

Theoretical Study of Omeprazole Behavior: Racemization Barrier and Decomposition Reaction

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ABSTRACT: Omeprazole is a substituted benzimidazole which suppresses gastric-acid secretion by means of H⁺, K⁺-ATPase inhibition. It is an optically active drug with the sulfur of the sulfoxide being the chiral center. This pro-drug can be easily converted into its respective sulfenamide at low pH. In this work, omeprazole has been studied in relation to racemization barrier and decomposition reaction. Quantum chemistry coupled to PCA chemometric method were used to find all minimum energy structures. Conformational analysis and calculation of racemization barriers were carried out by PM3 semiempirical method (Gaussian 98). The average racemization energy barrier for all minimum energy structures (43.56 kcal mol⁻¹) can be related to the velocity constant in Eyring's equation. The enormous half-life time at 100°C (9.04 × 10⁴ years) indicates that the process cannot be observed in human time scale. On the other hand, the difference of free energy change ($\Delta(\Delta G) = -266.78$ kcal mol⁻¹) for the decomposition reaction shows that the process is favorable to the sulfenamide formation. The highly negative $\Delta(\Delta G)$ obtained for the decomposition reaction shows that this process is extremely exothermic. This result explains why omeprazole decomposes and does not racemize. © 2008 Wiley Periodicals, Inc. *Int J Quantum Chem* 108: 1097–1106, 2008

Key words: omeprazole; racemization; quantum chemistry; conformational analysis; PCA

Introduction

Omeprazole is a substituted benzimidazole which suppresses the gastric-acid secretion by means of H⁺, K⁺-ATPase enzyme inhibition [1]. As a result of its efficacy and tolerability, omeprazole is

widely used and became the best-selling drug in the world [2]. An important characteristic of omeprazole is its optical activity. Its chirality is due to the asymmetrical substituted sulfoxide (see Fig. 1).

There are several pharmacokinetic and metabolic studies about these molecules, as well as their interaction with other drugs. There are some stereochemical investigations about omeprazole and related compounds [3, 4], and the pharmacodynamics of the two isomers have been also studied [5]. Ome-

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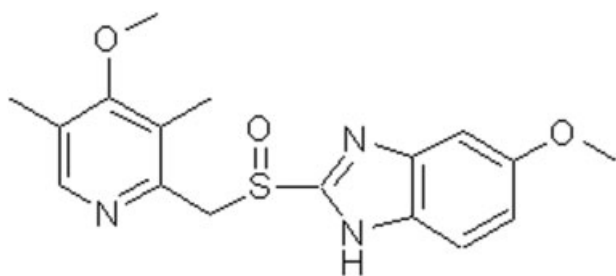


FIGURE 1. Omeprazole structure.

prazole is already commercialized, and it is generally administered as a racemate. It is a pro-drug and, at cellular level, both isomers are protonated and converted in the acidic compartment of the parietal cell in exactly the same way to form the active inhibitor of H^+ , K^+ -ATPase, the achiral sulfenamide. Figure 2 shows the decomposition reaction. Sulfenamide (4) - or the corresponding unstable sulfenic acid (3) - is the active inhibitor formed in vivo from omeprazole (1).

Omeprazole is extensively metabolized in the liver. Studies in human liver microsomes have shown that there is a significant stereoselectivity in the metabolism of the optical isomers of omeprazole [2, 6]. The metabolism may follow two distinct pathways, as presented in Figure 3 [7]. First, let us observe the target on the chiral center (sulfur atom). The formation of hydroxyomeprazole is mediated by cytochrome P450 2C19 enzyme (CYP2C19), and it is the preferential pathway of metabolism. In this case, the chiral center is not affected. Omeprazole is also metabolized, to a minor extent, by CYP3A4 enzyme, which mediates the formation of omeprazole-sulfone. In this case, the sulfur atom is oxidized, and the resulting sulfone does not have optical activity. This sulfone is subsequently hydroxylated by CYP2C19 enzyme. Studies found in literature show that CYP2C19 is a stereoselective enzyme and its activity is polymorphically distributed [7, 8]. About 3% of white populations are classified as poor metabolizers, i.e., there is a genetic absence of CYP2C19 enzyme. However,

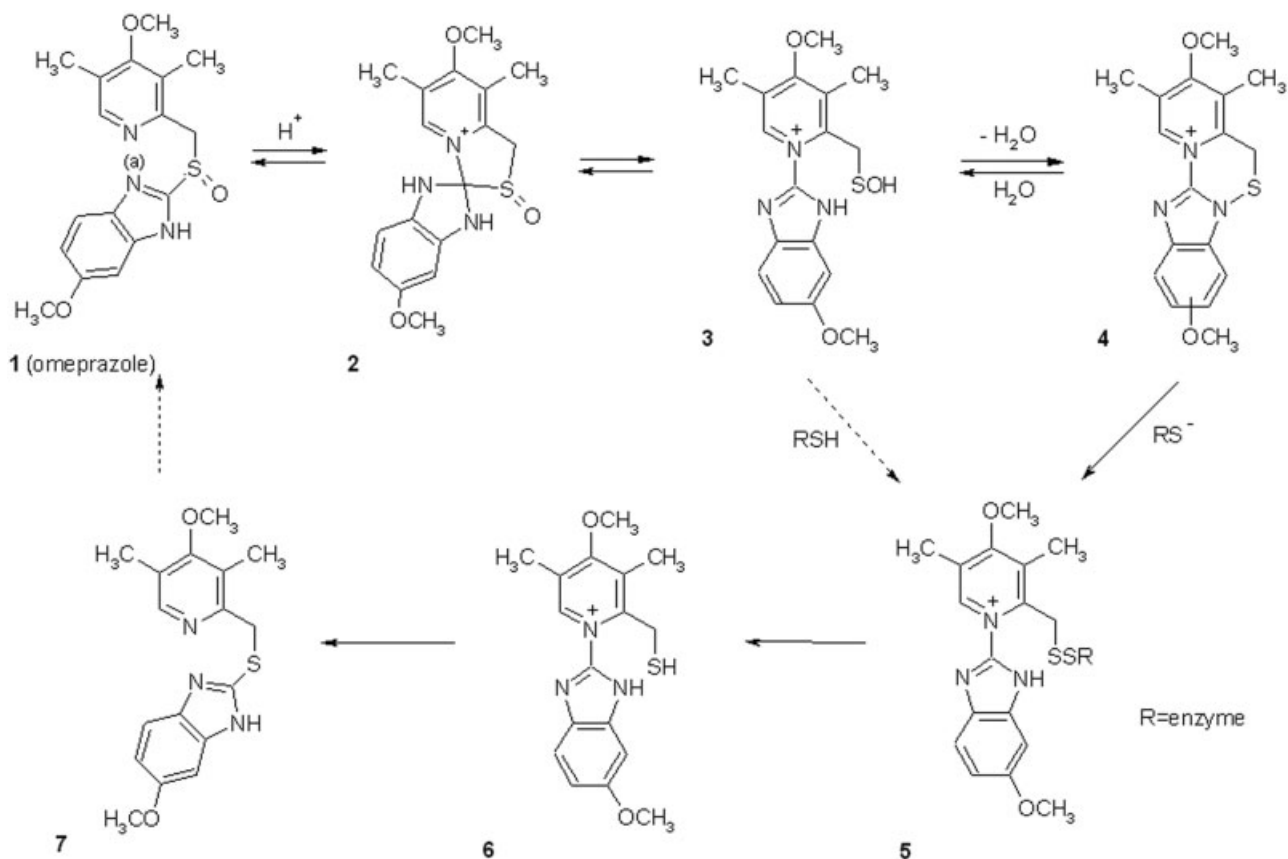


FIGURE 2. Omeprazole decomposition reactions in acid medium.

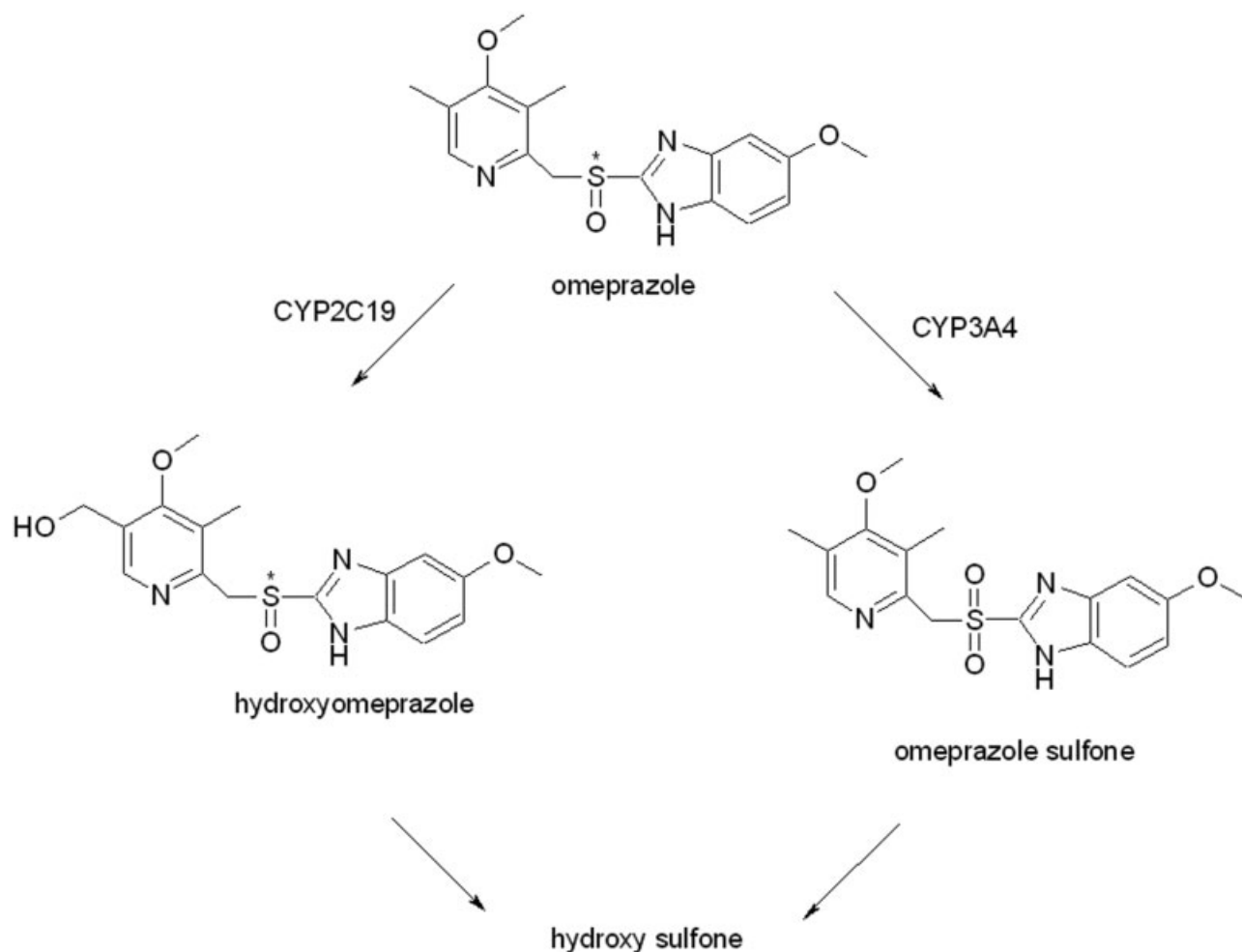


FIGURE 3. Omeprazole metabolism.

among oriental subjects, about 10–15% is classified as poor metabolizers. Thus, omeprazole sulfoxidation may be the predominant pathway in such individuals, and the drug elimination would spend more time to be performed. By the way, studies had shown that Esomeprazole, the *S*-isomer of omeprazole, is metabolized to a greater extent than the *R*-isomer by CYP3A4 and, to a lesser extent, by CYP2C19. It is the first proton pump inhibitor available for clinical use as a single isomer. It demonstrates pharmacological and clinical benefits beyond those found with the racemic omeprazole [1, 9, 10].

Considering all the information given previously, the motivation for this work is based on three factors: (1) there are in oriental populations a considerable amount of subjects phenotyped as poor metabolizers of CYP2C19 enzyme, which is stereo-

selective; (2) esomeprazole is more effective than omeprazole racemic mixture; (3) Erlandsson et al. found, using circular dichroism technique, a 26 kcal/mol value (at 75°C) for omeprazole racemization barrier. Summarizing, the main goal of this study is to define the omeprazole behavior by means of theoretical calculations. The energies required for racemization and decomposition concerning to omeprazole were investigated for providing any insight about the conduct of this drug.

Methodology

By observing Figure 1, one can note that there are some bonds with free rotation. Thus, the determination of possible minimum energy structures is very important and must be performed previously

of any property calculation. In traditional systematic search, for a given starting geometry, the torsion angles are varied by regular increments [11]. To perform a grid search in the conformational space, a series of conformations would be generated by systematically rotating the torsion angles around the single bonds between 0° and 360° . For each case, the number of conformations is given by

$$\text{Number of conformations} = S^N, \quad (1)$$

where N is the number of free rotation angles and S is the number of discrete values for each rotation angle. This number is given by $360/\theta_i$ with θ_i being the dihedral increment of angle i . However, it is sometimes impossible to use this method, due to the enormous combinatorial complexity of the problem. Targeting to handle this problem, the methodology where systematic search is coupled to Principal Component Analysis (PCA) was used to carry out the conformational analysis of omeprazole [12]. In this approach, the potential energy surfaces (PES) were obtained for pairs of angles with free rotation, aiming the decrease of the dimensional space. The number of conformations is thus given by:

$$\text{Number of conformations} = S^2 \frac{N(N-1)}{2}, \quad (2)$$

where S is defined as in Eq. (1).

One can observe that the number of conformations as given by Eq. (1) increases exponentially with the number of bonds which have free rotation. However, from Eq. (2), the number of studied conformations increases quadratically with N . As the number of free rotating angles increases, the difference in the number of conformations between these two equations becomes more evident. PCA was applied on the data set containing the referring potential energy surfaces values obtained in agreement with Eq. (2) [12].

Racemization barriers were calculated for the minimum energy conformations found to omeprazole. There are several articles involving theoretical methods for determining racemization barriers. Among them, there are studies which use computational programs for simulating gas chromatography and high performance liquid chromatography elution profiles [13]. In this article, racemization barriers are obtained by quantum chemistry calcu-

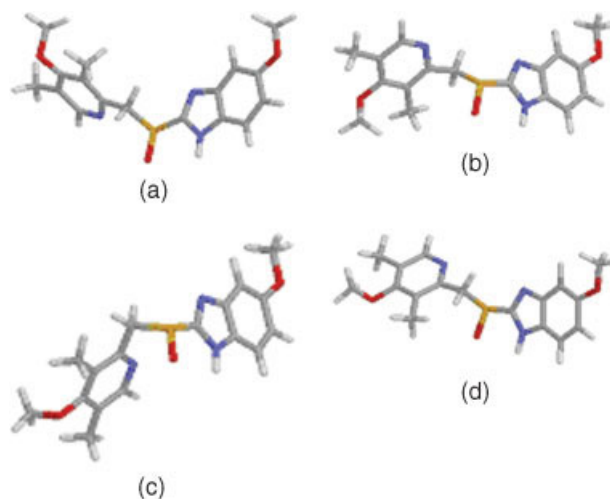


FIGURE 4. Optimized conformations for the omeprazole molecule. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

lations. In this sense, there are some articles which use quantum chemistry for calculating racemization barriers of helicenes [14], chiral biphenyl [15], sulfoxides [16], among others [17–19]. In the Allenmark and Oxelbark work [16], a planar intermediate was established as the transition state for sulfoxides, and the racemization barrier was calculated from the difference between ground and transition states for pyramidal inversion. In our study, the methodological procedure was different. The dihedral which contains the S—O bond was systematically varied. The potential energy surface was obtained for the trigonal twist pathway of the omeprazole minimum energy structures.

Finally, the energy involved in the omeprazole decomposition (see Fig. 2) reaction was also investigated and the result was compared with that required for pyramidal inversion.

Computational Details

For racemization barriers calculation, the initial structure of omeprazole was constructed using the Spartan software [20]. The PM3 [21] semiempirical method implemented in Gaussian 98 program [22] was used to carry out the calculations. After being constructed, omeprazole was preoptimized and the conformational analysis was performed. Rotation barriers were calculated for all minimum energy structures resulting from

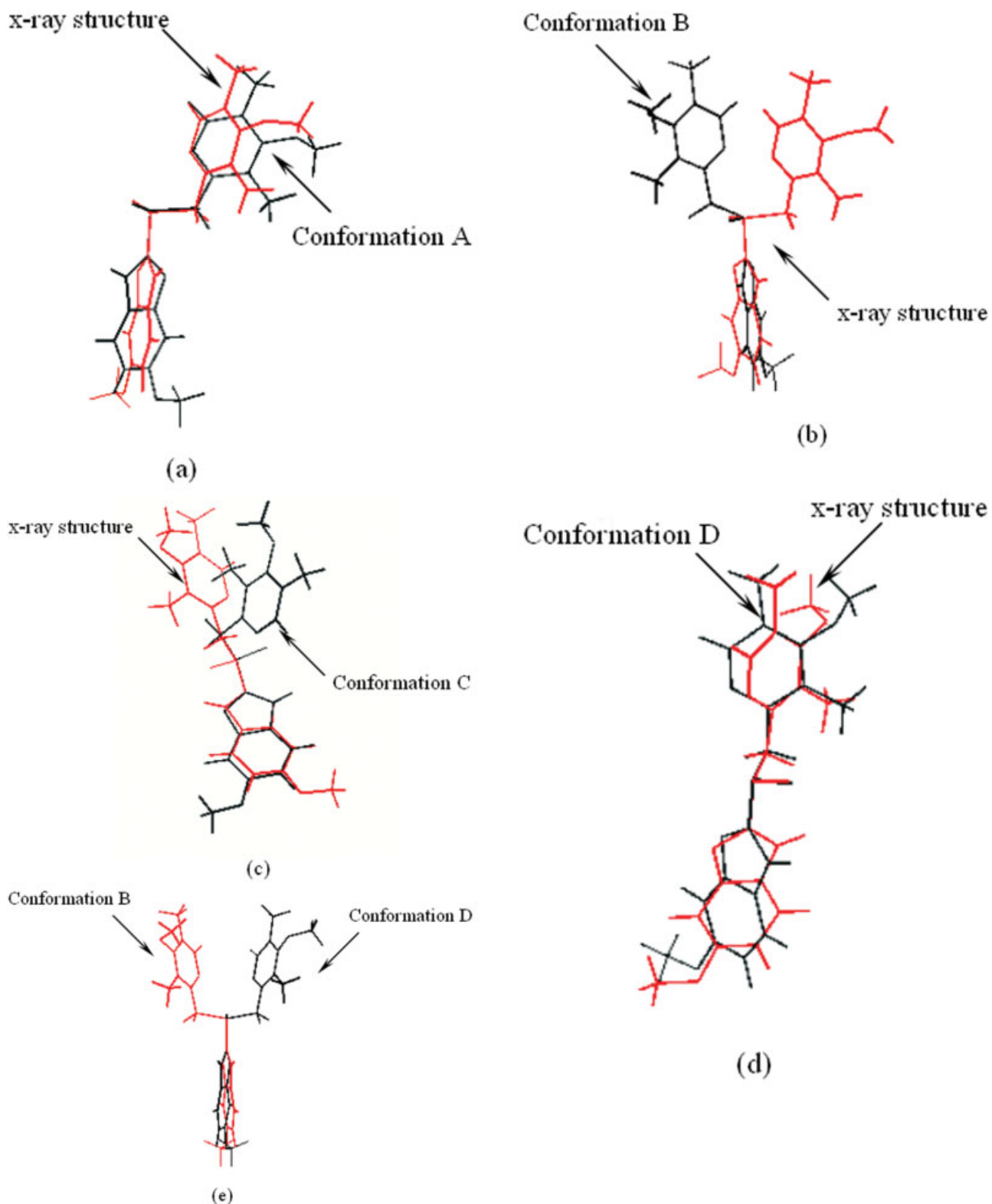


FIGURE 5. Omeprazole-optimized conformations and X-ray structure comparison: (a) superimposed conformation A and X-ray structure; (b) superimposed conformation B and X-ray structure; (c) superimposed conformation C and X-ray structure; (d) superimposed conformation D and X-ray structure; and (e) superimposed conformations B and D. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

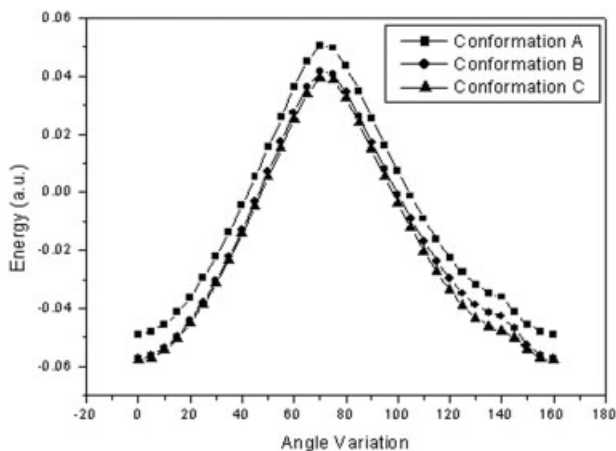


FIGURE 6. Racemization barrier results.

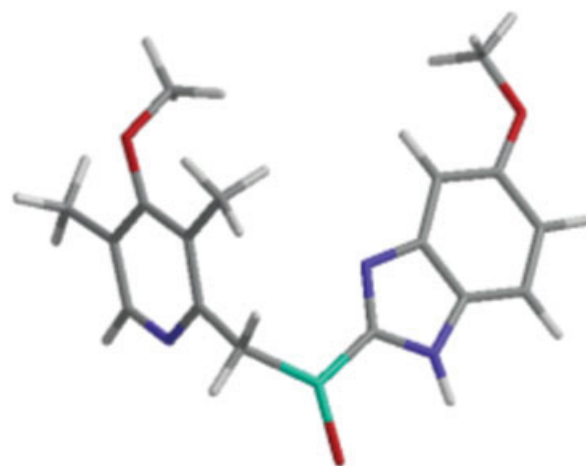
conformational analysis. A transition state calculation for each structure corresponding to the higher position on the rotation curves was performed. To verify correlation effects, a test was done for one minimum energy structure of omeprazole: single-point calculations for the transition and ground states were done with ab initio method in *Hartree Fock* level using the 6-31G** [23, 24] basis set. One of the major problems of Hartree Fock method is to neglect electronic correlation effects. For verifying the correlation effects, DFT calculations of B3LYP/6-31G** [23, 24] type were also done for the structures.

Semiempirical methods were enough to study the system when uncharged compounds are being handled, as in racemization barriers cases. However, no good results were obtained for the decomposition reaction in previous tests (authors can be contacted for these results). Ab initio method at Hartree Fock level with the 6-31G** [23, 24] basis set was therefore used to perform the electronic energy calculations. Vibrational and frequency calculations were also performed. Compounds were constructed and calculated by Titan software [20].

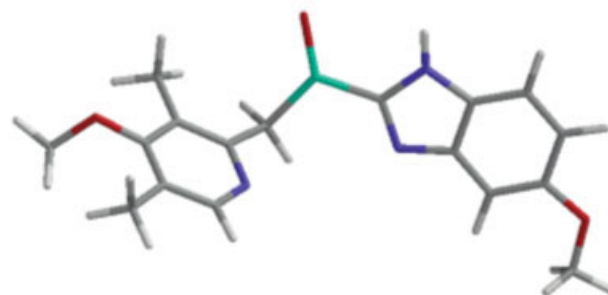
Results and Discussions

CONFORMATIONAL ANALYSIS

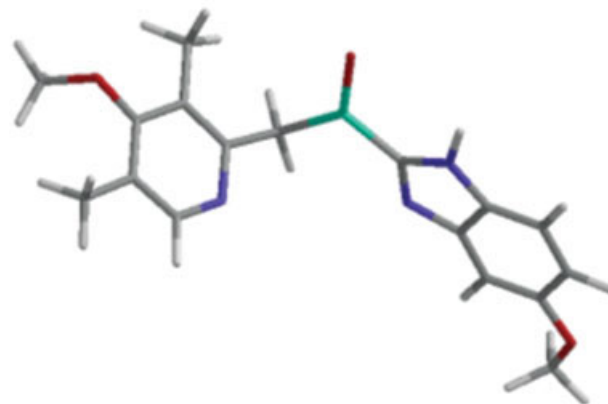
For omeprazole, four structures were obtained from the conformational analysis process. The corresponding optimized geometries are shown in Figure 4.



Transition State A



Transition State B



Transition State C

FIGURE 7. Omeprazole transition states. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

For better visualization, experimental X-ray structure [25] was individually compared with the obtained conformations. Figure 5 shows that conformation D [Fig. 5(d)] is practically superimposed on the X-ray structure and can be considered as being the same. On the other hand, conformation B [Fig. 5(b)] is practically the mirror image of X-ray structure. Consequently, it is expected that conformations B and D are enantiomerically related, what is confirmed when both conformations are compared in Figure 5(e). In conclusion, three minimum conformations for omeprazole have been obtained, since enantiomers have identical chemical properties except toward optically active reagents.

RACEMIZATION BARRIERS

Omeprazole

Results obtained for omeprazole are shown in Figure 6. Energy is given in hartrees (or atomic units, a.u.), and the dihedral angle is varied in degree units. Transition state and frequency calculations were performed for the structures corresponding to the highest points on each plot. A single negative value was obtained for frequency in all cases, ensuring that transition states were found. The sulfur geometry changed from pyramidal to planar, and this result is in agreement with the literature [16]. The transition state structures can be conferred on Figure 7. The energy difference between the transition and ground states was calculated for all plots, giving the racemization barrier values. Numerical results for rotation and racemization barriers energy are in Table I.

From the results, we observe that the energy difference of the rotational barriers is practically the same for all minimum energy structures. When the values for rotation and racemization are compared, a considerable energy decrease from the highest

TABLE I
Energies for rotation and racemization barriers.

Conformation	Rotation (kcal mol ⁻¹)	Racemization (kcal mol ⁻¹)
A	62.60	42.97
B	62.09	43.76
C	61.08	43.95

TABLE II
Rotation barriers (single-point calculation).

Method	ΔE_e (kcal mol ⁻¹)
HF/6-31G**	59.48
B3LYP/6-31G**	59.98

point on the plot (around 60 kcal mol⁻¹) to the transition state (around 40 kcal mol⁻¹) is observed.

Table II shows results for the single-point calculations. It is important to stress that these calculations were only performed to provide a qualitative result for verifying if there are electronic correlation effects. The values obtained indicate that the correlation effects are cancelled.

From the numerical barrier values, we can evaluate how easy is the racemization process for omeprazole. From Eyring's equation (Eq. 3) [26], the value obtained for the barriers can be correlated with the time required for the process, providing the racemization rate constant. As the energy values found were similar, the medium value for was used on calculation.

$$k = \frac{k_b}{h} T e^{\frac{-\Delta G}{RT}}, \quad (3)$$

where k , k_b and h are the velocity, Boltzmann and Planck constants, respectively, ΔG is the free energy for the process (racemization barrier). Equation (2) shows the relation between the velocity constant, obtained by eq. (1), and the half-life time. Table III shows the results and conditions for omeprazole half-time life calculations.

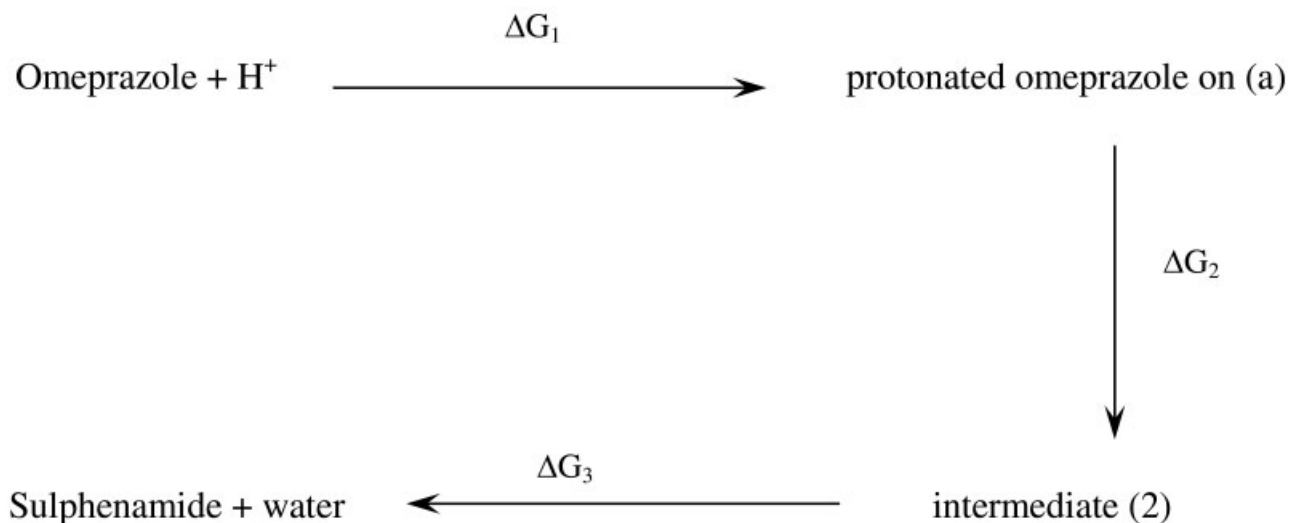
$$t_{1/2} = \frac{\ln 2}{k}. \quad (4)$$

Results showed that the racemization process is impossible at 100°C. The racemization would require temperatures around 200°C, but even at these

TABLE III
Estimated half life time.

	ΔG /kJ mol ⁻¹	k (s ⁻¹)	$t_{1/2}$ (years)
Omeprazole	182.12	2.43×10^{-13}	9.04×10^4

$$T = 100^\circ\text{C}, \Delta G = \sum \Delta G_i/n_i.$$



SCHEME 1. Sequence studied for decomposition reaction.

temperatures the process would take about 2 months to occur. A statistical mechanics calculation could be performed for evaluating a probable medium stabilization. The Thermodynamic Perturbation Theory is used as a tool in such cases [27], and it has been used to obtain the value concerning to the solvent stabilization of rotational barriers [28, 29].

The free energy variation for a given system is written as:

$$\Delta G = \Delta H - T\Delta S, \quad (5)$$

where ΔG , ΔH and ΔS are, the free energy, enthalpy and entropy variations, respectively, and T is the system temperature.

The difference for free energy values between vacuum and calculations including the medium influence is characterized by the inclusion of entropic

contribution regarding to the surrounding. A large change on the solvation free energy between the transition and ground states would be due to an expressive contribution from $T\Delta S$ term. In a theoretical sense, the value of entropic contribution is effective only if the system organization from an energetic state change significantly to another one [30, 31]. In this study, the calculation of the medium influence was not performed. The main reason is related with the calculation strategy used for the determination of the barriers. As mentioned earlier, the dihedral containing the S—O bond was systematically rotated for obtaining the pyramidal inversion of the sulfoxide group. Taking into consideration the dimension of the omeprazole and the fact that the difference between ground and transition states is only the sulfur configuration (it passed from pyramidal to planar), it is believed that the organization of the solvent will not change in a

TABLE IV
Calculation results for the species of Figure 2.

Compound	E_c^0 (u.a.)	H_v^0 (kcal mol ⁻¹)	H_v (kcal mol ⁻¹)	H_r (kcal mol ⁻¹)	H_t (kcal mol ⁻¹)	S (Total) (cal mol ⁻¹ K ⁻¹)
H ⁺	0	0	0	0	0.889	0
Omeprazole	-1440.2265	229.830	241.649	0.889	0.889	157.466
Prot.Omeprazole	-1440.6192	238.598	250.669	0.889	0.889	159.923
Intermediate (2)	-1440.6053	238.704	250.403	0.889	0.889	154.812
Sulfenamide	-1364.6210	221.202	231.785	0.889	0.889	145.051
Water	-76.0236	14.553	14.554	0.889	0.889	44.959

TABLE V
Free energy differences (Scheme 1).

	ΔG (kcal mol ⁻¹)
Protonated omeprazole → Omeprazole	-237.51
Intermediate (2) → Protonated omeprazole	9.98
Sulfenamide + Water → Intermediate (2)	-39.25
$\Delta(\Delta G)$ (kcal/mol)	-266.78

significant way to obtain sufficiently low values to allow the racemization. Thus, the decomposition reaction study became important for verifying the omeprazole behavior.

DECOMPOSITION REACTION

Compounds referents to the decomposition reaction (see Fig. 3) were calculated. For obtaining compound **2**, the nitrogen labeled as (**a**) was protonated, as indicated in the literature [1]. Compound labeled as **3** was not studied, because this compound (sulfenic acid) and sulfenamide **4** are both active. The only difference between them is a water molecule, which was taken into account in calculations. Scheme 1 shows the sequence used for calculations. Free energy difference was calculated for each step, obeying the set of equations as follows [32]:

$$\Delta G = \Delta H - T\Delta S, \quad \Delta H = \Delta E - \Delta(PV),$$

$$\Delta E = \Delta E_e^0 + \Delta E_v^0 + \Delta(\Delta E_v) + \Delta E_r + \Delta E_t, \quad (6)$$

where,

ΔE = internal energy variation (298.15 K);

$\Delta(PV)$ = system pressure and volume variations (298.15 K);

ΔE_e^0 = electronic energy difference between reactants and products (0 K);

ΔE_v^0 = vibrational energy difference between reactants and products (0 K);

$\Delta(\Delta E_v)$ = vibrational energy difference variation between 0 and 298.15 K;

ΔE_r = rotational energy difference between reactants and products (298.15 K); and

ΔE_t = translational energy difference between reactants and products (298.15 K).

Table IV presents values corresponding to each compound, whereas Table V shows the free energy variation for each step on Scheme 1. For free energy

variation, a large decrease is observed from omeprazole to protonated omeprazole. It increases again from protonated omeprazole to the intermediate **2**, and, finally, it decreases again to sulfenamide **4**. The total value for the difference of free energy variation ($\Delta(\Delta G)$) is favorable to the sulfenamide **4** formation. Besides, this value is very negative, indicating an extremely exothermic variation. It is needed to stress that this value is not realistic in terms of a human reaction, because it is a semireaction value. The contra-ion energy corresponding to H⁺ is not being considered. The solvent stabilization was not taken into account as well, because the calculation was performed in gas phase. Thus, this exothermic value must be evaluated only as a qualitative test, indicating the omeprazole tendency for decomposition.

Conclusions

We conclude, from the results, that the energy difference of the rotational barriers is practically the same for all minimum energy structures. A considerable energy decrease from the highest point on each rotation curve (around 60 kcal mol⁻¹) to the transition state (around 40 kcal mol⁻¹) was observed. From Eyring's equation, results showed that the racemization process is impossible at 100°C. For the decomposition reaction, the total value for the difference of free energy variation ($\Delta(\Delta G)$) is exothermic (-266.78 kcal mol⁻¹). The solvent stabilization was not taken into account. Thus, the exothermic value can be considered as a qualitative test, and it indicates the omeprazole tendency for decomposition. We conclude that for racemization to be feasible, the temperature would be too high, and the decomposition would be observed instead.

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