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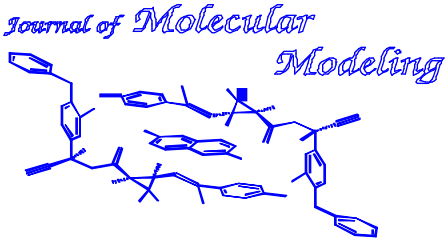

Structure-Activity Relationship for Some 2',3'-Dideoxynucleoside Anti-HIV Drugs Using Molecular Electrostatic Potential Mapping

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Abstract

Molecular electrostatic potential(MEP) maps of azido thymidine (AZT), some of its analogs and derivatives and certain other 2',3'-dideoxy nucleosides having different anti-HIV activities have been studied. The optimised hybridization displacement charges (HDC) combined with MNDO Löwdin charges, continuosly distributed in three dimension spherically symmetrically as a Slater cloud at each site were used to compute the MEP maps. The negative MEP region near the O5' sites of these molecules appears to be of primary importance from the point of view of their anti-HIV activity. The roles of the azido group in AZT and fluorine atoms substituted at different positions in the sugar moiety have been evaluated. The azido group in AZT behaves as a strongly electronegative group.

Keywords: Electrostatic potential, hybridization displacement charge, Azidothymidine, Anti-HIV drugs.

Introduction

Therapeutic utility of nucleic acid base analogs and their derivatives is well known [1-4]. Several 2',3'- dideoxy nucleosides having varying degrees of anti-HIV activity have been identified [5-26]. Azidothymidine (AZT), its analogs and certain other 2',3'-dideoxy nucleosides are particularly well known to be potent chain terminating inhibitors of the enzyme reverse transcriptase encoded by the HIV virus [5-26]. Since these molecules do not have a 3'-hydroxyl group each, their incorporation in HIV viral DNA terminates the DNA chain elongation which results in the control of HIV proliferation [5-26]. Though AZT is a popular and effective anti-HIV drug [15-26], it shows high toxic effects [23]. 2',3'-Dideoxy inosine (ddI) and 2',3'-dideoxy cytidine (ddC) are other anti-HIV drugs in clinical use against AIDS [17,19]. A combined administration of AZT, ddI and ddC is quite effective against HIV and is getting importance in the treatment of HIV infected patients [17]. A detailed conformational study of some 2',3'-dideoxy nucleosides has been performed using X-ray crystallography [27] and quantum chemical methods [28]. These studies suggest that active forms of compounds mostly have anti-conformation [27,28]. Recently, some non-nucleoside anti-HIV drugs have also been reported [29,30]

Attempts have been made to increase the drug potency and decrease toxicity using phosporylated compounds either in the form of phosphates or as phosphoramidates [31-33]. It is found that for high anti-HIV activity, the base moiety in a 2',3'-dideoxy nucleoside drug may be a natural base [18]. Further, fluorine substitution on the sugar moiety in general has been found to change antiviral activity of 2',3'-dideoxy nucleosides appreciably [20-25] while 2'-fluorine substitution increases acid stabilising properties of nucleosides [20,21]. Moreover, 2'-fluoro dideoxy cytidine (2'F-ddC) is found to be active, while 2'-fluoro-3'-azido dideoxy thymi-

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dine (2'F-AZT) is found to be inactive against HIV [23]. According to a report 3'-fluoro thymidine (FLT) is very active against HIV [23]. These results show that activities of 2',3'-dideoxy nucleosides with fluorine substitution at different positions of the sugar moiety depend in a complicated manner on the location of the fluorine atom.

It is well known that biomolecular recognition processes depend on stereochemical and electrostatic complementarity of molecules [34-39]. Molecular electrostatic potential (MEP) and molecular electric field (MEF) mapping are now established as useful tools in the study of biomolecular recognition and structure-activity relationships [40-46]. These aspects of large molecules are usually studied using point charge distributions, particularly Mulliken charges [40-46]. However, these charges as such are not accurate enough to enable reliable prediction of MEP and MEF. A concept of hybridization displacement charge (HDC) was introduced recently and, subsequently, an optimised approach to compute the same was developed [47-49]. When HDC are combined with Löwdin point charges, the molecular dipole moment computed using the SCF density matrix is fully preserved at the point charge level [47-49]. Further, MEP maps of large molecules can be studied reliably, usually reproducing *ab-initio* MEP features qualitatively, using semiempirical molecular orbital methods and optimised HDC-corrected Löwdin charges distributed continuously in three dimension [47-49].

In view of the above facts, we undertook the study of MEP maps of a series of anti-HIV 2',3'-dideoxy nucleosides with different substitutions on the sugar moiety using HDC-corrected Löwdin charges since a study of this aspect using a reliable method was lacking. The primary aim in this study was to obtain information regarding the effects of substituents located at the different positions of the sugar ring on the anti-HIV activities of various 2',3'-dideoxy nucleosides.

Calculation method

The molecular electrostatic potential V(r) at a point r is defined as

$$V(\mathbf{r}) = \sum_i \left[\frac{Z_i}{|\mathbf{R}_i - \mathbf{r}|} \right] - \int \rho(\mathbf{r}')\, d\mathbf{r}' \Big/ |\mathbf{r}' - \mathbf{r}| \qquad (1)$$

where Z_i is the charge on nucleus i located at $\mathbf{R}_i$ and $\rho(\mathbf{r})$ is the molecular electron density function for the given molecule. To improve the accuracy of MEP calculations with respect to the point charge model which may be used in place of equation (1), the electronic charges may be considered to be distributed spherically and symmetrically on each atomic and HDC site in 3-dimension according to the form of the square of the corresponding valence Slater s atomic orbital [47-49]. When this is done, the electronic contribution $V^{el}(\mathbf{r})$ to MEP $V(\mathbf{r})$ for hydrogen atoms (principal quantum number n=1) is given by [47-49]

$$V^{el}(\mathbf{r}) = \sum_i \left[\frac{q_i}{|\mathbf{R}_i - \mathbf{r}|} \right] \left[1 - (1 + \eta_i) \exp - 2\eta_i \right] \qquad (2)$$

Where $\eta_i = \zeta_i |\mathbf{R}_i - \mathbf{r}|$

ζ being the Slater exponent of the 1s atomic orbital. q_i is the total electronic charge at the site i.

For n=2, we have

$$V^{el}(\mathbf{r}) = \sum_i \left[\frac{q_i}{|\mathbf{R}_i - \mathbf{r}|} \right] \left[1 - \left(1 + \eta_i \left(1.5 + \eta_i \left(1 + \frac{\eta_i}{3} \right) \right) \right) \exp - 2\eta_i \right] \qquad (3)$$

The MEP $V(\mathbf{r})$ is obtained by adding $V^n(\mathbf{r})$ to $V^{el}(\mathbf{r})$, $V^n(\mathbf{r})$ being given by

$$V^n(\mathbf{r}) = \sum_i \frac{Z_i}{|\mathbf{R}_i - \mathbf{r}|} \qquad (4)$$

The hybridization dipole moment along the x-direction due to mixing of 2s and $2p_x$ atomic orbitals of the atom is given by

$$\mu_x = D_{\mathbf{x}}\, Q_1 \qquad (5)$$

Where $D_x = (\, 2s \mid x \mid 2p_x\,)$ and $Q_1 = -2p_{2s2px}$

It can be shown that

$$D_x = \frac{160 \left(\zeta_s \zeta_p \right)^{5/2}}{\sqrt{3} \left(\zeta_s \zeta_p \right)^6} \qquad (6)$$

where ζ_s and ζ_p are the Slater exponents of the 2s and 2p atomic orbitals and they may be taken to be equal [50,51].

Hybridization displacement charge (HDC) is defined as

$$Q = \mu_h / R \qquad (7)$$

where μ_h is the total hybridization dipole moment of the atom under consideration arising due to displacement of the charge to a distance R from the atom. Further,

$$\mu_h = \sqrt{\mu_x^2 + \mu_y^2 + \mu_z^2} \qquad (8)$$

and

$$R = \sqrt{D_x^2 + D_y^2 + D_z^2} \quad (9)$$

From these equations, we get

$$Q = \sqrt{\frac{Q_1^2 + Q_2^2 + Q_3^2}{3}} \quad (10)$$

The displacement takes place along the direction given by

$$\theta = \tan^{-1}\left(\frac{\mu_y}{\mu_x}\right) \quad (11)$$

$$\phi = \tan^{-1}\left(\frac{\mu_z}{\mu_h}\right) \quad (12)$$

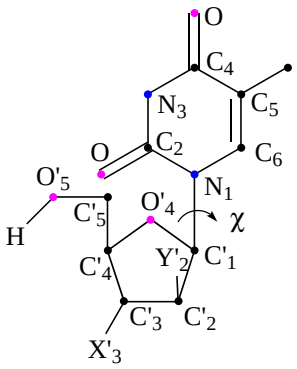
The equation (5) can also be written as

$$\mu_h = (KD_x)\left(\frac{Q_1}{K}\right) = D'_x Q'_x \quad (13)$$

Where K is an adjustable parameter which controls the magnitude of charge (Q'_1) and the distance (D'_X) of HDC along the X-direction. Along with K, Slater exponents of HDC (ζ) have also been treated as adjustable parameters, as discussed earlier [47-49]. Further, these parameters (K and ζ) have been optimised for different types of atoms so as to reproduce *ab initio* MEP features using semiempirical methods as far as possible [47-51]. Here, we used the MNDO method [51]. Crystal geometries of the molecules were used as far as available [24-27,52,53]. Geometries of 2'-F-AZT-B, FLT and ddI were obtained by optimising the bond lengths and bond angles at the site of substitution, keeping the other geometrical variables the same as those in the crystal geometries of AZT-B and 2'-F-dd-araI. Three dimensional colour graphic representation of MEP surfaces of some molecules calculated using HDC-corrected Löwdin charges was obtained using software from Oxford Molecular [54].

Results and discussion

The molecular structures of 3'-azido-2',3'-dideoxy thymidine (AZT-A and AZT-B corresponding to the A and B conformations of AZT), 3'-fluoro-2',3'-dideoxy thymidine (FLT), 2'-fluoro-2',3'-dideoxy thymidine (2'F-AZT-B), 5-endo-

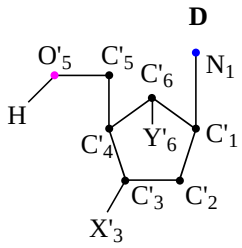


AZT-A: $X'_3 = N_3$, $Y'_2 = H$
$\angle C_6N_1C'_1O'_4 = \chi = 53.4°$

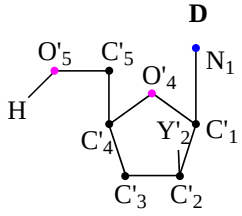
AZT-B: $X'_3 = N_3$, $Y'_2 = H$
$\angle C_6N_1C'_1O'_4 = \chi = 2.3°$

FLT: $X'_3 = F$, $Y'_2 = H$

2'F-AZT-B: $X'_3 = N_3$, $Y'_2 = F$



CarbF: $X'_3 = F$, $Y'_6 = F$ **D** = Thymine



ddA: $Y'_2 = H$ **D** = Adenine

ddI: $Y'_2 = H$ **D** = Hypoxanthine

ddC $Y'_2 = H$ **D** = Cytosine

2'F-dd-araA: $Y'_2 = F$ **D** = Adenine

2'F-dd-araI: $Y'_2 = F$ **D** = Hypoxanthine

Figure 1. *Structures and atomic numbering scheme of AZT (A and B conformations), FLT, 2'F- AZT, Carb-F, ddA, ddI, ddC 2'F-dd-araA and 2'F-dd-araI.*

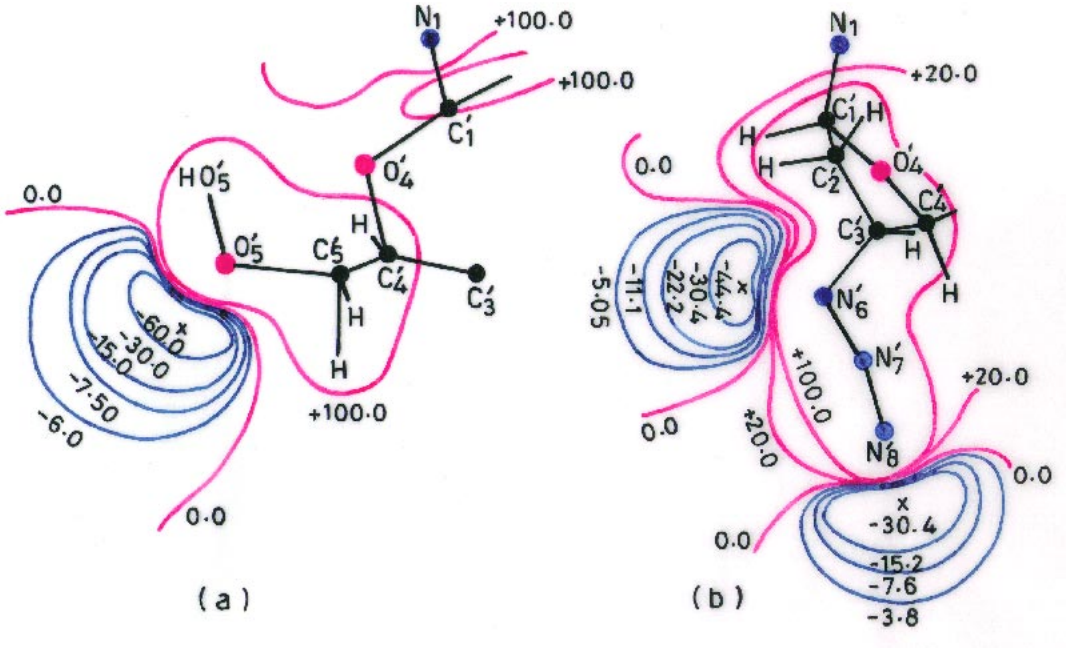


Figure 2. *(a) MEP map of AZT-B in the HO5'O5'C5' plane,(b) MEP map of AZT-B in the azido group plane.*

benzyloxy-7anti-di-fluoro (2.2.1) heptan-2-one (hereafter referred as Carb-F), 2',3'-dideoxy adenosine (ddA), 2'3'-dideoxy inosine (ddI), 2',3'-dideoxy cytidine (ddC), 9-(2,3-dideoxy-2-fluoro-b-D-threo-pentofuranosyl) adenine (2'F-dd-araA), and 9-(2,3-dideoxy-2-fluoro-b-D-threo-pentofuranosyl) hypoxanthine (2'F- dd-araI) are presented in Figure 1. Some selected MEP maps only around the sugar moieties of different molecules drawn in appropriate planes are presented in Figures 2-4. The MEP maps of AZT-A, AZT-B and 2'F-AZT-B were computed in the HO5'O5'C5' plane as well as in the plane of the three nitrogen atoms of the azido group. The MEP maps of AZT-B in the two planes mentioned above are presented Figures 2(a,b). There are three potential minima in this case, one each located near O5', N6' and N8' atoms of the molecule (Figure 2(a,b)). In 2'F-AZT-B, a minimum of MEP occurs near the 2'-F atom in addition to that near the

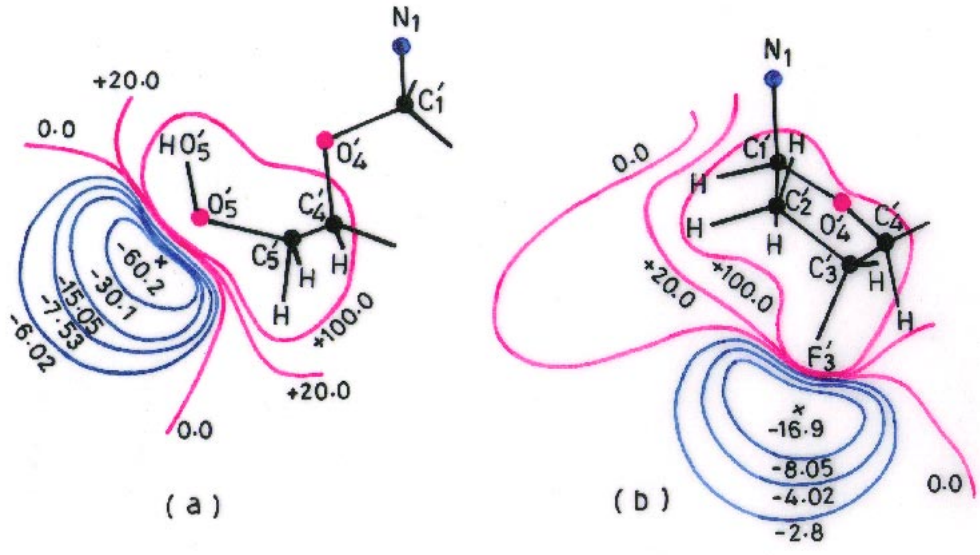


Figure 3. *(a) MEP map of FLT in the HO5'O5'C5' plane and (b) MEP map of FLT in the F3'C3'C2' plane.*

Table 1. *Minimum MEP values near the different sites of AZT-B, FLT, AZT-A, Carb-F, 2'F-AZT-B and their anti-HIV activities.*

Molecule [a]	Activity [b]	Electrostatic Potential (Kcal/mol) near different sites [c]			
		O5'	X3'	Y2'	O4'/Y6'
AZT-B	Highly active	–60.0	–30.4	+ve	–42.1
FLT	Highly active	–60.3	–16.9	+ve	–39.2
AZT-A	Weakly active or inactive	–47.3	–24.7	+ve	–56.0
Carb-F	Weakly active or inactive	–55.3	–20.1	+ve	–22.8
2'F-AZT-B	Inactive	–57.3	–21.6	–21.4	–38.3

[a] For structure, see Figure 1
[b] For activity, see Ref. [19-24].
[c] For MEP maps of AZT-B, FLT and Carb-F, see Figures 2(a,b), Figures 3(a,b) and Figures 4(a,b) respectively.
X3'= azido group in molecules AZT-B, AZT-A and 2'F-AZT-B and X3' = F in FLT and Carb-F.
Y2' = F in 2'F-AZT-B and H in other cases.
Y6' = F in Carb-F and oxygen in other cases.

O5' atom. The MEP maps computed in the HO5'O5'C5' and F3'C3'C2' planes of FLT show two minima each, one near the O5' atom and the other near the F3' atom (Figures 3(a,b)). The MEP map of Carb-F, computed in the HO5'O5'C5' plane showing a minimum near the O5' atom is presented in Figure 4(a). There is another MEP minimum near the 3'-fluoro substituent in this case (Figure 4(b)). The minimum MEP values near the sites O5', X3' (the terminal atom of the azido group or fluorine), Y2' (fluorine atom in 2'F-AZT-B) and O4' or Y6' (a fluorine atom in Carb-F and an oxygen atom in other cases) of the molecules are given in Table 1. Positive MEP values are found near Y2' where Y2'= H in the different

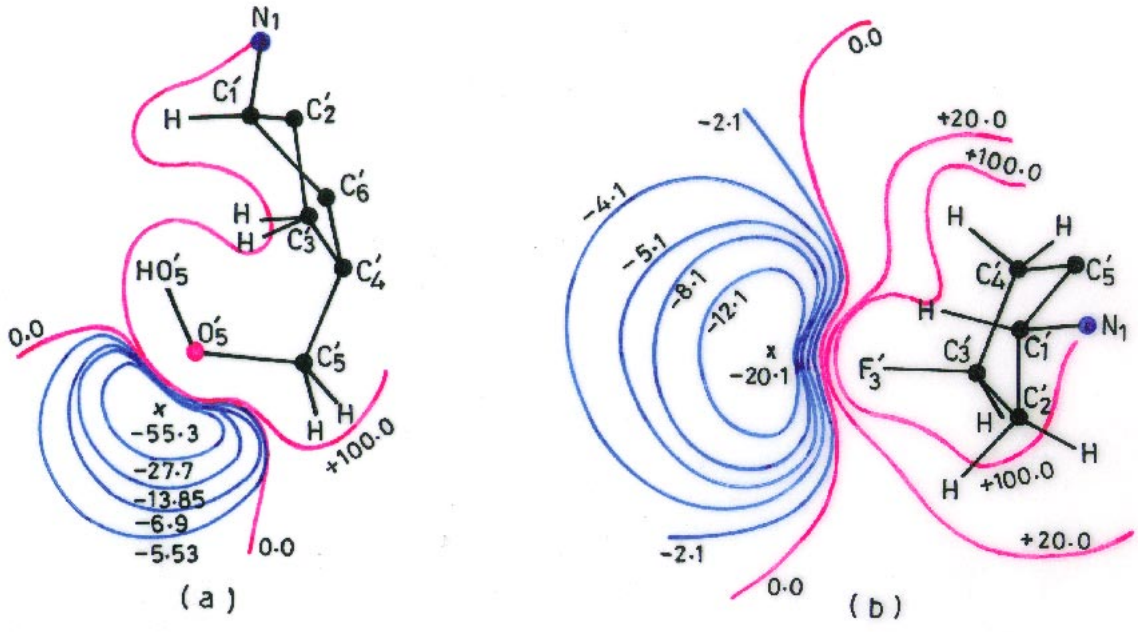


Figure 4. *(a) MEP map of Carb-F in the HO5'O5'C5' plane and (b) MEP map of Carb-F in the F3'C3'C2'plane.*

Table 2. *Minimum MEP values near the different sites of ddA, ddI, ddC, 2'F-dd-araA and 2'F-dd-araI and their anti-HIV activities.*

Molecule [a]	Activity [b]	Electrostatic Potential (Kcal/mol) near different sites [c]			
		O5'	X3'	Y2'	O4'
ddA	Active	-62.4	+ve	+ve	-59.5
ddI	Active	-63.2	+ve	+ve	-61.3
ddC	Active	-64.5	+ve	+ve	-62.4
2'F-dd-araA	Active [d]	-60.2	+ve	-17.1	-65.7
2'F-dd-araI	Active [d]	-60.3	+ve	-17.1	-56.7

[a] For structure, see Figure 1.
[b] For activity, Ref. [17,19,21].
[c] X3'= Hydrogen. Y2'= Hydrogen in ddA, ddI and ddC and Y2'= fluorine in 2'F-dd-araA and 2'F-dd-araI.
[d] Almost as active as the parent compounds (ddA or ddI) against HIV-1 but someswhat less active against HIV-2 [21].

cases (Table 1). Three-dimensional surface MEP maps of 2'F-AZT-B, AZT-B and Carb-F are presented in Figure 5 using colour graphics. The MEP map of ddA in the HO5'O5'C5' plane is presented in Figure 6(a), while the corresponding map of 2'fluoro-dd-araA is presented in Figure 6(b). The minimum MEP values near the different sites of ddA, ddI, ddC, 2'-fluoro derivative of ddA and 2'-fluoro derivative of ddI are given in Table 2.

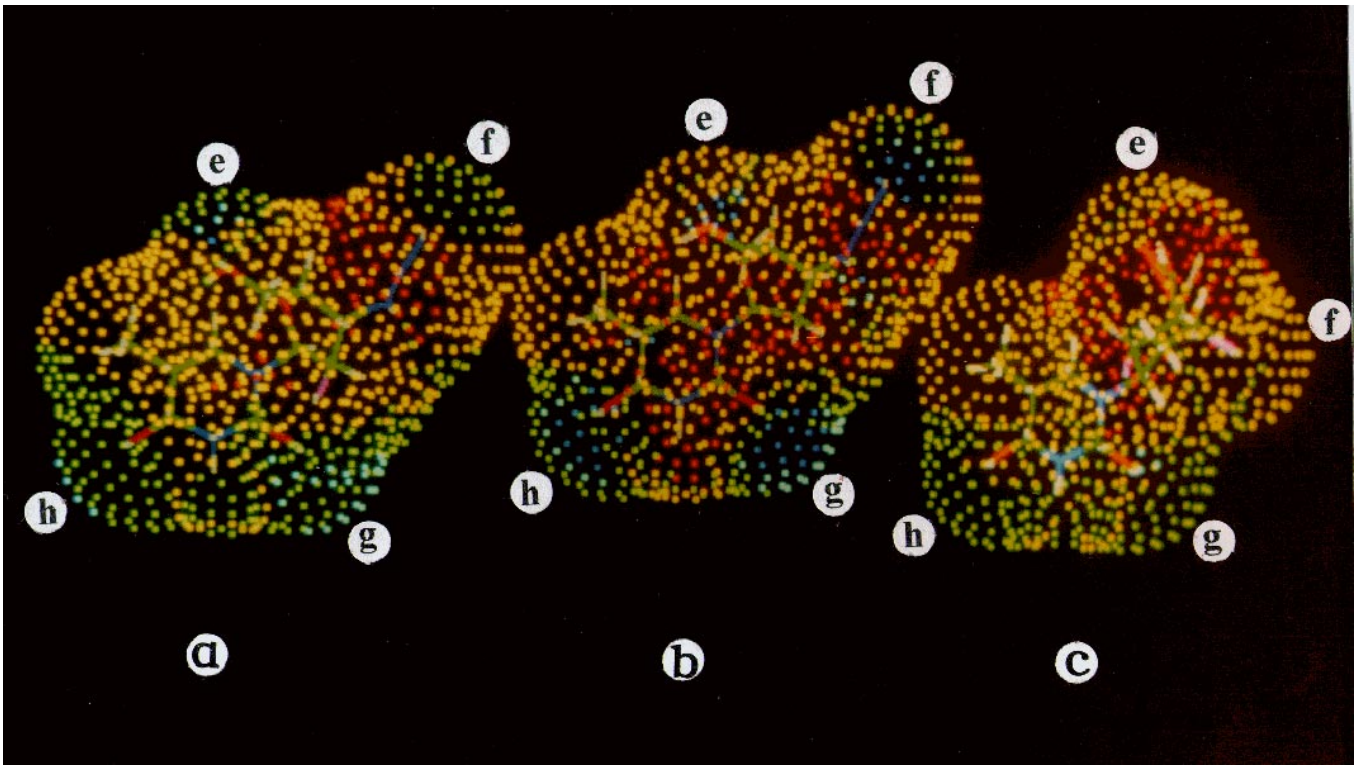


Figure 5. *Three-dimensional surface MEP patterns of three molecules: (a) 2'F-AZT-B, (b) AZT-B and (c) Carb-F. The colour codes are as follows: Deep-blue ≤ –30 Kcal/mol, –30 ≤ Light-blue ≤ –15 Kcal/mol, –15 ≤ Green ≤ 0 Kcal/mol, 0 ≤ Yellow ≤ 15 Kcal/mol and Red ≥ 15 Kcal/mol. The O5', substituent attached to C3', O2 and O4 atomic sites are marked by the letters e, f, g and h respectively.*

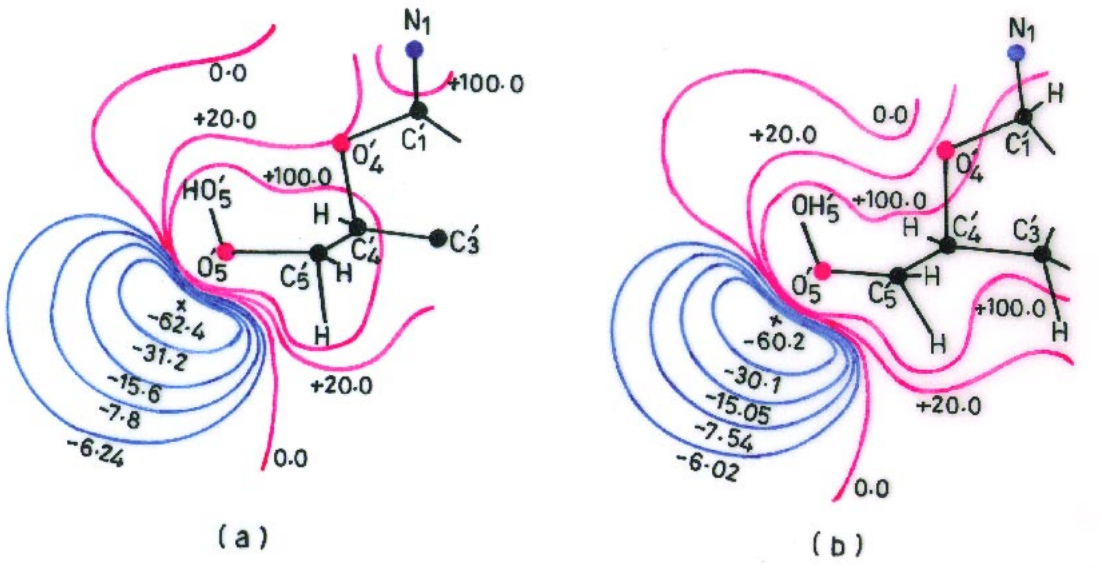


Figure 6. *(a) MEP map of ddA in the HO5'O5'C5' plane and (b) MEP map of 2'F-dd-araA in the HO5'O5'C5' plane.*

AZT-B is a highly active anti-HIV agent [5-26]. Further, when the azido group is replaced by a fluorine atom, the resulting molecule (FLT) remains highly active against HIV [23]. We find that there is only one MEP minimum near the fluorine atom in this case (Figure 3(b)) while there are two minima near the azido group in AZT-B (Figure 2(b)). Thus it appears that the MEP minimum near the terminal nitrogen of the azido group only is important the molecule to function as an anti-HIV agent. Further, in going from AZT-B to FLT, the minimum MEP magnitude near O5' remains almost unaffected while the minimum MEP magnitude near the substituent attached to C3' (X3') is appreciably reduced. In Carb-F, the base moiety is thymine but the O4' atom of the sugar ring is replaced by a CHF group [24]. Further , in this case, the minimum MEP magnitude near O5' is appreciably less than those in AZT-B and FLT, and activity of the compound is also strongly reduced in comparison to those of the other two molecules. The negative MEP values near O4' in the molecules studied here (Tables 1,2) do not show any correlation with their anti-HIV activities. Therefore, it is possible that the modification of MEP pattern in going from AZT-B to Carb-F near the fluorine atom attached to C6' (Y6' in Table 1) does not strongly control the activity of Carb-F. The conformational differences between AZT-B and Carb-F i.e. the differences between the locations of atoms of their sugar moieties with respect to those of the corresponding pyrimidine moieties appear to be partly responsible for poor activity of Carb-F, as suggested by other authors earlier [24], besides the difference in MEP values near the corresponding O5' sites which would also contribute to this aspect. It has been reported that AZT-B is the medicinally active form of AZT and the activity of AZT-A is very low [26] (Table 1). The magnitude of minimum MEP values near O5' and the azido group are appreciably less in AZT-A than the corresponding MEP magnitude in AZT-B. The above facts show that the negative MEP region around O5' is of primary importance for anti-HIV activity of the molecules. Further, for high anti-HIV activity of a molecule, the terminal atom of the X3' group should be associated with a strongly negative MEP region beside the requirement that it should not be phosphorylable. In an earlier study [55], outward MEF corresponding to positive MEP values were found near the terminal azido group nitrogen atom of AZT. These results were obtained using net charges alone which do not provide a satisfactory picture for groups like the azido group where hybridization effects which are included in HDC need to be accounted.

A fluorine substitution at the 2'-position in AZT-B reduces the minimum MEP magnitude near O5' and the terminal nitrogen atom of the azido group with respect to those in AZT-B (Table 1). However, these MEP differences between AZT-B and 2'F-AZT-B are not drastic whereas the difference in activity is drastic [23] (Table 1). Since the 2'-fluro substitution in ddC [23] does not make the molecule inactive (Table 2), it appears that the reason for inactivity of 2'F-AZT-B is not totally based on the negative MEP values near O5', X3' or O4'. It may be noted that 2',3'-dideoxy azido uridine is also weakly active as an anti-HIV agent [56]. Thus though the substitution of a CH3 group at the C5 atom of the pyrimidine moiety [18] increases the anti-HIV activity of the molecule, the absence of this substituent does not make the molecule inactive. In other words, the presence or absence of the CH3 group as a substituent at the C5 atom of the pyrimidine moiety does not play a drastic or deciding role regarding anti-HIV activity of the molecule. Therefore, the observed inactivity of 2'F-AZT-B may be partly understood

in terms of this molecule not being readily incorporated in DNA as it may be misrecognised by DNA polymerase despite the presence of CH3 group as a substituent at the C5 atom of the pyrimidine moiety, as a uridine analog, in view of a negative MEP region near the 2'-F atom. It may be noted that when a hydroxyl group was attached in place of the 2'-F atom in 2'F-AZT-B, the minimum MEP value near the oxygen atom of the hydroxyl group was found to be -49.4 Kcal/mol, the corresponding MEP value near the 2'-F atom being -21.4 Kcal/mol (Table 1).

Thus there is a qualitative similarity between the negative MEP regions of the two molecules near the atom or group substituted at C2'. It may be mentioned here that 2'-azido 2',3'-dideoxy thymidine has also been found to be inactive as an anti-HIV agent while 2'-azido 2',3'-dideoxy adenosine is active [57]. A similar explanation as that given above regarding the role of 2'-fluoro substitution may be valid in this case also.

Three-dimensional MEP surfaces of 2'F-AZT-B, AZT-B and Carb-F are presented in Figures 5(a,b,c) respectively using colour graphics. These surfaces were generated using a van der Waals expansion factor of 1.5 (multiplier for each van der Waals radius) and HDC-corrected Löwdin point charges. It may be mentioned that use of HDC-corrected Löwdin point charges yields reliable MEP values on the van der Waals or higher surfaces [48,49]. Use of a van der Waals expansion factor greater than 1 ensures reliability of the results. In the Figures 5(a,b,c), the three molecules are presented in similar perspectives, showing the pyrimidine rings almost parallel to the plain of the paper. We see that the MEP surfaces of Figures 5(a,c) are similar and also they have similar differences from that of Figure 5(b). The following specific features may be noted: (i) Negative MEP regions are more pronounced near the O5' site and the terminal nitrogen atom of the azido group in AZT-B than those in the other two molecules near the corresponding sites, (ii) There is no pronounced negative MEP near the 2'F site on the surface in 2'F-AZT-B (Figure 5(a)) since the corresponding region is localised around the 2'F atom, (iii). The conformation of the sugar moiety in Carb-F and the location of the O5' atom (Figure 5 (c) are quite different in this case from those of the other two molecules (Figure 5(a,b)). It may be quite important in making the molecule inactive, as discussed earlier, and (iv) It is also interesting to note that the negative MEP regions near both the carbonyl oxygens attached to the pyrimidine ring are much more pronounced in AZT-B in the chosen perspective than those in the other two molecules. It is possible that this aspect also contributes to differences in anti-HIV activity of the molecules.

The minimum MEP values near the O5', X3', Y2' and O4' sites of ddA, ddI, ddC, 2'-F-dd-araA and 2'-F-dd-araI are presented in Table 2. Two hydrogen atoms are attached to C3' in each of these molecules and so the MEP values near these sites are all positive. It is known that no local characteristic extrema of MEP are associated with positive MEP regions [58]. In going from ddA and ddI to their 2'-fluoro derivatives (Table 2), the magnitude of minimum MEP near O5' are somewhat reduced (Figure 6(a,b). These compounds are almost as active against HIV-1 as the parent compounds (ddA and ddI), but somewhat less active against HIV-2 [21]. These results qualitatively support the view that the negative MEP region near O5' plays a major role in controlling the anti-HIV activity of the 2',3'-dideoxy nucleosides. It has been suggested that triphosphates of nucleosides are formed at O5' which complex with DNA polymerase making the latter inactive [57]. This view is broadly supported by the present results.

One may like certain additional calculations to be done e.g. consideration of different O5'HO5' rotamers, evaluation of lipophilicity and solubility, and study of frontier orbitals, sterics and different conformations. However, there is no obvious need for such additional computations. For example, as our calculations have shown, the O5' atom would be involved in interaction with the appropriate receptor and, therefore, the O5'HO5' bond would not be free to rotate. Thus there is no need to consider different O5'HO5' rotamers. There is no lipophilic substituent attached to the sugar ring controlling molecular activity, hence lipophilicity is not likely to be of much importance in the present context. Solubility is expected to be similar within the two groups of molecules considered here and so it is not likely to be a discriminating factor. We did not study short range drug-receptor interactions as such interactions are not likely to be involved in the molecular recognition under study. Therefore, we did not consider frontier orbitals. Since crystal geometries are available for the molecules studied, similar accuracy could be maintained in the calculations on the different cases, and this is quite important. Search for possible bioactive conformations in the solution phase is certainly an important aspect. However, it is a complex issue, and we believe the results obtained using crystal geometries would provide a good basis for a comparative study of activities of the molecules.

Conclusions

The present study shows that the negative MEP region near O5' is of primary importance for the anti-HIV activity of 2',3'-dideoxy nucleosides. The presence of a negative MEP region near the atom or terminal atom of the group attached to C3' which cannot be phosphorylated is also essential. The azido groupin AZT-B acts as a strongly electronegative group and, therefore, replacement of its azido group by a fluorine atom retains activity of the molecule. Partial or drastic reduction of activity due to substitution of a fluorine atom at the other sites in the sugar ring of 2',3'-dideoxy nucleosides appears to be caused by different combinations of certain effects e.g. reduction of the negative MEP magnitude mainly near O5' and modification of conformation of the sugar moiety.

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