H	H	H
R_2								
Panel (b) Molecule	(9)	(10)	(11)	(12)	(13)	(14)	(15)	
X	CH_2	NH	CH_2	NH	NH	NH	NH	
R_1	H	H	H	H	H	H	H	
R_2								
Panel (c) Molecule	(16)	(17)	(18)	(19)	(20)	(21)	(22)	
X	NH	NH	NC_2H_5	NH	NH	NH	NH	
R_1	H	H	H	CH_3	H	H	H	
R_2								

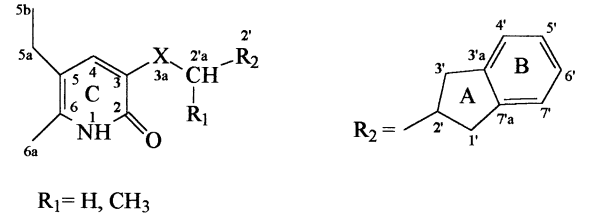


Figure 3. General numbering scheme for pyridinones ((**1**)–(**22**)) and identification of the aromatic groups present in their structures

Charges obtained by fit of electrostatic potential were calculated by the Singh–Kollmann (MK) scheme.[37]

3. Results and discussion

A series of twenty-two pyridinones ((**2a**), Table 1, items (a), (b) and (c)) was analysed.[38–42] These molecules were chosen due to their different substituents, which should influence conformational preferences. A general numbering scheme is presented in Fig. 3. A comparison between the conformations obtained by the AM1 and B3LYP/6-31G(d) methods was initially made, followed by an analysis of the geometric and electronic parameters involved in the interactions studied in the present investigation.

3.1. Comparison between the structures obtained by the AM1 and B3LYP/6-31G(d) methods

To show that the conformations obtained by the AM1 method correspond to those predicted by the B3LYP/6-31G(d) method, the geometries of molecules (**1**), (**2**), (**5**), (**13**), (**16**) and (**19**) (Table 1) were optimised using the latter. A subset of the possible pyridinone molecules with different chemical natures and a series of molecules spanning different substituents were studied by DFT methods to judge the reliability of semi-empirical results. The root mean square (RMS) deviations for the superposition of non-hydrogen atoms were determined. The results presented in Table 2 indicate that there are some differences in the conformation calculated by the two methods due to the small rotational barrier of the single bonds that connect the aromatic rings. In all cases, the obtained conformation was the butterfly-like one. For the molecules belonging to the other classes of NNRTI, the most evident conformational preference for the butterfly-like conformation was obtained with molecule (**2b**).

Table 2. RMS values (Å) obtained from the superpositions between the heavy atoms present in the molecules optimised through the AM1 and B3LYP/6-31G(d) methods

Molecules	RMS (Å)
(**1**)	1.782
(**2**)	1.045
(**5**)	1.710
(**13**)	1.203
(**16**)	1.256
(**19**)	0.775
(**2b**)	0.751
(**2c**)	1.964
(**2d**)	0.748

Conformational analysis revealed a marked preference for the butterfly-like conformation. Eight to eleven minimum energy conformers were obtained for each pyridinone, and most of them had the butterfly-like conformation. For example, a conformational analysis of molecule (**2**) using the Monte Carlo method has produced nine conformers, seven of them butterfly-like and two planar. The energy difference between the most stable butterfly-like conformation and a planar one was about 2.5 kcal/mol. Some sets of conformers were reoptimised in water using the SM2.1 method,[43] but there seemed to be no significant changes in conformational preferences, indicating that the butterfly-like conformation is maintained in aqueous solution.

3.2. Study of the geometric and electronic factors involved in hydrogen bonds and criteria used for the establishment of the π-type interactions between aromatic planes

The great majority of publications that establish the criteria for an interaction to be considered a hydrogen bond are based on: (i) intermolecular bonds, (ii) crystallographic data, and (iii) frequency of occurrence of an interaction.

Due to the relative diversity of substituent groups present in the analysed molecules, various types of possible hydrogen bonds were observed: NH···O (Fig. 4(i)), NH···OC (Fig. 4(ii)), CH···OC (Fig. 4(iii)), CH···N (CH···N(sp^2)), CH···O, CH···S and NH···N (NH···N(sp^2)) (Fig. 4(i)). For each of the molecules and interaction types, interatomic distances were compared to criteria established in the literature. Angles were not used as a criterion because there are no established criteria about intramolecular hydrogen bond angles based on the analysis of crystallographic databases.

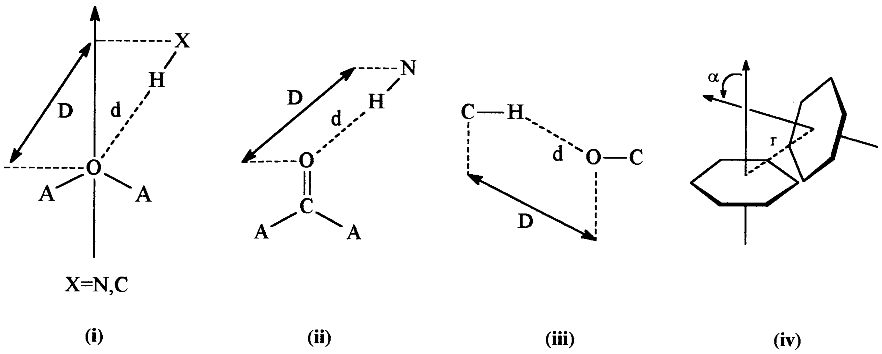


Figure 4. Representation of some of the geometric criteria used in the study of hydrogen interactions (i)–(iii) and aromatic ring π-interactions (iv).

For the interactions of the NH···O, NH···OC and NH···N types, the interatomic distance parameters adopted were those proposed by Mills and Dean.[44] These researchers have carried out a survey of the compounds containing intermolecular hydrogen bonds in the Cambridge Structural Database (CSD),[45] where the crystalline structures were obtained by X-ray diffraction. They have established the criteria for the occurrence of such bonds in an analysis of frequency distribution. For the first two cases, the N···O distances (*D*, Fig. 4(i) and (ii)) must be shorter than 3.42 and 3.30 Å, respectively. In the third case, the H···N distance must be less than 2.48 Å.

From a CSD survey of the X-ray crystalline structures containing the CH···OC group, Desiraju[46] established a standard distance value (*D*) (Fig. 4(iii)) between the carbon atom bound to hydrogen and the oxygen carbonyl atom by statistical distribution. *D* was found to be $3.00\text{ Å}<D<4.00\text{ Å}$. To study the distances (*d*) (Fig. 4(iii)) between the oxygen (electron donor) and hydrogen (electron acceptor) atoms, an upper limit of 2.80 Å was found. The most relevant interactions occurred at shorter distances ($2.00\text{ Å}<d<2.30\text{ Å}$).[46] The question as to whether the CH···OC interaction constitutes a true H-bond has been recently posed and has been clarified by experimental and theoretical studies.[47]

The interactions of the CH···N, CH···O, CH···Cl and CH···S types have been studied by Taylor and Kennard.[48] With the aid of a large series of crystalline structures from CSD obtained by neutron diffraction, these authors have established a contact relationship between the nearest neighbours (d') through frequency distribution, using the equation

$$d' = \nu(\mathrm{H}) + \nu(\mathrm{Y}) - r(\mathrm{H–Y}),$$

where $\nu(\mathrm{H})$ is the (C–)H van der Waals radius (hydrogen atom which is covalently bound to carbon), $\nu(\mathrm{Y})$ is the Y van der Waals radius for the heteroatom, and $r(\mathrm{H–Y})$ is the interatomic distance between (C–)H–Y. An important geometric feature of hydrogen bonds is that the distance between the proton and the acceptor is shorter than the sum of the van der Waals radii.[48] The values of the van der Waals radii used by the authors in this study were: $\nu(\mathrm{C})=1.75$ Å, $\nu(\mathrm{N})=1.55$ Å, $\nu(\mathrm{S})=1.80$ Å, $\nu(\mathrm{H})=1.20$ Å and $\nu(\mathrm{O})=1.50$ Å. It was observed that for the contacts where $d'>0.3$ Å, i.e. significantly shorter than the sum of the van der Waals radii, the bonds of the CH···O type were more frequent. This was probably due to the electrostatic stabilisation phenomenon.[48] For the CH···N bonds, the authors did not obtain conclusive proof of these interactions due to the limited data sample. Nevertheless, it was mentioned that the electronegativities of the oxygen and nitrogen atoms were comparable and that the majority of the (C–)H···O contacts were attractive. This demonstrated that the short CH···N contacts will also be of an attractive nature.[48] The nature of the CH···S bonds was not determined. In the present study, this analysis of the contact between the nearest neighbours was applied to all types of hydrogen interactions. Therefore, it must be understood that any contact with $d'>0.0$ Å, except for CH···O ($d'>0.3$ Å), may indicate the existence of such hydrogen bonds.

It should be taken into account that a ring is formed in an intramolecular hydrogen bond. The stability of this ring is related to the number of ring members. In a study of hydrogen bonds as design elements in organic chemistry, Etter used a series of crystallographic data from the CSD and succeeded in establishing some general rules for these bonds.[49] Among such rules is the one that states that a system containing a hydrogen bond involving six members preferentially forms an intramolecular bond, instead of an intermolecular one. This consideration can be extrapolated to other stable systems that are not six-membered rings.

Nevertheless, NNRTI preferential conformations cannot only be attributed to hydrogen bonds. The interactions between aromatic rings (the π interactions) also contribute to stabilisation of the molecular structure. This type of interaction is still not well understood, particularly when the rings involved are polarised due to the presence of heteroatoms. Hunter and Sanders[50] have proposed a series of rules for the π–π interactions. For the interaction between atoms of high charge, the charge-to-charge interactions should be predominant. In non-polarised systems, the *T*, edge-shaped or offset π-stacked conformations should be preferable, where there is a π–σ interaction. An example in the variation of aromatic ring behaviour with fluorination has been observed in the interaction of compounds containing the phenyl and pentafluorophenyl groups.[51] However, the authors have not established the geometric criteria that would allow one to detect the existence of π bonds. For the interaction between the phenyl groups of aromatic rings, Burley and Petsko,[52] on the basis of frequency distribution, determined that the preferential distance (Fig. 4 (iv)) between the aromatic pairs in peptides and proteins is $4.5\text{ Å}<r<7.0\text{ Å}$. They also found that the majority of dihedral angles between such pairs are in the range of $50°<\alpha<90°$, and that they are more often closer to the latter value.

However, it is not possible to establish the existence of an intramolecular bond only through geometric parameters, i.e. without a complementary discussion about the electronic factors involved in the interactions. Therefore, the hydrogen bond dipole moments, $\mu(\mathrm{H}\cdots\mathrm{Y})$, calculated on the basis of MNDO/ESP and MK charges were also considered. The energy of the interaction between the heteroatom lone pair and the antibonding orbitals of the hydrogen bond donor group, as well as the occupation of such orbitals, were obtained by NBO analysis.

Table 3. Average values for the geometric parameters observed for all the types of hydrogen bonds studied in the substituted pyridinones. Distances are given in Å

Interaction type	Number of ring members	Number of observed interactions	Average distance (*d*)	Average distance (*D*)
NH···OC	5	9		
	6	1	2.313	2.932
	8	2		
CH···OC	5	1		
	6	11	2.298	3.002
NH···N	5	6	2.879	–
NH···O	5	4	2.703	2.998
CH···N	5	2	2.786	–

Table 4. Average charges (q) for Y and H and average H···Y dipole moments, $\mu(\mathrm{H\cdots Y})/D$, calculated by MNDO/ESP and MK methods

Interaction type	Atom	q MNDO/ESP	q MK	μ(H···Y) MNDO/ESP	μ(H···Y) MK
NH···OC	H	0.465	0.347		
	O	−0.680	−0.577	6.360	4.924
CH···OC	H	0.133	0.076	4.431	3.413
	O	−0.670	−0.547		
NH···N	H	0.430	0.336	7.190	6.282
	O	−0.610	−0.636		
NH···O	H	0.440	0.339	4.560	3.714
	O	−0.268	−0.230		
CH···N	H	0.043	–	3.706	–
	O	−0.511	–		

The hydrogen bonds could be classified into two groups: the more favoured bonds (NH···OC and CH···OC) and the less favoured ones (NH···N, NH···O and CH···N). Each of these types of interaction will be discussed separately. Tables 3 and 4 show the average values obtained for some of the geometric and electronic parameters studied.

The bonds of the NH···OC type are very common among the studied compounds (Tables 3 and 4) and most of them (75%) are formed by the O[C(2)] and H[N(3a)] atoms, i.e. they involve five-membered rings. This once again demonstrates that such interactions are highly favourable. In addition, the hydrogen and oxygen atoms respectively display high positive and negative charges. The distances involved in these interactions are short and are within the limit established by Mills and Dean.[44] The contact relationship between the nearest neighbouring atoms was extended to this type of interaction, where the average value found for d' was 0.386 Å, with the value being higher than 0.3 Å in 75% of the case analysed. Molecule (**6**) presents an interaction involving a six-membered ring. The NH···OC interactions for molecules (**7**) and (**14**) involve eight-membered rings. The distance (d) between the hydrogen and oxygen atoms and the charges of such atoms presented values compatible with the existence of strong hydrogen bonds.

CH···OC bonds are also frequent and favourable (Tables 3 and 4). Practically all the interactions involve the O[C(2)] and H[C(2′a)] atoms, leading to the formation of six-membered rings. The data concerning the analysis of the contact between the nearest neighbours fulfil by 66.7% the conditions for the d' values proposed by Taylor and Kennard[48] for interactions of this nature. The mean value for d' is 0.402 Å. For the oxygen atoms, the average charge value is high, while for hydrogen this value is moderate. The dipole moments for these interactions, μ(H···O), and the H···O and C···O distances present values that are in agreement with the existence and importance of hydrogen bonds in the compounds studied. For molecule (**9**), the hydrogen interaction corresponds to the O[C(2)] and H[C(3a)] atoms and involves a five-membered ring. At first, this could be considered a favourable bond, but this interaction is also disfavoured when the d' values are considered.

By analysing the NH···N bonds (Tables 3 and 4), it can be seen that they all involve six-membered rings and occur between the N(3′) and H[C(3a)] atoms. The average charges and dipole moments are high. However, the average distance (d) between the nitrogen and hydrogen atoms is longer than that proposed by Mills and Dean.[44] These factors, together with a not very favourable orientation of the acceptor atom lone pairs, demonstrate the weak intensity of this type of intramolecular interaction within the analysed series.

The interactions of the NH···O type (Tables 3 and 4) present an average distance between the different hydrogen atoms (D) that is within the limit established by Mills and Dean.[44] The average nitrogen charge is low, but that of the hydrogen is comparable to the values found for the NH···OC and CH···OC interactions. The dipole moments of these interactions are very high. Again, in this case, the oxygen lone pair's orientation is not suitable for the establishment of a strong interaction.

Finally, the CH···N bonds are not favoured and are of little importance (Tables 3 and 4). Considering the van der Waals radii, a d' average value of 0.036 Å was obtained. The fact that the hydrogen atom is directly bound to a weakly electronegative element makes it display a very low positive charge. In this way, the average dipole moment for the interaction is also low. The distances between the hydrogen and nitrogen atoms are relatively longer than the distances involved in the NH···OC and CH···OC bonds. So, any criterion indicates that these bonds should be very weak. Recently, it has been observed that this type of interaction is weak in 'host–guest' complexes.[53]

For the three cases in which the interactions are not favoured, the distance that separates the donor and acceptor atoms is longer or very close to the sum of their respective van der Waals radii. Interactions involving sulphur atoms were not observed and there was no indication of the existence of interactions involving halogens and bonds of the CH···O(sp^3) type.

By comparing the geometric criteria shown in Table 3 with the electrostatic criteria shown in Table 4, one can conclude that they are not correlated and that the latter do not allow a good discrimination between the types of hydrogen bonds that are more or less favourable. This may indicate that the electrostatic contribution does not predominate in the stabilisation of the hydrogen bond. Therefore, only the geometric criteria permit us to determine whether a hydrogen bond will be strong or not. The use of charges obtained through the electrostatic potential obtained by semi-empirical or DFT methods led to similar results in the description of the hydrogen bonds studied here.

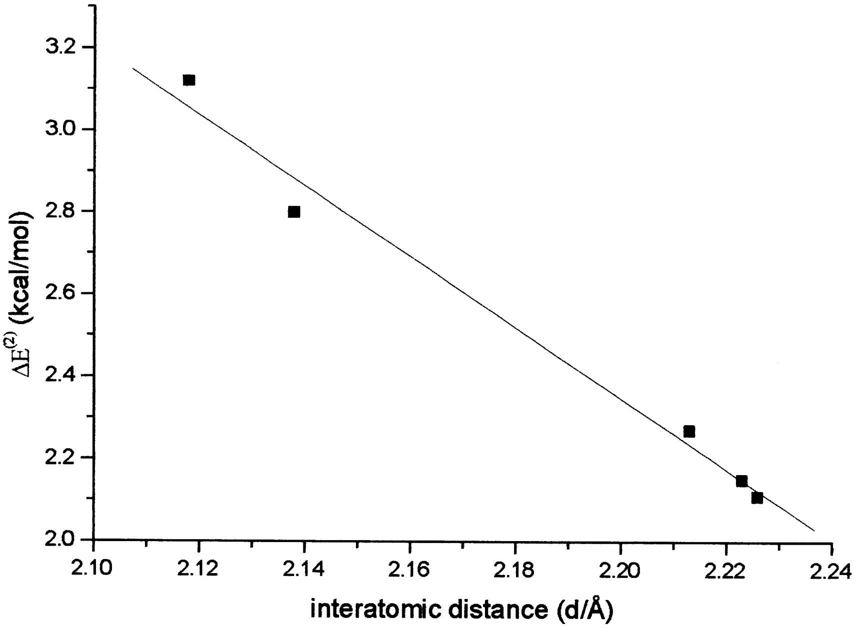


Figure 5. Linear correlation between the distances of atoms directly involved in hydrogen bonds and interaction energy $\Delta E^{(2)}$. The correlation coefficient is 0.992±0.064.

NBO theory indicates that the stabilisation of a hydrogen bond is ascribed to a charge transfer from the lone pairs of electron donor, n_Y, and the antibonding orbitals, $\sigma_{HX}{}^*$, of the X–H bond of the electron acceptor, in the Y···HX hydrogen bond.[31–34] The second order interaction energy, $\Delta E^{(2)}$, is a measure of this interaction. The energies for the O(1′)···H[N(3a)] interactions in molecules (**2**) and (**13**) are lower than 0.05 kcal/mol. Thus, this type of bond should be very weak in the series studied. The energy data obtained strongly indicate that the O[C(2)]···H[N(3a)] and O[C(2)]···H[C(2′a)] bonds are favourable in the cases studied. If one considers that the CH···O bond stabilisation energy due to charge transfer is in the range 1–2 kcal/mol,[54] it is possible to conclude that the calculated values are in good agreement from a qualitative point of view. It has been observed that the distance between the atoms directly involved in the hydrogen bonds (*d*) is linearly correlated with the values for the stabilisation energy due to the interaction between the n_Y and $\sigma_{HX}{}^*$ orbitals, $\Delta E^{(2)}$, where the correlation coefficient is 0.992±0.064 (Fig. 5). This indicates that the charge transfer significantly contributes to the stabilisation of the hydrogen bonds studied, as previously observed by Ammal and Venuvanaligam for HF and LIF complexes with *n* donors.[55] The hydrogen bonds in the studied compounds present the characteristic pattern observed in the NBO analysis of various systems,[34] displaying an electronic density transfer from a hydrogen bond lone pair acceptor orbital, n_Y, to the $\sigma_{HX}{}^*$ orbital. This causes a decrease in the level of occupation of the former orbital, and an increase in the latter.

Analysis of the aromatic rings indicates that they are highly polar. Therefore, the interactions between charges should be predominant. However, due to the long distances between the rings (longer than 4.0 Å), the electrostatic interactions should present a small contribution if compared to hydrogen bonds. A qualitative analysis allows one to conclude that this contribution should be energetically favourable. By using the criteria proposed by Burley and Petsko[52] (Fig. 4(iv) and Table 5), it is possible to observe that π interactions occur between the aromatic rings C and A. The average value found for this distance is 5.210 Å, the average value found for the distance between rings C and B was 7.000 Å, and in 83.3% of cases the distance is within the proposed limits. In all molecules, the aromatic planes assume an edge-shaped conformation and the angle between these planes is qualitatively found within the expected range: 50°<α<90°. Thus, the π–π interactions should contribute to the 'butterfly-like' conformation.

It is possible to conclude that the most favourable hydrogen bonds are NH···OC and CH···OC and the distances are very close to the proposed values. Particularly for these types of

Table 5. Distances (*r*/Å) between the aromatic planes in NNRTI

Molecule	*r*(C→A)	*r*(C→B)	*r*(C→D)
(**1**)	6.280	8.440	–
(**2**)	5.032	6.679	–
(**3**)	4.848	6.478	–
(**4**)	5.248	6.753	–
(**5**)	5.169	6.919	–
(**6**)	5.084	6.804	–
(**7**)	4.965	6.612	–
(**8**)	5.197	6.756	–
(**9**)	4.825	6.474	–
(**10**)	5.127	6.829	–
(**11**)	4.903	6.560	–
(**12**)	6.352	8.750	–
(**13**)	5.048	8.000	–
(**14**)	5.055	6.989	–
(**15**)	5.034	6.692	8.026
(**16**)	5.548	–	–
(**17**)	5.149	6.893	–
(**18**)	5.062	6.803	–
(**19**)	4.974	6.560	–
(**20**)	5.298	–	–
(**21**)	5.189	–	–
(**22**)	5.222	–	–

interaction, it is possible to observe that they occur between an oxygen atom of the 5-ethyl-6-methylpyridin-2(1*H*)-one carbonyl group, O[C(2)], and a hydrogen atom situated in the flexible chain of molecules (C(3)–X(3a)–C(2′a)– C(2′), X=CH_2, NH or NC_2H_5) (Table 1 and Fig. 3). Such hydrogen bonds may act as a kind of 'bridge' between these two parts of the molecule, bringing them closer and getting the planes that are separated by the flexible extension of the structures nearer to each other. These factors operating together should contribute to the stabilisation of the butterfly-like conformation.

Crystallographic structures for the pyridinones belonging to the NNRTI group were not found in a survey in the CSD. These semi-empirical calculations suggest, even in the absence of supporting crystallographic data, that these coumpounds form preferential butterfly-like conformations, as verified by high-level calculations.

The conclusions about the role of hydrogen bonds and π interactions in the pyridinone preferential conformation were extended to some other NNRTI, compounds (**2b**), (**2c**) and (**2d**) (Fig. 2). By firstly analysing nevirapine, we noticed that hydrogen bond formation is unlikely to aid the above-mentioned conformation. The position of the cyclopropyl group in the structure optimised by the DFT (B3LYP/6-31G(d)) method does not favour the interaction between the cyclopropyl hydrogen and the pyridine nitrogen atoms. The seven-membered ring separates the pyrimidic ring centres in 4.817 Å, which could be an acceptable distance for the establishment of a π-type interaction between these weakly polar aromatic rings. Qualitatively, the angle between these rings should be within the range predicted by Burley and Petsko.[52] The π interaction should contribute to the stabilisation of the compound, but considering that the rings are polar, the observed stacked interaction should be disfavoured. In this way, the main reason for the establishment of a butterfly-like conformation would be related to the pyramidalisation of the nitrogen atom bound to the cyclopropyl group.

The TIBO (B3LYP/6-31G(d)) structure does not present hydrogen bonds capable of helping the preferential conformation either. This conformation is also not favoured by π interactions between aromatic rings, since TIBO presents fused aromatic systems. The butterfly-like conformation is obtained between the cyclic groups and the acyclic ramification. This is due to nitrogen pyramidalisation in the seven-membered ring to which the ramification is bound. In addition, there are the probable steric effects and the π-type interaction between the double bond of the acyclic chain and the aromatic rings contributing to the preferential conformation. In a recent study from our laboratory, a complete conformational analysis of TIBOs was performed.[56] The structures obtained were compared with monocrystal[18] and the TIBO–RT complex[14,15] crystalline geometries. The most interesting fact observed in the present study is that the active conformation (found in the complex) is not a global minimum. Nevertheless, these two conformations are encountered in the monocrystal.[18] The main difference between these two forms is related to the possibility of puckering of the seven-membered ring and folding of the dimethylallyl substituent, which favours the preference for the butterfly-like conformation. This places the aromatic ring and the acyclic ramification double bond in a position that intensifies the interaction between their respective π electrons in the active conformation. These factors, allied to the observations concerning pyridinone conformation, indicate that the NNRTI preference for the butterfly-like conformation is not only related to the form and interaction with the enzyme 'binding-pocket', but also to the intramolecular interactions, as shown in the present study. It is also possible to conclude that the active form conformation may be easily found in a conformational search, even under vacuum, since it is favoured by various factors, including the studied ones.

For delavirdine, geometry optimisation by the DFT method indicates that the most stable conformation when the molecule is not bound to reverse transcriptase is not the butterfly-like one. However, this molecule somehow structurally resembles pyridinones and hydrogen bonds can be established between the carbonyl group oxygen and the NH hydrogen present in the five-membered ring and/or the hydrogens bound to carbons close to the oxygen. In both cases, the bonds would form five-membered rings. As mentioned earlier, the NH···OC and CH···OC bonds are well defined. In these cases, the distances between the acceptor and donor atoms (*d*) are 2.313 Å (NH···OC) and 2.246 Å (CH···OC), while the distances (*D*) between the oxygen and the nitrogen or carbon atoms to which the hydrogen is bound are 2.658 Å (NH···OC) and 2.744 Å (CH···OC). These data are in good agreement with the average values found in the study of this type of interaction in the substituted pyridinones (Table 3). This would enable the occurrence of such bonds.

Analysis of these other NNRTI shows that the criteria for the establishment of hydrogen bonds and aromatic interactions obtained for pyridinones may also be applied to all the other inhibitors of this group. However, one cannot exclude the possibility that other factors are also responsible for the butterfly-like conformation assumed by this class of inhibitors.

4. Conclusions

In the present investigation, a series of 22 pyridinone inhibitors of the HIV-1 RT was studied. Our main aim was to outline a series of structural patterns and electronic parameters that could indicate the most important intramolecular interactions. By analysing the existence and magnitude of intramolecular interactions without taking into account the non-covalent interactions between the inhibitors and RT, it was possible to discuss the reasons why NNRTI prefer the butterfly-like conformation. The results show that both hydrogen bonds and aromatic ring π interactions contribute to the stability of the pyridinone butterfly-like structure. The solvation effects appear not to change the relative stability of different conformations, butterfly-like or linear. It was possible to obtain a profile of the intramolecular hydrogen bonds that contribute more efficiently to this conformational preference by a qualitative study of the geometric parameters (interaction distances and the number of ring members) of these interactions and by comparing the data obtained to the crystallographic data. On the other hand, electrostatic parameters such as charges and dipole moments do not permit the determination of the most favourable bonds. This factor, allied to the existing correlation between stabilisation energies $\Delta E^{(2)}$ and bond distances, indicates that these interactions are mainly stabilised through charge transfer. A comparative study of other inhibitors of the same class (NNRTI) demonstrated that interactions of this type are not necessarily responsible for the conformational preference of other NNRTI, since in many cases they do not have the importance they have in pyridinones. These findings reinforce the conclusions obtained by Mager that affinity is directly related to the stability of the butterfly conformation.

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Appendix A

Supplementary material

See Tables 6–11.

Table 6. Molecules with bonds of the NH···OC type (q is the atomic charge of the atom, D is the interatomic distance between N···O, d is the interatomic distance H···O and d' is the contact relationship between atoms calculated through the equation $d' = \nu(\mathrm{H}) + \nu(\mathrm{Y}) - r\ (\mathrm{H{-}Y})$)

Panel (a)				
Molecule	(**2**)	(**6**)	(**7**)	(**8**)
Bond	O[C(2)]–H[N(3a)]	O[C(1′)]–H[N(3a)]	O[C(2)]–H[N(1′)]/ O[C(2)]–H[N(3a)]	O[C(2)]–H[N(3a)]
Number of members	5	6	8/5	5
q(H)	0.468	0.440	0.599/0.440	0.486
q(O)	−0.675	−0.572	−0.748	−0.677
D (Å)	2.987	3.042	3.029/2.859	2.837
d (Å)	2.226	2.436	2.126/2.433	2.362
d' (Å)	0.474	0.264	0.574/0.267	0.338

Panel (b)				
Molecule	(**12**)	(**13**)	(**14**)	(**15**)
Bond	O[C(2)]–H[N(3a)]	O[C(2)]–H[N(3a)]	O[C(2)]–H[N(1′)]	O[C(2)]–H[N(3a)]
Number of members	5	5	8	5
q(H)	0.446	0.419	0.498	0.463
q(O)	−0.689	−0.698	−0.682	−0.679
D (Å)	2.837	2.750	3.462	2.839
d (Å)	2.404	2.223	2.222	2.370
d' (Å)	0.296	0.477	0.478	0.330

Panel (c)			
Molecule	(**16**)	(**20**)	(**21**)
Bond	O[C(2)]– H[N(3a)]	O[C(2)]– H[N(3a)]	O[C(2)]– H[N(3a)]
Number of members	5	5	5
q(H)	0.422	0.462	0.435
q(O)	−0.688	−0.699	−0.675
D (Å)	2.861	2.846	2.838
d (Å)	2.213	2.365	2.379
d' (Å)	0.487	0.335	0.321

Table 7. Molecules with bonds of the CH···OC type (*q* is the atom charge, *D* is the interatomic distance between C···O, *d* is the interatomic distance H···O and *d′* is the contact relationship between atoms calculated through the expression $d' = \nu(\mathrm{H}) + \nu(\mathrm{Y}) - r(\mathrm{H–Y})$)

Panel (a) Molecule	**(1)**	**(4)**	**(5)**	**(6)**
Bond	O[C(2)]– H[C(2′a)]	O[C(2)]– H[C(2′a)]	O[C(2)]– H[C(2′a)]	O[C(2)]– H[C(2′a)]
Number of members	6	6	6	6
q(H)	0.080	0.176	0.141	0.100
q(O)	−0.677	−0.666	−0.660	−0.630
D (Å)	3.214	2.967	2.965	2.991
d (Å)	2.614	2.176	2.118	2.209
d′ (Å)	0.086	0.524	0.582	0.491
Panel (b) Molecule	**(9)**	**(10)**	**(11)**	**(14)**
Bond	O[C(2)]–H[C(3a)] O[C(2)]–H[C(2′a)]	O[C(2)]–H[C(2′a)]	O[C(2)]–H[C(2′a)]	O[C(2)]–H[C(2′a)]
Number of members	5/6	6	6	6
q(H)	0.200/0.154	0.100	0.081	0.155
q(O)	−0.700	−0.649	−0.686	−0.682
D (Å)	2.889/3.174	2.956	3.168	2.813
d (Å)	2.730/2.485	2.156	2.486	2.143
d′ (Å)	−0.030/0.215	0.544	0.214	0.557
Panel (c) Molecule	**(17)**	**(19)**	**(22)**	
Bond	O[C(2)]–H[C(2′a)]	O[C(2)]–H[C(2′a)]	O[C(2)]–H[C(2′a)]	
Number of members	6	6	6	
q(H)	0.187	0.106	0.118	
q(O)	−0.675	−0.650	−0.694	
D (Å)	2.962	3.002	2.918	
d (Å)	2.170	2.138	2.148	
d′ (Å)	0.530	0.562	0.552	

Table 8. Molecules with bonds of the NH···N type (*q* is the atom charge, *d* is the interatomic distance H···N and *d′* is the contact relationship between the atoms calculated through the expression $d' = \nu(\mathrm{H}) + \nu(\mathrm{Y}) - r(\mathrm{H}–Y)$)

Panel (a) Molecule	**(4)**	**(5)**	**(8)**
Bond	N(3′)–H[N(3a)]	N(3′)–H[N(3a)]	N(3′)–H[N(3a)]
Number of members	5	5	5
q(H)	0.397	0.431	0.486
q(N)	−0.552	−0.710	−0.451
d (Å)	2.843	2.695	3.114
d′ (Å)	−0.093	0.055	−0.364
Panel (b) Molecule	**(14)**	**(17)**	**(22)**
Bond	N(3′)–H[N(3a)]	N(3′)–H[N(3a)]	N(3′)–H[N(3a)]
Number of members	5	5	5
q(H)	0.444	0.408	0.415
q(N)	−0.751	−0.531	−0.666
d (Å)	2.985	2.876	2.764
d′ (Å)	−0.235	−0.126	−0.014

Table 9. Molecules with bonds of the NH···O type (*q* is the atom charge, *D* is the interatomic distance N···O, *d* is the interatomic distance H···O and *d′* is the contact relationship between the atoms calculated through the expression $d' = \nu(\mathrm{H}) + \nu(\mathrm{Y}) - r(\mathrm{H–Y})$)

Molecule	**(2)**	**(10)**	**(13)**	**(15)**
Bond	O(1′)–H[N(3a)]	O(1′)–H[N(3a)]	O(1′)–H[N(3a)]	O(1′)–H[N(3a)]
Number of members	5	5	5	5
q(H)	0.468	0.410	0.419	0.463
q(O)	−0.330	−0.289	−0.165	−0.288
D (Å)	2.987	2.974	3.027	3.006
d (Å)	2.701	2.658	2.735	2.719
d′ (Å)	−0.001	0.042	−0.035	−0.019

Table 10. Molecules with bonds of the CH···N type (q is the atom charge, d is the interatomic distance H···N and d' is the contact relationship between atoms calculated through the expression $d' = \nu(\mathrm{H}) + \nu(\mathrm{Y}) - r(\mathrm{H–Y})$)

Molecule	(**3**)	(**9**)
Bond	N(3′)–H[C(3a)]	N(3′)–H[C(3a)]
Number of members	5	5
q(H)	0.040	0.046
q(N)	−0.556	−0.465
d (Å)	2.789	2.782
d' (Å)	−0.039	−0.032

Table 11. NBO stabilisation energies obtained for some interactions between lone pair of the hydrogen bond acceptor atom (n_Y) and the antibonding orbital of the hydrogen bond donor (σ_{HX}^*)

Molecule	Interaction	$\Delta E^{(2)}$ (kcal/mol)	Occupation	
	$n_Y \rightarrow \sigma_{HX}^*$		n_Y	σ_{HX}^*
(**1**)	$n_{\mathrm{O[C(2)]}} \rightarrow \sigma_{\mathrm{HC(2'a)}}^*$	0.40	1.85949	0.01594
(**2**)	$n_{\mathrm{O[C(2)]}} \rightarrow \sigma_{\mathrm{HN(3a)}}^*$	2.11	1.85618	0.02536
(**2**)	$n_{\mathrm{O(1')}} \rightarrow \sigma_{\mathrm{HN(3a)}}^*$	–	–	–
(**5**)	$n_{\mathrm{O[C(2)]}} \rightarrow \sigma_{\mathrm{HC(2'a)}}^*$	3.12	1.85726	0.02521
(**5**)	$n_{\mathrm{N(3')}} \rightarrow \sigma_{\mathrm{HN(3a)}}^*$	–	1.90797	0.01550
(**13**)	$n_{\mathrm{O(1')}} \rightarrow \sigma_{\mathrm{HN(3a)}}^*$	–	–	–
(**13**)	$n_{\mathrm{O[C(2)]}} \rightarrow \sigma_{\mathrm{HN(3a)}}^*$	2.15	1.85633	0.02552
(**16**)	$n_{\mathrm{O[C(2)]}} \rightarrow \sigma_{\mathrm{HN(3a)}}^*$	2.27	1.85615	0.02441
(**19**)	$n_{\mathrm{O[C(2)]}} \rightarrow \sigma_{\mathrm{HC(2'a)}}^*$	2.80	1.85748	0.03010

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