

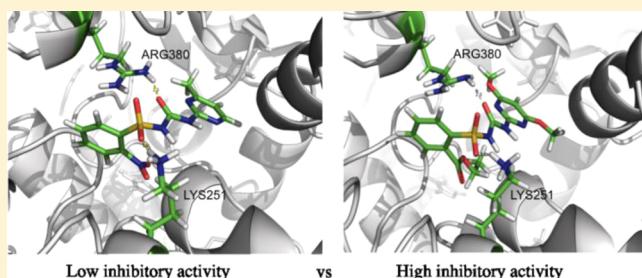
How Important Is the Synclinal Conformation of Sulfonylureas To Explain the Inhibition of AHAS: A Theoretical Study

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ABSTRACT: The inhibitory activity of 15 sulfonylureas on acetohydroxyacid synthase (AHAS) is addressed theoretically in order to stress how important the conformation is to explain their differences as AHAS inhibitors. The study includes calculations in gas phase, solution, and in the enzymatic environment. The results suggest that both the activation Gibbs free energy and Gibbs free energy change associated with the conformational change in solution allow for determining if sulfonylureas should have high or low inhibition activity. QM/MM calculations were also carried out in order to identify the role of the amino acid residues and the effects involved in the stabilization of the active conformation in the binding pocket. On the other hand, the analysis of the frontier molecular orbitals of the sulfonylureas in the binding pocket allowed us to explain the inhibitory activity in terms of the reactivity of the carbonyl carbon.



INTRODUCTION

Acetohydroxyacid synthase (AHAS; also known as acetolactate synthase, EC 2.2.1.6) belongs to a homologous family of thiamin diphosphate (ThDP)-dependent enzymes and participates in the biosynthetic pathway of branched-chain amino acids, including valine, leucine, and isoleucine, in plants and a wide range of microorganisms.^{1–3} The AHAS catalyzes two parallel reactions: the condensation of two molecules of pyruvate to form acetolactate in the biosynthesis pathway leading to valine and leucine and the condensation of pyruvate and 2-ketobutyrate to form 2-keto-2-hydroxybutyrate in the biosynthesis of isoleucine. In addition AHAS has been proven to be an efficient catalyst in chiral synthesis and a potent target in biochemistry engineering.⁴

The inhibition of AHAS interrupts the catalytic cycle and prevents the synthesis of acetolactate and 2-keto-2-hydroxybutyrate, interrupting the biosynthetic pathway toward the synthesis of branched amino acids, which are essential for the subsistence of plants and microorganisms. Consequently, this enzyme is the target of several commercial herbicides, fungicides, and bactericides.^{1,2,5}

AHAS is recognized as a promising target for new antituberculosis drugs.⁶ For example, *Mycobacterium tuberculosis* (MtB) is the pathogen of tuberculosis that remains a major threat to the human populations. This human disease is responsible for 2–3 millions deaths per year worldwide.^{7,8} It was shown that branched amino acids auxotrophic strain of *Mycobacterium* failed to proliferate because of the inability to use amino acids from their host, indicating that inhibitors for the branched-chain amino acid biosynthesis could be used as an antituberculosis agent.⁹ These observations suggested that

AHAS could be a potential target of new antituberculosis drugs. In this sense, Zohar et al. demonstrated that four of six tested sulfonylureas strongly inhibited the AHAS of *Mycobacterium avium*, which is another human tuberculosis pathogen.¹⁰

The sulfonylureas are compounds widely used as herbicides, which are distinguished by their unique advantages such as broad-spectrum weed control at very low applications rates and flexible application timing for a wide variety of crops.^{3,11,12} Furthermore, the lack of this biosynthetic pathway in animals such as mammals, birds, fish, amphibians, etc., suggest that these compounds should be nontoxic to animals.

Sulfonylureas are compounds composed by one *ortho*-substituted benzene ring attached to a sulfur atom and one heterocyclic ring substituted in both *meta* positions attached to the distal nitrogen atom of the sulfonylurea bridge. The heterocyclic ring may be either a pyrimidine ($X = CH$) or triazine ($X = N$). The general structure of sulfonylureas is characterized by two dihedral angles Φ_1 and Φ_2 , as shown in Figure 1.

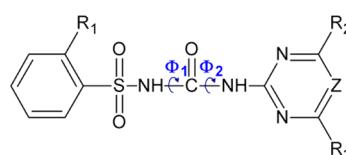


Figure 1. General structure for sulfonylureas.

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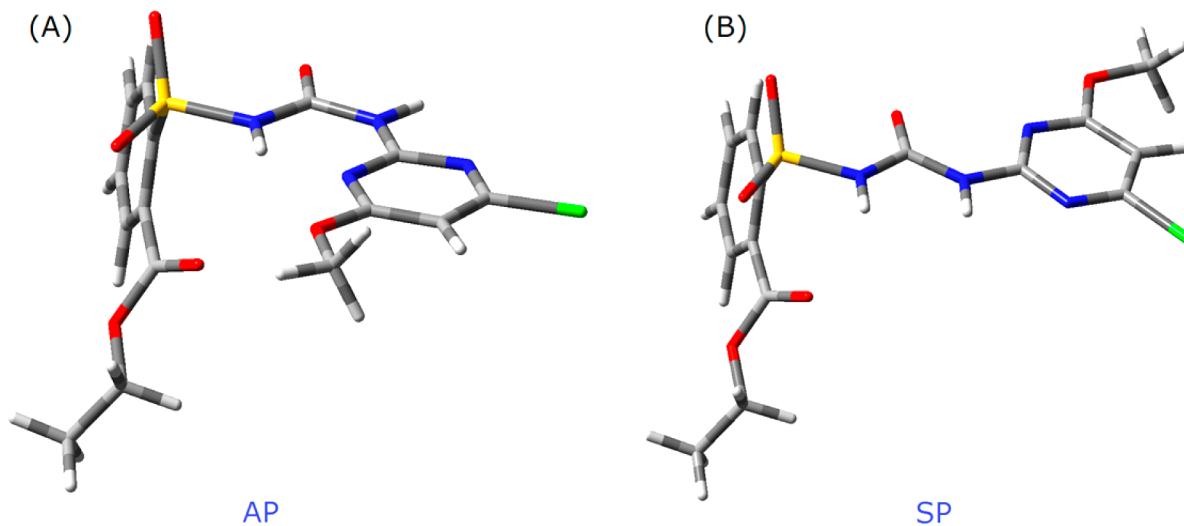


Figure 2. Antiperiplanar (AP) and synclinal (SP) conformations of sulfonylureas.

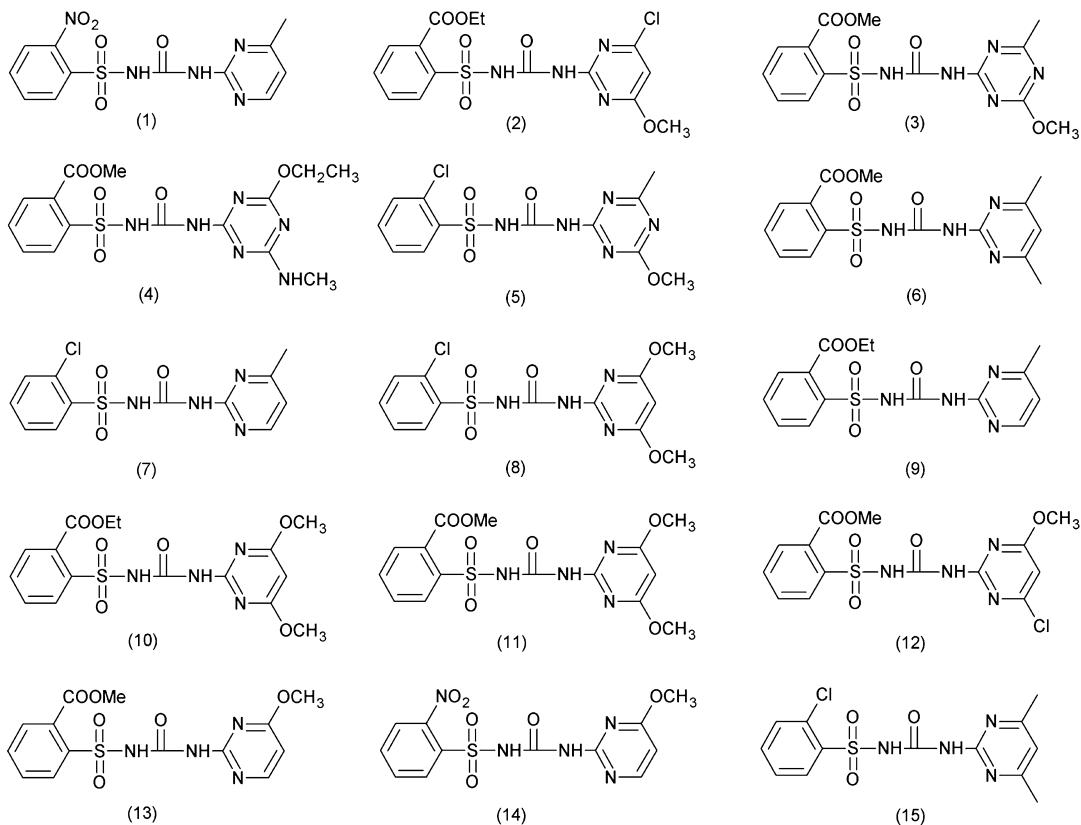


Figure 3. Structures of the sulfonylureas considered in this study.

X-ray data¹³ and theoretical studies in the gas phase¹¹ of isolated sulfonylureas have shown that the most stable structure corresponds to the antiperiplanar conformation (Figure 2A). However, from the X-ray structure of AHAS crystallized with chlorimuron ethyl (CIE) and other sulfonylureas,^{14,15} it is possible to observe that sulfonylureas adopt a unique conformation accord to the orientations of the HNCONH group, which is the synclinal conformation (SP) (Figure 2B). Actually, QM/MM molecular dynamics simulations confirm this empirical evidence.¹⁶ Therefore, considering that the sulfonylureas must undergo a conformational change to bind the enzyme before the inhibition takes places, in this study, we

hypothesize that the energy cost of moving from the AP to the SP conformation should be related to the inhibitory activity of sulfonylureas. In order to validate this hypothesis, we develop a criterion based in a decision tree using two descriptors, namely, the activation Gibbs free energy and the Gibbs free energy change associated with the conformational change, to classify the sulfonylureas as having high or low inhibitory activity. Moreover, in order to obtain deeper insights into the role of the amino acid residues and the effects involved in the stabilization of the active conformation in the binding pocket, we carried out hybrid quantum mechanics/molecular mechanics (QM/MM) calculations. In addition, we performed an analysis of the

frontier molecular orbitals of the sulfonylureas in the binding pocket to explain the inhibitory activity in terms of the reactivity of the carbonyl carbon.

METHODS AND COMPUTATIONAL DETAILS

Gas Phase and Solutions Study. All geometries and energies in gas phase were computed at the B3LYP/6-311+G** level of theory. All calculations were carried out using the Q-Chem program package.^{17,18} The conformational study was carried out by means of the simultaneous variation of dihedral Φ_1 and Φ_2 , generating in this way a potential energy surface (PES) in gas phase. Afterward, a representative structure of the antiperiplanar structure (AP), transition state (TS), and synclinal structure (SP) were selected from the PES. All stationary points were characterized as minimum or transition states by means of frequency calculations. The effect of solvation was included as single-point calculations on the critical points of the PES using the Langevin dipoles (LD) approximation¹⁹ at the same level of theory.

QM/MM Calculations. The structure of yeast AHAS in complex with the chlorimuron ethyl herbicide determined at 2.8 Å (PDB code 1N0H) was used as the starting structure for all calculations. An extended model of the active site and the C₂-α-hydroxyethyl thiamin diphosphate (HETHDP-) intermediate equilibrated by QM/MM stochastic boundary molecular dynamics (SBDM) was used according to the methodology described in a previous work.¹⁶ For the other 14 sulfonylureas, the models were built by superimposing their respective structures on that of the chlorimuron ethyl, which in turn was deleted.

The resulting system of about 12000 atoms was partitioned into a quantum region (QM) defined by the atoms of the herbicides and a molecular mechanics region (MM) containing the rest of the system. The QM subsystem was described at the B3LYP/6-311+G* level theory. The Charmm27-all²⁰ atoms force field was used to describe the rest of the system, and the electronic embedding scheme was applied in the QM/MM treatment. CHARMM^{21,22} and Q-Chem packages were employed to carry out the exploration of the conformational change from the SP to AP conformation by means of variation of the Φ_2 dihedral from 0° to 360°, with step of 10°.

Experimental Data. The sulfonylureas considered in this study are shown in Figure 3, and their respective inhibitory activities, taken from two literature sources,^{23,24} are shown in Table 1. The values are expressed as the logarithm of the reciprocal apparent inhibition constant K_i , in mol L⁻¹ units, sorted in descending order. As it was not possible to find the same source of experimental data for all compounds, we classified the compounds as high inhibitory activity (H) or low inhibitory activity (L). Because compound 1, having a pK_i value of 6.6, has the lowest inhibition activity and considering that the difference between the values of both sources of experimental data is about 0.3 units of pK_i , it was decided to classify those compounds having pK_i values less than 6.9 as low inhibitory activity, whereas compounds with pK_i values greater than 6.9 are considered as high inhibitory activity.

Decision Tree. A decision tree (DT) is a classification model^{25–27} that consists of a tree-like structure that possesses nodes and links. Usually, in each node, a test using a single descriptor is made. On the basis of the result of the test, the algorithm is directed to other nodes emerging from the parent node. The final decision is related with the activity class associated with the nodes. Hence, the whole decision process is

Table 1. Inhibitory Activity of Sulfonylureas Expressed as the Logarithm of the Reciprocal Apparent Inhibition Constant (K_i in mol L⁻¹ units)

inhibitory ranking	pK_i^{23}	pK_i^{24}	compound ID
1st	—	9.2	10
2nd	—	8.6	11
3rd	8.1	8.3	2
4th	—	7.8	12
5th	8.0	—	3
6th	7.4	7.7	6
7th	7.8	—	5
8th	7.3	—	4
9th	—	6.9	8
10th	—	6.7	9
11th	—	6.7	13
12th	6.6	—	1
13th	—	5.8	14
14th	—	5.2	7
15th	—	4.7	15

based on a series of simple tests that define the path between the different nodes. The tests applied in each node were based on descriptors values. D_i is the value of the i^{th} descriptor associated with the sulfonylureas. The particular architecture of the decision tree used in this study and the nature of each of its nodes are associated with both the activation Gibbs free energy (D_1) and the Gibbs free energy change (D_2) associated with the conformational change from the AP to SP conformation. The threshold values have been defined in terms of the values of the descriptors D_1 and D_2 for compound 8. This compound was chosen because it represents a limit value between compounds having high and low inhibition activity.

RESULTS AND DISCUSSION

Gas Phase and Solutions Studies. The obtained potential energy surface in gas phase upon the simultaneous variation of

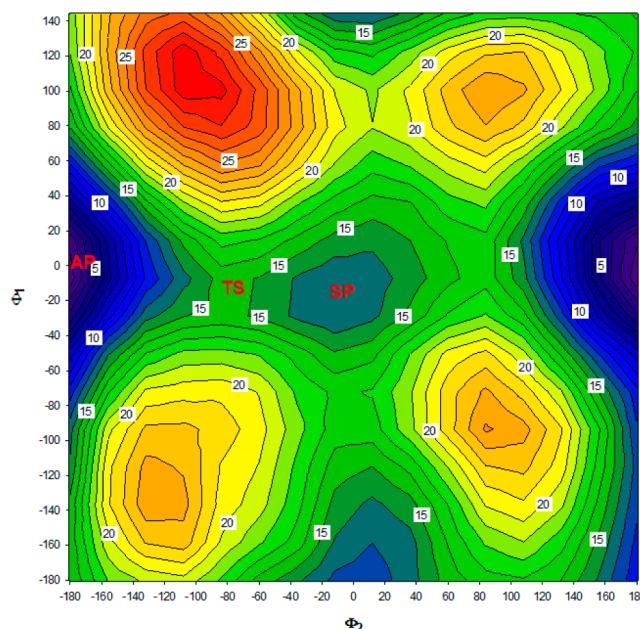
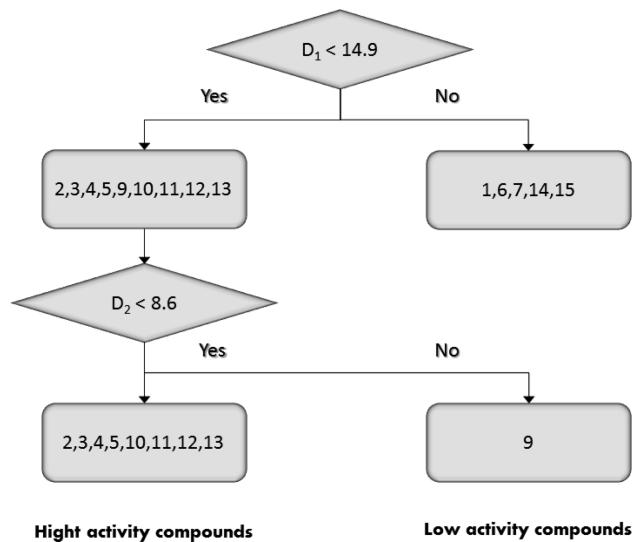


Figure 4. 2D-Potential energy surface in gas phase for compound 1 upon variation of dihedral angles Φ_1 and Φ_2 .

Table 2. Calculated Free Energies in Gas Phase and Solution (in parentheses)

compound ID	$\Delta G^\circ(\text{kcal mol}^{-1})$		
	AP	TS	SP
1	0	15.07 (15.73)	10.81 (9.21)
2	0	13.64 (11.34)	11.34 (8.24)
3	0	15.89 (12.59)	10.78 (7.68)
4	0	12.38 (8.18)	12.37 (8.17)
5	0	14.53 (12.83)	13.15 (8.05)
6	0	16.88 (15.21)	11.41 (10.01)
7	0	14.39 (15.39)	12.98 (10.88)
8	0	15.96 (14.96)	14.31 (8.61)
9	0	14.13 (13.93)	10.93 (9.53)
10	0	15.00 (13.7)	9.76 (7.76)
11	0	11.63 (7.93)	12.41 (7.71)
12	0	12.93 (10.83)	7.85 (4.55)
13	0	14.40 (12.60)	9.18 (5.88)
14	0	14.82 (15.52)	10.46 (7.26)
15	0	15.61 (16.51)	13.23 (12.93)

Scheme 1. Tree Decision Scheme Used in This Study To Classify Sulfonylureas According to Their Inhibitory Activity^a



^aD1: Activation Gibbs free energy. D2: Gibbs free energy change. Both descriptors are associated with the conformational change from AP to SP conformation in solution.

dihedral Φ_1 and Φ_2 is shown in Figure 4 for compound 1 as example. It is possible to observe that the AP structure is the most stable conformation at about 13 kcal mol⁻¹ with respect to the SP conformation. The barrier associated with change from AP to SP is about 15 kcal mol⁻¹ represented as TS in the PES. For the remaining compounds, the PES is topologically identical but different energetically. In order to characterize the critical points of the PES and to obtain the associated free energy changes, frequency calculations were carried out. Afterward, we included water solvation effects on each stationary structure in order to evaluate the effect of the solvent over the stabilization of the SP conformations. The results of these calculations are displayed in Table 2.

Table 2 shows that for all compounds the conformation SP is more stabilized in solution than in gas phase. On the other hand, the TS values are also stabilized in solution for most of

the compounds, except for compound 1 having a lower inhibitory activity. Moreover, those compounds exhibiting the highest energy barriers (compounds 1 and 15) have the lowest inhibitory activities.

Furthermore, it is also possible to observe that those compounds having higher stabilization of the conformation SP in solution are compounds having high inhibitory activity (compounds 2, 10, 11, and 12). On the basis of these observations and in order to establish a predictive rule for classifying the sulfonylureas as compounds having either very high or low inhibitory activity, we have developed a decision tree associated with the two descriptors mentioned above, as shown in Scheme 1. Thus, it was possible to rationalize that those compounds showing an activation barrier, descriptor D_1 , less than 14.9 kcal mol⁻¹ are classified as those having high activity because these compounds could more easily reach the synclinal conformation. On the other hand, compounds having values less than 8.6 kcal mol⁻¹ of the Gibbs free energy change, descriptor D_2 , will show high inhibitory activity.

From Scheme 1, it is possible to observe that only two compounds (6 and 13) are badly classified. Therefore, it is evident that there exists a conformation–activity relationship that in principle could properly differentiate between compounds having high or low inhibitory activity. Furthermore, it is important to stress that the relationship, having a 87% of success, only can be established when the solvation effects are considered. A similar analysis carried out in gas phase did not lead to any acceptable correlation.

On the other hand, in order to identify the role of the amino acid residues and the effects involved in the stabilization of the active conformation in the binding pocket, QM/MM calculations were carried out.

QM/MM Calculations. To identify which factors are relevant to the stabilization of the SP conformation inside the enzyme, the conformational change from AP to SP inside the binding pocket was studied by mean QM/MM calculations. The results show that the SP conformation is stabilized with respect to the AP conformation in 13 of 15 compounds.

In order to gain insights into the role of the protein environment on the stabilization of the SP conformation and if this fact can be rationalized to explain why some compounds present high inhibition activity and others show low inhibition, the analyses will be centered in compounds having high inhibition activity (compounds 10 and 11) and compounds showing low inhibition activity (compounds 1, 14, and 15). The SP conformations adopted by these compounds in the binding pocket of AHAS are shown but only for compounds 1 and 10 for brevity (Figure 5). As observed, both compounds show similar orientations inside the enzyme. In addition, in this figure, the relative locations of the residues Lys251 and Arg380 are shown because these residues show important interactions between the carbonyl group of the sulfonylureas with the guanidinium group of arginine by means of hydrogen bond interactions. Besides the hydrogen bond interactions with the carbonyl group, arginine may show additional hydrogen bonding interactions in those compounds having a methoxy group in the *meta* position in the pyrimidine ring (Figure 5B). However, this second hydrogen bonding should not be responsible for the high inhibitory activity because there are compounds having this group that show low inhibitory activity, for example, compound 14.

An analysis of the energetic contributions of each of these residues was carried out in order to obtain deeper insights on

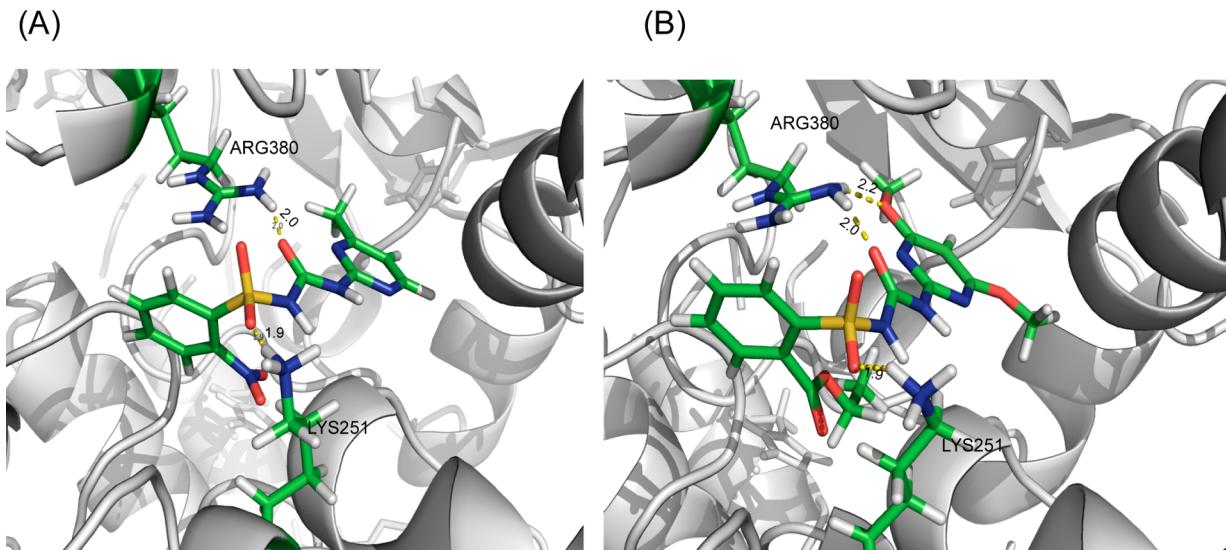


Figure 5. SP conformation inside of AHAS. (A) Compound 1. (B) Compound 10.

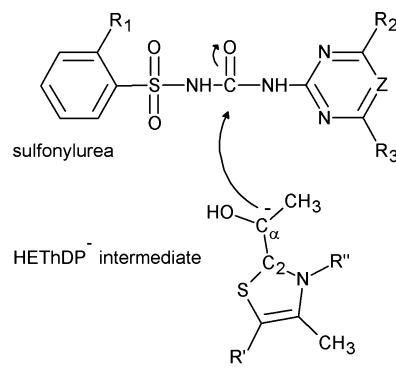
Table 3. Energetic Contribution of Arg and Lys on Stabilization of the SP Conformation and Polarization Effect Driven by Arg

compound	ΔE (kcal mol ⁻¹)	$\Delta\Delta E_{\text{Lys}}^{i}$ (kcal mol ⁻¹)	$\Delta\Delta E_{\text{Arg}}^{i}$ (kcal mol ⁻¹)	$\Delta\Delta P$
1	-5.98	-4.98	1.28	0.013
10	-25.56	-4.44	11.86	0.150
11	-16.33	-8.69	15.06	0.144
14	-16.78	-5.68	4.58	0.014
15	13.47	-7.99	-1.77	0.063

the stabilization of the SP conformation. Thus, the charges of the Lys and Arg were set off for both conformations, and the energy was recalculated. Therefore, the contribution of each residue on the stabilization was evaluated by means of eq 1

$$\Delta\Delta E_i = \Delta E_i^{\text{off}} - \Delta E \quad (1)$$

where ΔE_i^{off} is the difference of energy (kcal mol⁻¹) between the SP and AP conformation when the charges of the i^{th} residue are set off, and ΔE corresponds to the actual difference of energy between both conformers. Thus, more positive values of $\Delta\Delta E_i$ are associated with large contributions of the i^{th} residue on the stabilization of SP conformation. The results of this analysis are displayed in Table 3. From this table, it is possible to observe that Lys is not relevant for stabilization of the SP



R' = ethyl diphosphate
R'' = 1,4-aminopyrimidine

Figure 7. Schematic representation of the proposed reaction between the sulfonylurea and HEThDP⁻ intermediate.

conformation in both compounds, suggesting that this residue is probably more relevant for the anchorage of the herbicides in the binding pocket than the stabilization of the SP conformation. On the other hand, the values show that residue Arg380 is very important for the stabilization of the SP conformation, being more relevant for the active compounds. This difference may be associated with polarization effects

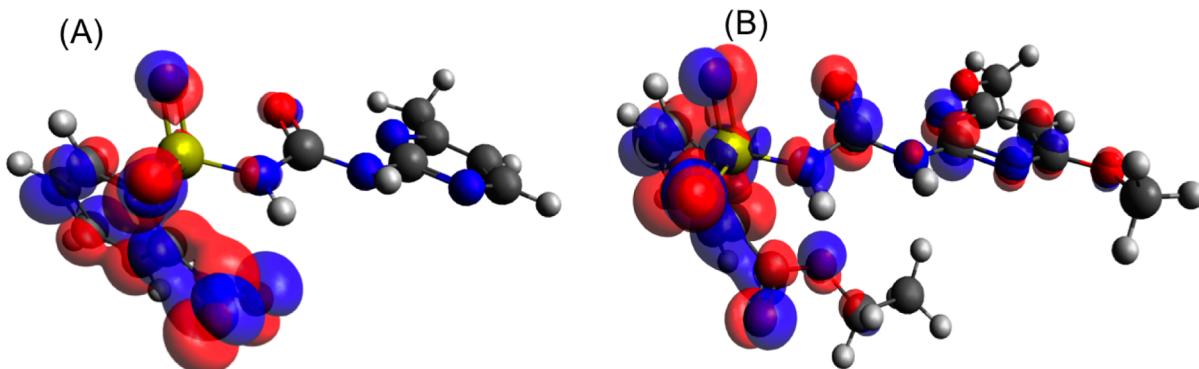


Figure 6. 3D View of LUMO molecular orbital. (A) Compound 1. (B) Compound 10.

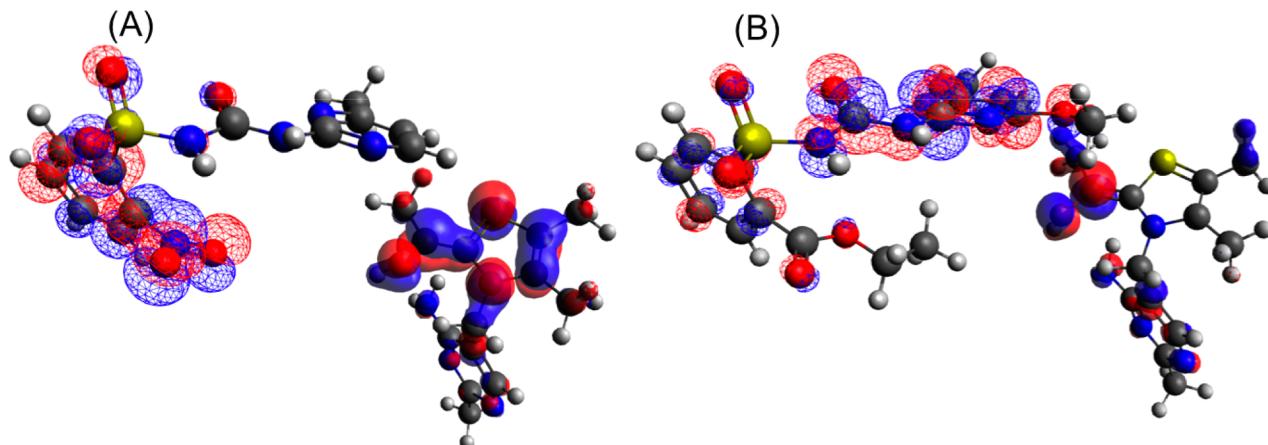


Figure 8. 3D View of HOMO and LUMO molecular orbitals. (A) Compound 1. (B) Compound 10. HOMO (solid); LUMO (lines).

triggered by this residue. In order to quantify this effect, a natural bond orbital (NBO) analysis was performed for the SP and AP conformations. Thus, to evaluate the polarization effect on the sulfonylureas, the difference between the NBO charges on its carbonyl group was calculated according to eq 2

$$P_i = q_C - q_O \quad (2)$$

where P_i denotes the polarization effect calculated in the AP or SP conformations, and q_C and q_O are the atomic NBO charges on the C and O atoms of the carbonyl group. On the other hand, the change in the polarization between the AP and SP conformations was calculated by means of eq 3

$$\Delta P = P_{\text{SP}} - P_{\text{AP}} \quad (3)$$

Therefore, the gradient in the polarization effect of arginine on the SP conformation can be calculated according to the following expression

$$\Delta \Delta P = |\Delta P - \Delta P^{\text{off}}| \quad (4)$$

where ΔP^{off} is evaluated as indicated in eq 3 when the charges of Arg380 have been set off. The calculated $\Delta \Delta P$ values are summarized in Table 3. It is possible to observe that compounds having high inhibitory activity, compounds 10 and 11, show greater polarization effects than compounds 1, 14, and 15, which have low inhibitory activity. This finding allows us to conclude that the high energetic stabilization effect driven by arginine on the active compounds is a consequence of the polarization effects triggered by this residue on the SP conformation.

In light of these results, one may conclude that in order for the inhibition of the enzyme to be high, not only must the interactions for anchoring the sulfonylurea in the active site be present, but also the residues must promote the stabilization of the SP conformation by means of polarization effects.

In the literature, it has been suggested that sulfonylureas combine better with the HEThDP⁻ intermediate than the physiological substrates.¹⁵ This fact should be a consequence of the strong nucleophilic character of the C₂ atom of the intermediate and the strong electrophilic character of the carbonyl carbon of the herbicide. This preference should be increased by inhibitors showing strong polarization effects, which in turn increase the electrophilic character on the carbonyl carbon of the sulfonylurea, as was observed in all active compounds.

In order to confirm this affirmation, the LUMO orbitals of compounds 1 and 10 are depicted in Figure 6. The LUMO orbital in compound 1 is delocalized around the benzene ring, mainly in contrast to compound 10, where the LUMO orbital is delocalized around all the molecules passing by the carbonyl group. In closing, the compound having the higher inhibitory activity shows a higher electrophilic character on the carbonyl group in order to favor the reaction with the HEThDP⁻ intermediate as shown schematically in Figure 7.

In all of the above calculations, the intermediate HEThDP⁻ not was considered inside the quantum region. However, if the intermediate is incorporated in the quantum domain, another molecular orbital distribution is obtained (Figure 8). In this figure, both the HOMO and LUMO molecular orbitals are depicted. The HOMO orbital is delocalized in the HEThDP⁻ intermediate in both compounds, while the LUMO orbital remains delocalized in the sulfonylurea as shown above. In addition, it is possible to observe that in compound 1 (low activity) the LUMO is delocalized in the same way as observed in Figure 6A, that is, the LUMO orbital is centered mainly in the benzene ring far away from the HOMO orbital of HEThDP⁻ in contrast to that observed in compound 10, where the LUMO is delocalized mainly in the carbonyl group and close to the HOMO orbital centered in the HEThDP⁻. In conclusion, compound 10 shows an ideal frontier molecular orbital distribution that could favor the reaction between the nucleophile HEThDP⁻ intermediate and the electrophile sulfonylurea compound and thus promote the inhibition of AHAS.

CONCLUSIONS

The results of this study allowed us to establish a predictive rule based on a decision tree to classify sulfonylureas as compounds having either high or low inhibitory activity on acetohydroxy acid synthase. The conformation–activity relationship, having 87% of predictive success, is based on two descriptors, activation Gibbs free energy (D_1) and Gibbs free energy change (D_2), associated with the conformational change in solution from AP to SP conformation.

The results of the QM/MM calculations, on the other hand, suggest that within the binding pocket of the enzyme, the synclinal conformation (SP) is favored with respect to the antiplanar conformation (AP) by means of a high energetic stabilization effect driven by arginine as a consequence of the polarization effects triggered by this residue on the SP

conformation. The synclinal conformation allows for an optimal molecular orbital distribution on the reaction partners that increases both the nucleophilic character on the C2 carbon atom of the intermediate HEThDP⁻ intermediate and the electrophilic character of the carbonyl atom of the sulfonylurea. These complementary characteristics favor the reaction promoting the inhibition of the enzyme.

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Notes

The authors declare no competing financial interest.

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