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Electronic Structure of Some Antiviral Compounds

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Electronic Structure of Some Antiviral Compounds[#]

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Abstract

Motivation. As a first step in a theoretical approach on the multidrug resistance (MDR) process occurring during long–time therapy with antiviral and antitumoral drugs and the molecular modeling of the interaction of the drugs with the P–Glycoprotein (P–gp) overexpressed in these cases, we have investigated the electronic structure of some antiviral compounds, Zidovudine (AZT, **1**), 3'–azido–3'–deoxy–5'–O–oxalylthymidine acid (AZT–Ac, **2**), 3'–azido–3'–deoxy–5'–O–oxalyl–*N*–valinethymidine (AZT–Val, **3**) and 3'–azido–3'–deoxy–5'–O–iso–nicotinoyl–thymidine (AZT–Iso, **4**).

Method. The calculations were performed by semiempirical, AM1, and *ab initio* 6–31G* methods using the AMSOL and GAMESS programs. A conformational search considering the most significant torsions was previously made using the Hyperchem program and the lowest energy conformers were further subject to a fully optimization in octanol, model for a nonpolar solvent and water. To establish the position of the azide group in respect with the ribose cycle, the potential energy surface was built, considering as coordinate the torsion about the ribose–azide bond. The solvation effects in the *ab initio* method were treated in the frame of the selfconsistent reaction field (SCRF).

Results. For all the compounds, the conformational search revealed similar relative positions of the thymine and ribose ring, slightly influenced by the solvent. Concerning the azide group the semiempirical results were drastically changed in going from *in vacuo* to water optimizations. A strongly stabilized solvated species, with a different charge distribution than *in vacuo* was evidenced in water. The calculated free energies of solvation are larger in water in comparison with octanol, excepting compound **3** for which the difference is small in agreement with its larger expected lipophilicity. The solvation effects predicted by the *ab initio* method are smaller.

Conclusions. The essential change in the electronic charge distribution of the azide nitrogens in water in comparison to *in vacuo* calculations shows that in order to have a correct estimation of the electrostatic contributions in the modeling of protein–AZT derivatives interaction the solvation processes must be taken into account.

Keywords. Zidovudine; AMSOL; azides; solvent–dependent optimizations; SCRF; *ab initio* calculations.

Abbreviations and notations

MDR, multidrug resistance	SCRF, selfconsistent reaction field
AZT, zidovudine	CM1, charge model 1 for the atomic charge
NRT, nucleoside reverse transcriptase	SM5.4, solvent model 5.4
P–gp, P–Glycoprotein	M, Mulliken atomic charge densities
PES, potential energy surface	ΔG_{sol}, free energy of solvation

[#] Dedicated to Professor Nenad Trinajstić on the occasion of the 65th birthday.

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1 INTRODUCTION

One of the main problems encountered in chemotherapy is the multidrug resistance (MDR) acquired by the cells upon administration of antitumoral or antiviral drugs [1]. This implies an enhanced resistance to all the drugs, not only to those previously used. Among the cellular factors that are involved in MDR, the acceleration of the efflux system (multidrug resistance transporter 1, MDR1/ P–glycoprotein) is known to be the major mechanism [2]. P–gp, a membrane glycoprotein that is overproduced in multidrug–resistant cells [3–4], is thought to act as an energy–dependent drug efflux pump which maintains intra–cellular drug concentrations below cytotoxic levels. It has a remarkably broad specificity of substrates that interact with and are transported by P–glycoprotein.

During the experimental and theoretical investigation of the multidrug resistance process we were interested in obtaining more information on a series of drugs, inhibitors or modulators of the action of the P glycoprotein (P–gp, MDR1). This is the first step in the molecular modeling of the drug–protein interaction, that requires data on the molecular structure of both the ligand and the biopolymer binding sites.

In the present work we focused on the electronic structure of zidovudine (**1**) and some analogues, 3'–azido–3'–deoxy–5'–O–oxalylthymidine acid (AZT–Ac, **2**), 3'–azido–3'–deoxy–5'–O–oxalyl–*N*–valinethymidine (AZT–Val, **3**) and 3'–azido–3'–deoxy–5'–O–isonicotinoylthymidine (AZT–Iso, **4**) presented in Figure 1.

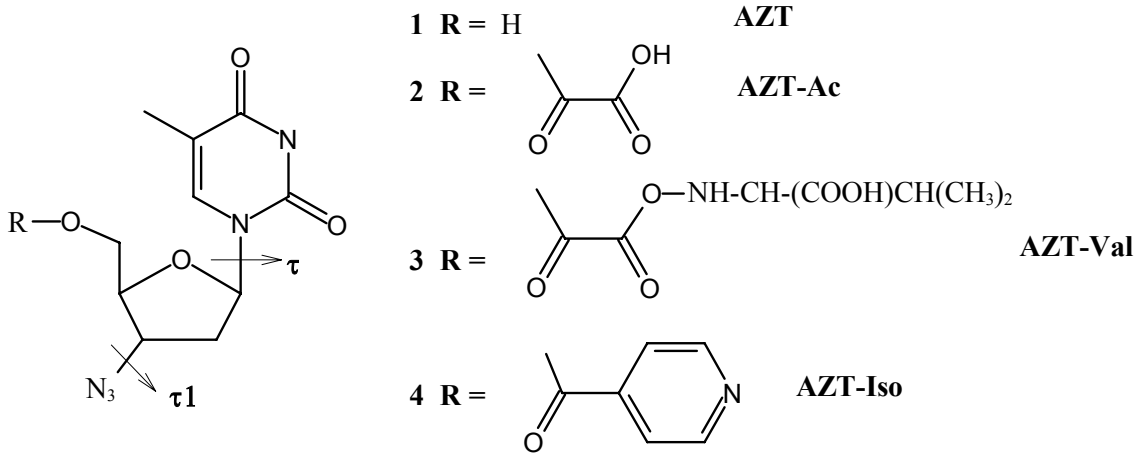


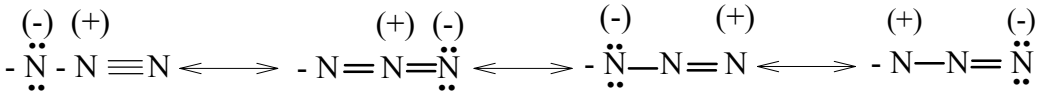
Figure 1. The investigated compounds.

Zidovudine, 3'–azido–3'–deoxythymidine (AZT), belongs to the class of nucleoside reverse transcriptase (NRT1) inhibitors and was the first drug licensed for clinical use by the Food and Drug Administration (FDA–USA). It inhibits HIV "in vitro" and induces virological and neurological improvements in HIV infected patients. In order to improve the efficiency of the drugs in this class, some other compounds were synthesized and their antiretroviral activity and

cytotoxicity analyzed. A report of the state of art of the antiviral drugs is given by De Clerck [5,6]. The actual direction in synthesizing new antiviral agents is the design of prodrugs, pharmacologically inactive compounds, which release the active drug upon enzymatic biotransformations, achieving an increased bioavailability. The mechanism of action of these prodrugs is based on the hydrolysis of the 5'–O bond between the AZT fragment and an attached side chain [7–10]. However, the development of MDR correlated with long–term AZT chemotherapy is widely discussed and several mechanisms have been suggested [11–13]. Concerning the theoretical data on the electronic structure of the AZT *ab initio* calculations must be mentioned [14].

As can be seen all the investigated compounds contain the azide group, N3 bound to the position 3' of the ribose ring. The azides belong to a very interesting class of compounds, known as 1,3 dipoles. These are characterized by three linear atoms A–B–C, with single and multiple bonds between them and that can not be represented as usual by a single chemical formula but rather by several resonant forms in which the electronic charges migrate from one end to the other.

Several possibilities, **a–d**, characterized by the displacement of an entire electron are shown in the scheme; in fact, the charges on each atom are not quite +1 or –1 electron, rather fractional charges.



a **b** **c** **d**

An important characteristic is that the system posses 4 π electrons, the 1,3 dipoles being isoelectronic with the allyl anion. Another observation concerning the electronic structure of these compounds is the fact that, in spite of their names, they posses a small dipole moment.

Recent experimental data attest the stability of the ribose–azide bond. It was found, that during the biotransformation of zidovudine by *Stenotrophomonas* Maltophilia [15] the azide group remains intact, the main structural change being the attachment of an OH group at C2' on the ribose ring.

Taking into account the very special electronic structure of the azide group, attention was paid in the followings to the behavior of the compounds in the presence of the solvents. In the same direction, the data of Quevedo *et al*. [16] show that the Human Serum Albumin (HSA) binding of AZT derivatives occurs on site I (warfarin binding site), domain IIA. A high affinity binding for this site has been observed for drugs possessing electronegative functional groups. These observations enhance the importance of the electrostatic contributions to the binding properties and reactivity of these drugs.

Our paper is focused on two points: the search of the most stable conformers and the influence of

the solvation processes on the electronic features of the compounds. The semiempirical calculations were performed using octanol and water as models for the nonpolar and polar protic media, respectively. The *ab initio* calculations were performed for compounds **1** and **2** *in vacuo* and water.

2 COMPUTATIONAL DETAILS

Semiempirical MO calculations were performed using the AMSOL program [17–20] considering the AM1 hamiltonian and the SM5.4 model for solvent dependent optimizations. The solvents used were octanol and water to mimic the behavior in lipophilic and hydrophilic media, respectively. HF/6–31G*//HF/6–31G* calculations were performed using the GAMESS program [21]. In the frame of this method the solvation process was modeled using the Self Consistent Reaction Field (SCRF) technique. The following strategy was used. Firstly, a conformational search was performed *in vacuo* using the Hyperchem program. In the case of the simplest compound, zidovudine (**1**) the conformational search was performed using the torsions describing the position of the thymine and the azide group in respect with the ribosyl fragment, τ, $\tau 1$, respectively. For the compounds with a longer side chain, **3** and **4**, some dihedral angles describing the conformation of the chain were included too. Secondly, the more stable conformations were subjected to a fully optimization in octanol and water at the semiempirical level and in water at the HF level. Due to the importance of the position of the azide group, a potential energy surface (PES) was built for compounds **1** and **2**, considering the already mentioned torsion about the azide – ribosyl bond, $\tau 1$. The torsion was maintained at a fixed value in the range –180° to 180°, all the other internal coordinates being fully optimized. The electronic distribution is discussed in terms of Mulliken and CM1 charge densities [20].

3 RESULTS AND DISCUSSION

3.1 Conformational Search

The conformational search for compound **1** predicts that the most stable conformers correspond to a quasi–orthogonal position of the aromatic cycle, τ in the range **65–68** deg. As concern the position of the azide group, the semiempirical potential energy surfaces built in terms with $\tau 1$ are presented in Figure 2. The potential energy *in vacuo* (Figure 2a) shows two non–symmetric minima for $\tau 1$ about –70° and 70°. The estimated energy barrier is 3.21 kcal/mol. As expected, in octanol and water the energy barriers were strongly diminished and, in water, the minimum at –60° was practically no more visible (Figure 2b). However, a very special behavior was noted in the water optimizations.

Starting with a slightly different geometry of the azide group, a second potential energy curve was obtained, characterized by a very deep minimum, situated at an energy about 18 kcal/mol lower

than the first one (Figure 2c).

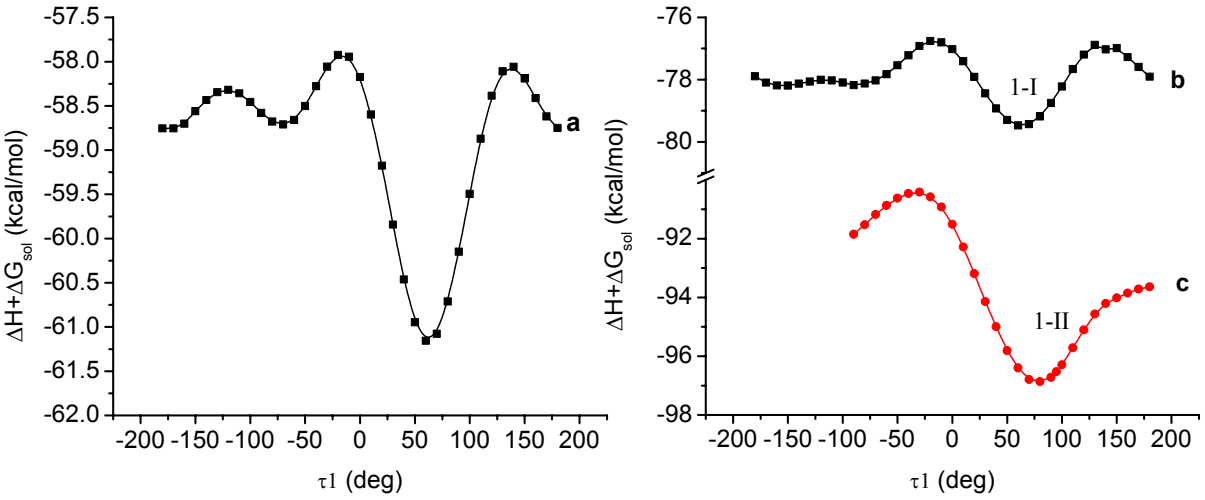


Figure 2 Semiempirical potential energy surfaces in respect with the torsion about the azide – ribose cycle, τ1: a) *in vacuo* calculations; b,c) two sections through the PES obtained in water–dependent optimizations.

Considering the geometry of the two minima, **1–I** (curve b) and **1–II** (curve c) it was found that they differ by a slight change in the structure of the azide group. The optimized parameters for the azide group in the two geometries in water together with the *in vacuo* and octanol values are listed in Table 1. The geometric parameter that distinguishes mostly the two minimum points on the PES is the length of the N2–N3 bond, $r_{N2–N3}$; for the less solvated species (**1–I**) the value is about 1.258 Å, similar with the *in vacuo* result, while for **1–II** the value is increased, 1.313 Å. A slight lower value was obtained for the solvated species in octanol. It can be observed that in the case of **1–I**, the azide fragment has a more pronounced deviation from the expected linear structure. The *ab initio* results are also included in Table 1. Differing from previous reported optimized geometry of AZT we have found that the calculations predict the same position of the azide group in the minimum point energy as the semiempirical ones.

Table 1. Optimized geometric parameters for the azide group (N1–N2–N3–R) in the minimum energy points of zidovudine, by HF/6–31G*//HF/6–31G* (*in vacuo* and SCRF) and semiempirical AM1 (*in vacuo*, water and octanol) calculations (r– distances in Å; a– angles in degrees).

	HF/6–31G*// HF/6–31G*		Semiempirical			
	in vacuo	SCRF	*in vacuo*	I–1 (water)	1–II (octanol)	1–II (water)
τ1	56.6	55.1	60.8	60.5	68.2	79.5
$r_{N1–N2}$	1.103	1.102	1.134	1.159	1.146	1.164
$r_{N2–N3}$	1.226	1.229	1.258	1.258	1.313	1.303
$r_{N3–R}$	1.468	1.466	1.446	1.440	1.450	1.446
$a_{N1–N2–N3}$	175.14	174.8	168.7	160.1	171.8	174.2
$a_{N2–N3–R}$	114.9	115.0	116.7	128.8	117.3	120.2

It can be seen that for species **1–I**, the *ab initio* and semiempirical results, either in vacuo or in water, are similar as concerns the main geometric parameters. The main differences consist in larger values at the semiempirical level for τ1, $r_{N1–N2}$ and $r_{N2–N3}$. The strongly solvated (**1–II**) species was

evidenced only in semiempirical calculations and is characterized by even slightly larger values for τ1 and $r_{N2–N3}$.

The conformational search for the other derivatives lead to quite similar values for the torsions defining the relative position of the thymine and azide fragments in respect with the ribose. The presence of two potential energy curves, one corresponding to a strongly solvated species was also found for compound **2**, (curve not shown); in this case too, the minimum energy point in water was located 7 kcal/mol deeper. The *ab initio* results for compound **2** are presented in Table 2. Three conformers were considered. The first two conformers, **2–I** and **2–II** differs by the side chain position, τ2 and τ3. In conformer **2–III** a different position of the azide group was considered. The energies are given relative to the energy of the lowest conformer, **2–I**. ΔE represents the stabilization energy of each conformer due to the solvation process in SCRF calculations.

Table 2. *Ab initio* relative energies (E_{rel}, kcal/mol) and geometric parameters for three conformers of compound **2** (ΔE, kcal/mol, the stabilization energy due to the inclusion of solvation effects)

		HF/6–31G*				HF/6–31G* – SCRF				
	E_{rel}	τ	τ1	τ2	τ3	τ	τ1	τ2	τ3	ΔE
2–I	0.00	60.7	60.9	0.7	134.5	63.4	61.7	–0.9	143.7	–4.33
2–II	6.88	65.2	58.9	–174.6	46.3	64.3	63.4	169.2	101.3	–5.95
2–III	3.51	65.4	–103.1	–172.9	47.5	63.7	–109.3	–179.4	93.2	–3.23

It can be seen that the conformers characterized by τ1 in the range 59–61° are more strongly stabilized by solvation. In what concerns the thymine and azide positions in respect with the ribose, the SCRF calculations do not change to a great extent the geometric configurations. The more significant changes occurred in the τ3 values.

Starting with the dihedral angles τ and τ1 established for **1**, a conformational search was performed considering the minimum energy conformations for the side chain for **3** and **4**. The valine substituted AZT, **3**, presents the largest flexibility. The three rotations considered are presented in Figure 3. The rotation about the NH–CO bond was not considered, to preserve the known amide structure. Several conformers with energies within 2 kcal/mol were found attesting the high mobility of the chain. The values for the most stable conformer are given in Table 3. It can be seen that although the calculations started with the same *in vacuo* geometry, the solvent–dependent optimizations predict different values for some angles.

Table 3. Geometric parameters for the torsions defining the side chain conformation in **3**

	in vacuo	Octanol	water
τ	–84.23	–87.50	–98.42
τ2	–178.8	–175.7	–175.7
τ3	56.56	112.27	106.26
τ4	–130.41	–138.60	–139.78

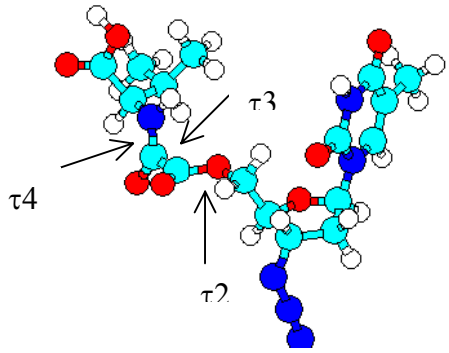


Figure 3. The most stable conformer of **3**.

The semiempirical results for the most stable conformers are summarized in Table 4. The calculations show that all the four derivatives are sensitive to the environment polarity. In octanol, for zidovudine a species similar with **1–I** in water was not properly characterized, and the corresponding values are not given in Table 4. In all cases the free energy of solvation in water is larger than in octanol. However, for compound **3**, this difference is very small and reflects an enhanced lipophilicity in comparison with the other compounds.

Table 4 The heats of formation ($\Delta H+\Delta G_{sol}$ –kcal/mol) and the solvation free energies ΔG_{sol} (kcal/mol) for the most stable conformers of the investigated compounds

	1–I	**1–II**	**2**	**3**	**4**
ΔH (in vacuo)	–61.65	–61.67	–167.70	–221.64	–50.24
$\Delta H+\Delta G_{sol}$ (oct)	–	–83.05	–198.69	–257.43	–81.19
$\Delta H+\Delta G_{sol}$ (water)	–79.96	–91.16	–207.06	–259.01	–86.61
ΔG_{sol} (oct)	–	–21.38	–30.99	–35.79	–30.95
ΔG_{sol} (water)	–18.31	–29.49	–39.37	–37.37	–36.37
ΔG_{sol} (oct – water)	–	8.11	8.38	1.58	5.42

3.2 Charge Distribution

The presence of two potential energy curves describing the azide position and, mainly, the strong stabilization reflected by curve c in Figure 2 prompted us to look at the charge distribution in the minimum energy points of zidovudine (**1–I**: curve b and **1–II**: curve c).

The results for the minimum point **1–I** were not very different from those obtained by *in vacuo* calculations. In comparison, considering the minimum **1–II**, the charge distribution on the azide nitrogens is very different and reflects the enhanced contribution of one mesomeric form of the azide group. The CM1 and Mulliken (M) charge distributions are listed in Tables 5 and 7 for compounds **1** and **2**, respectively. The strongly solvated species (**1–II**) is characterized by a positive charge on the terminal nitrogen, N1, and negative values for the other two atoms; the charge distribution corresponds more to form **c** of the azide group. The localization of a positive charge on the terminal atom of the azide, N1, mostly exposed to the solvent explains the large free energy of solvation.

For species **1–I** the charges are reversed, the end nitrogen bearing a negative charge as in form **b**. The same effect is also observed in octanol but the charge polarization is less pronounced than in water. The presence of two adjacent negative charges on the atoms N2 and N3 in the solvated species **1–II** explains the increase in the bond length N2–N3. The destabilizing repulsion between these two nitrogen atoms is overwhelmed by the strong stabilization gained by the solvation process, but determines however a larger separation between them.

Table 5. CM1 and Mulliken (M) atomic charges on the azide nitrogens for the two minimum energy points (**1–I**) and (**1–II**) on the potential energy surfaces of zidovudine. (N1–N2–N3–R). Σq is the total charge on the azide group.

	HF/6–31G*		**1–I**		**1–II**		**1–II**	
	in vacuo	SCRF	Water		Octanol		Water	
	M	M	CM1	M	CM1	M	CM1	M
N1	–0.225	–0.215	–2.108	0.016	2.157	0.848	2.744	1.080
N2	0.420	0.421	2.163	0.629	–1.316	–0.341	–1.776	–0.494
N3	–0.441	–0.451	–0.203	–0.785	–1.193	–0.623	–1.395	–0.736
Σq	–0.246	–0.245	–0.148	–0.14	–0.352	–0.116	–0.427	–0.150

The bond orders in the azide group, listed in Table 6 show also the changes in the electronic structure for the geometries corresponding to the two minimum energy points, **I** and **II**. Although in both cases the bond order N1–N2 is larger than that for the N2–N3 bond, for the strong solvated species the difference between both bonds is significantly increased in water.

Table 6. AM1 bond orders for the azide bonds in zidovudine (N1–N2–N3–R)

		1–I		**1–II**	
	in vacuo	Octanol	Water	Octanol	Water
N1–N2	2.394	2.362	2.138	2.371	2.263
N2–N3	1.279	1.034	1.515	1.032	0.998

The comparison of the *in vacuo* and SCRF *ab initio* calculated Mulliken charges reflects a decrease of the negative charge on the terminal nitrogen of the azide group and no significant changes on N3. The charge distribution is more similar with the water pattern for the minimum **1–I**, less solvated. In all cases the *ab initio* calculations predict a negative charge of about –0.250 on the azide group. The semiempirical Mulliken population analysis leads to a lower charge on the azide, but for the solvated species **1–II** to another distribution on the three nitrogen atoms.

Table7. HF calculated Mulliken charge distribution and bond orders for the considered conformers of compound **2**. Σq represents the total charge on the azide group. (N1–N2–N3–R)

	2–I		**2–II**		**2–III**	
	in vacuo	SCRF	*in vacuo*	SCRF	*in vacuo*	SCRF
N1	–0.217	–0.184	–0.214	–0.194	–0.190	–0.236
N2	0.421	0.418	0.420	0.420	0.436	0.434
N3	–0.446	–0.462	–0.440	–0.470	–0.472	–0.453
Σq	–0.242	–0.228	–0.234	–0.244	–0.226	–0.255
N1–N2	2.343	2.347	2.343	2.346	2.374	2.362
N2–N3	1.300	1.270	1.300	1.279	1.295	1.341

4 CONCLUSIONS

The calculations performed predict significant changes in the electronic distribution of the azide group in going from *in vacuo* to solvent–dependent optimizations. Although in all types of calculations the position predicted for the azide group in respect with the ribose ring is the same, the charge distribution is totally different. For all the investigated compounds, in water and to a less extent in octanol, a strongly solvated species, characterized by a positive charge density on the terminal nitrogen atom and negative charge densities on the other two atoms was evidenced. This fact, which reflects a general behavior of the azide–substituted nucleosides in water, not influenced by the nature of the side chains, has major implications in the molecular modeling of the protein–AZT interaction. As long as the electrostatic contributions are important, it is expected that the *in vacuo* calculations will lead to a wrong estimation of the main interactions and the need of taking in account the contribution of the solvent it is necessary to take into account the solvation processes, fact that would have a major importance of the parameterization in molecular mechanics. Another point to be outlined is that the relative values of the solvation free energies in water and octanol can give an estimate on the different lipophilicity of the compounds and consequently on the affinity of the potential active substances toward certain binding sites of the target proteins characterized by different lipophilic/hydrophilic character.

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