Racemization of the Gastrointestinal Antisecretory Chiral Drug Esomeprazole Magnesium via the Pyramidal Inversion Mechanism: A Theoretical Study

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ABSTRACT The pyramidal inversion mechanisms of the 6-methoxy and the 5-methoxy tautomers of (*S*)-omeprazole were studied, employing ab initio and DFT methods. The conformational space of the model molecule (*S*)-2-[(3-methyl-2-pyridinyl)-methyl]sulfinyl-1*H*-benzimidazole was calculated, with respect to rotations around single bonds, at the B3LYP/6-311G(d,p) level. All of the resulting conformations were used as starting points for full optimizations of (*S*)-omeprazole, at B3LYP/6-31G(d), B3LYP/6-311G(d,p), B3LYP/6-311++G(d,p), B3LYP/6-311G(2df,2pd), MP2/6-31G(d), and MP2/6-311G(d,p) levels. Four distinct pathways were found for enantiomerization via the pyramidal inversion mechanism for each of the tautomers of (*S*)-omeprazole. Each transition state, in which the sulfur, the oxygen and the two carbon atoms connected directly to the sulfur are in one plane, connects two diastereomeric minima. The enantiomerization is completed by free rotation around the sulfur–methylene bond, and around the methylene–pyridine ring bond. The effective Gibbs' free energy barrier for racemization $\Delta G^{\ddagger}_{rac}$ of the two tautomers of (*S*)-omeprazole are 39.8 kcal/mol (5-methoxy tautomer) and 40.0 kcal/mol (6-methoxy tautomer), indicating that the enantiomers of omeprazole are stable at room temperature (in the gas phase). The 5-methoxy tautomer of (*S*)-omeprazole was found to be slightly more stable than the 6-methoxy tautomer, in the gas phase. The energy barrier ($\Delta G^{\ddagger}$) for the (*S,M*) $\rightleftharpoons$ (*S,P*) diastereomerization of (*S*)-omeprazole due to the rotation around the pyridine chiral axis was very low, 5.8 kcal/mole at B3LYP/6-311G(d,p). *Chirality 22:798–807, 2010.*

KEY WORDS: omeprazole; chirality; sulfoxide drugs; racemization; DFT; ab initio

INTRODUCTION

Omeprazole, 5-methoxy-2-[4-methoxy-3,5-dimethyl-(2-pyridinyl)methyl]sulfinyl-1*H*-benzimidazole (Fig. 1), was the first gastrointestinal antisecretory proton pump (H^+/K^+-ATPase) inhibitor (PPI) drug to reach the market, for the treatment of gastric acid-related problems, such as gastroesophageal reflux disease (GERD).[1–3] It was developed by Astra in Sweden and launched in the E.U. in 1988 (Losec®) and in the U.S. in 1989 (Prilosec®).[2] Omeprazole is a racemic sulfoxide. The chirality of omeprazole stems primarily from the presence of a chiral center at the sulfur atom of the methylsulfinyl bridge between the 1*H*-benzimidazole and the pyridine moieties. The absolute configurations of the (+)- and (−)- enantiomer of omeprazole have been shown to be (*R*) and (*S*), respectively[4] (Fig. 1). Other prominent racemic PPI sulfoxide drugs, are Pantoprazole, Lansoprazole, and Rabeprazole.[5–7] The racemic PPI inhibitor Ilaprazole (2-[(4-methoxy-3-methyl-2-pyridyl)methyl]sulfinyl-5-(1*H*-pyrrol-1-yl)1*H*-benzimidazole), CAS [172152-36-2] was approved by the Korean Food and Drug Administration (KFDA) in 2008. Ilaprazole is marketed in some countries but has not yet reached the market in the US.[8] AstraZeneca has developed the chiral switch of omeprazole to its (*S*)-(−)-enantiomer, as esomeprazole magnesium.[2,3,5,7,9] Chiral switches are chiral drugs that have already been developed and claimed as racemates or as mixtures of diastereomers but have since been redeveloped as single enantiomers.[5,10] Esomeprazole magnesium was launched in the E.U. in 2000 and in the U.S. in 2001 under the trade name Nexium™.[2,11] The active ingredient in Nexium™ is (*S*)-bis(5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1*H*-benzimidazole-1-yl) magnesium trihydrate, a compound that inhibits gastric acid secretion.[12] Nexium has been approved for the following indications: treatment of Gastroesophageal Reflux Disease (GERD), risk reduction of NSAID-associated gastric ulcer, *H. pylori* eradication to reduce the risk of duodenal ulcer recurrence and pathological hypersecretory conditions including Zollinger-Ellison syndrome.[13] Compared to the racemate, esomeprazole magnesium has unique metabolic properties that led to

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Received for publication 15 May 2009; Accepted 5 February 2010
DOI: 10.1002/chir.20839
Published online 12 April 2010 in Wiley Online Library (wileyonlinelibrary.com).

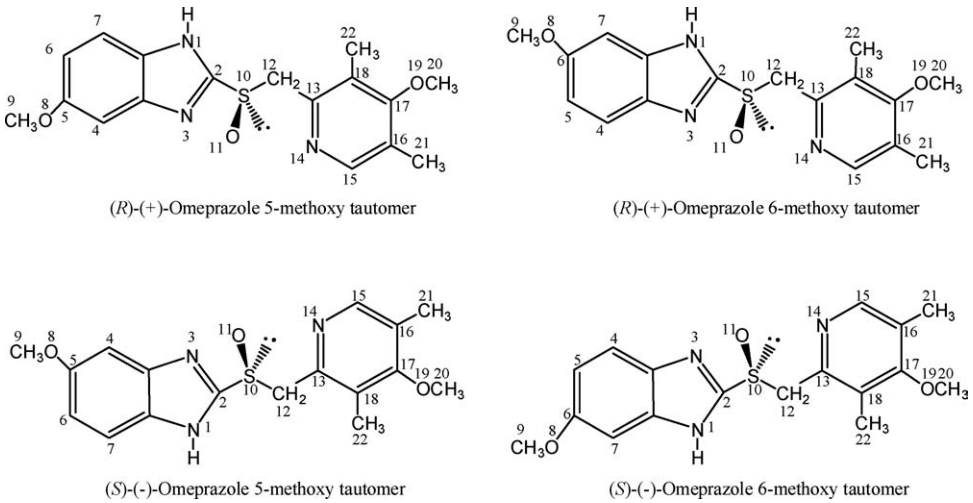

Fig. 1. Enantiomers and tautomers of omeprazole.

several clinical advantages, for example higher bioavailability in the majority of patients, i.e., the extensive metabolizers (EMs; 97% in Caucasian and 80–85% in Asian populations), lower exposure in poor metabolizers (PMs; 3% in Caucasian and 15–20% in Asian populations) and lower interindividual variation.[7] Takeda Pharmaceutical has developed the chiral switch of Lansoprazole to its (*R*)-(+)-enantiomer, as Dexlansoprazole, and launched it under the trade name Kapidex in 2009.[14]

In 1990, Erlandsson et al.[15] reported the resolution of omeprazole into its enantiomers on a preparative scale, using a cellulose-based chiral phase and a mobile phase prepared by mixing *n*-hexane, 2-propanol and diethylamine (since omeprazole is not stable at low pH values of the mobile phase). The racemization half-life of omeprazole was estimated to be 1.3×10^2 h at 37°C.[15]

In addition to the chiral center at the sulfur atom, omeprazole contains a chiral axis at the pyridine ring due to the spatial orientation of the 4-methoxy-3,5-dimethylpyridine moiety and the "hindered" rotation of the 4-methoxy substituent.[16] Furthermore, omeprazole exists as two tautomers: 5-methoxy- and 6-methoxy-2-[4-methoxy-3,5-dimethyl-(2-pyridinyl)methyl]sulfinyl-1*H*-benzimidazole (Fig. 1); they undergo fast isomerization in solution.[16] Recently, a few experimental and theoretical results of the energy differences between the tautomers of omeprazole in solution, in the gas phase and in the solid phase have been reported.[16-18] The crystallographic structure of omeprazole (the racemate) was reported in 1989 and in 2000 and described the molecular structure of the 6-methoxy tautomer[19,20] (even though in both references the authors referred to the molecule as the 5-methoxy tautomer of omeprazole).

Chiral sulfoxides undergo racemization thermally, photochemically, or involving the chemical environment, via different pathways.[21] The simplest and most common mechanism for thermal racemization of chiral sulfoxides is the pyramidal inversion mechanism, also called "pyramidal atomic inversion."[22] According to this mechanism, the racemization takes place without breaking bonds, via a transition state in which the four atoms, oxygen and sulfur of the sulfinyl group, and the two atoms connected to sulfur, lie in one plane.[23,24] Mislow et al., reported in 1966–1968 kinetic evidence indicating several distinct pathways of racemization for simple sulfoxides.[24-27]

Quantum-mechanical calculations may be applied to the determination of energy barriers and mechanisms for chemical processes, including mechanisms of racemization.[28] These methods may also be applied to mechanisms of degenerate reactions.

Recently, we reported a theoretical study of the pyramidal inversion mechanism of simple sulfoxides,[29] using ab initio and DFT methods and various basis sets. Very recently, a theoretical study of the racemization barrier of omeprazole was reported, using the semiempirical PM3 method.[30] The reported racemization barrier was 43.5 kcal/mol (half-life of 9.04×10^4 years at 100°C).

The objectives of the present study were to determine, by means of quantum-mechanical methods, the energy barriers for racemization of esomeprazole, the active pharmaceutical ingredient of esomeprazole magnesium, via the pyramidal inversion mechanism and to establish whether the enantiomers of esomeprazole would be expected to be stable at room temperature. We report here the results of ab initio and DFT calculations of the energy barriers for racemization of esomeprazole via the pyramidal inversion mechanism.

METHODS

The programs Gaussian98[31] and Gaussian03[32] were used for ab initio second-order Møller-Plesset (MP2), and density functional theory (DFT) calculations. Becke's three-parameter hybrid density functional B3LYP,[33] combining Becke's 1988 exchange functional, Hartree-Fock exact exchange, and the correlation functional of Lee, Yang and Parr[34-36] were used with a variety of basis sets (vide infra). Frequencies were calculated at B3LYP/6-

311G(d,p), B3LYP/6-311++G(d,p) and MP2/6-31G(d) levels of calculation for all fully optimized structures in order to characterize them as bona fide minima or transition states. Unscaled frequencies were used to calculate zero point energy corrections (ZPE), thermal corrections to enthalpy (H_{corr}), thermal corrections to Gibbs energy (G_{corr}) at 298 K, and the temperature dependence of $\Delta G^{\ddagger}$. At B3LYP/6-311G(2df,2pd) and MP2/6-311G(d,p) levels the unscaled frequencies at B3LYP/6-311G(d,p) and MP2/6-31G(d) levels were used, respectively.

The energy barriers $\Delta E^{\ddagger}$ for the pyramidal inversion mechanism were calculated by subtracting the energies of the global minima from the respective energies of each of the transition states. The barriers were corrected for zero point vibrational energy using $\Delta E^{\ddagger}_{ZPE} = \Delta E^{\ddagger} + \Delta ZPE^{\ddagger}$. The activation enthalpies were calculated according to $\Delta H^{\ddagger}_{298} = \Delta E^{\ddagger} + \Delta H^{\ddagger}_{corr}$, and the Gibbs' free activation energies as $\Delta G^{\ddagger}_{298} = \Delta E^{\ddagger} + \Delta G^{\ddagger}_{corr}$. The entropy differences $\Delta S^{\ddagger}_{298}$ were calculated by subtracting the entropies of the global minima from the respective entropies of each of the transition states.

We explored the conformational space of omeprazole with respect to rotations around these single bonds (Fig. 1): (i) Rotation around the S—$C^{12}H_2$ bond (D_1); (ii) Rotation around the $C^{12}H_2$—C^{13} bond, which determines the relative position of the substituted pyridine ring (D_2); (iii) Rotation around the S—C^2 bond, which determines the relative position of the benzimidazole ring system (D_3).

As an initial step, the conformational space of the model molecule (*S*)-2-[(3-methyl-2-pyridinyl)methyl]sulfinyl-1*H*-benzimidazole was calculated. This model molecule was based on the structure of (*S*)-omeprazole, by omitting the $C^{21}H_3$ methyl substituent and the two methoxy substituents. This partially unsubstituted (*S*)-omeprazole derivative maintains the stereochemical feature at the sulfinyl moiety of (*S*)-omeprazole (Fig. 2). The potential energies of the minima and the transition states for the pyramidal inversion of the model molecule were calculated as a function of the torsion angles D_1, D_2, and D_3, at the B3LYP/6-311G(d,p) level, for the pyramidal structure (in which the sulfur configuration is approximately tetrahedral) and for the planar structure (in which the oxygen, the sulfur, and the two atoms connected directly to the sulfur are coplanar), respectively. The B3LYP/6-311G(d,p) level was chosen as a suitable level based on the results of our previous sulfoxide calculations.[29] The torsion angles D_1, D_2, D_3 were each rotated in 20° steps, while all the other torsion angles were free, resulting in a one-dimensional potential energy surface (1D-PES) for each scanned torsion angle. The pyramidal structure was scanned without additional constraints. The planar structure was scanned with the improper torsion angle C^2—S—O—C^{10} constrained to 180°. All minima located on the 1D-PES maps of the pyramidal structure were used as starting points for full optimization (after releasing all constraints). All minima located on the 1D-PES maps of the structures with a planar sulfur atom were used as starting points for full optimizations of the transition states for pyramidal inversion (after releasing all constraints on D_1, D_2, D_3 and the improper torsion angle C^2—S—O—C^{10}). The $C^{21}H_3$ methyl substituent and the two methoxy substituents were then added to the fully optimized conformations found for the model molecule, and the resulting conformations were used as starting points for full optimizations of (*S*)-omeprazole.

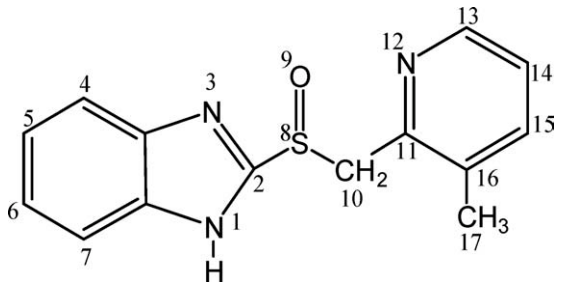

Fig. 2. 2-[(3-Methyl-2-pyridinyl)methyl]sulfinyl-1*H*-benzimidazole.

RESULTS AND DISCUSSION

We explored the conformational space for the pyramidal inversion mechanism of (*S*)-omeprazole, taking into consideration the calculated results for simple sulfoxides.[29] The mechanism under study results in the inversion of the absolute configuration of the chiral sulfur center, while maintaining the orientation around the chiral axis at the pyridine ring. Therefore, this mechanism does not lead to enantiomerization, but to diastereomerization: it connects two diastereomeric minima, differing in the absolute configuration of their stereogenic sulfur atom, but identical in the orientation around the chiral axis: (*S*,*M*) ⇌ (*R*,*M*) or (*S*,*P*) ⇌ (*R*,*P*). The (*S*,*M*) ⇌ (*S*,*P*) diastereomerization was expected to be very fast at room temperature (vide infra). Any future reference in this work to the term "enantiomerization" is only in the context of the chirality element chiral center of (*S*)-omeprazole, not of the chirality element chiral axis of (*S*)-omeprazole, or of both of these two chirality elements.

*Conformational Space for the Pyramidal Inversion of 2-[(3-Methyl-2-pyridinyl)methyl]sulfinyl-1*H*-benzimidazole*

As a starting point for the (*S*)-omeprazole calculations, the conformational space for the pyramidal inversion mechanism of the model molecule (*S*)-2-[(3-methyl-2-pyridinyl)methyl]sulfinyl-1*H*-benzimidazole (Fig. 2), was first calculated (vide supra). The relevant components of this molecule that directly participate in the pyramidal inversion (sulfur, oxygen, the two carbon atoms connected directly to the sulfur, and the atoms connected to them) are identical to the respective components of (*S*)-omeprazole. The search for the conformational space for the pyramidal inversion mechanism of (*S*)-omeprazole was based on the results obtained for the model molecule.

Scanning the conformational space for the (*S*)-2-[(3-methyl-2-pyridinyl)methyl]sulfinyl-1*H*-benzimidazole at B3LYP/6-311G(d,p) revealed six minima and two transition states for the pyramidal inversion. All of these conformations have C_1 symmetry and hence are chiral. The scanning hinted at a third transition state for the pyramidal inversion mechanism; however attempts to locate it at full

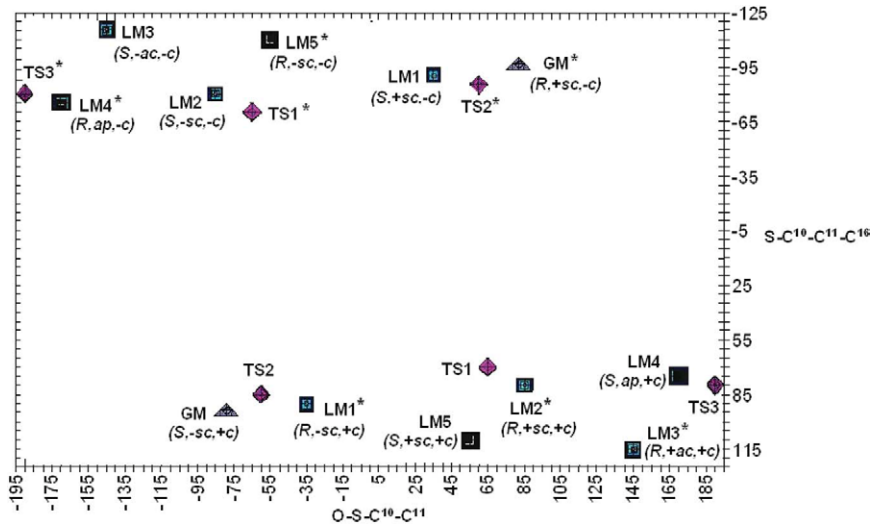

Fig. 3. The conformational space for the pyramidal inversion mechanism of 2-[[(3-methyl-2-pyridinyl)methyl]sulfinyl]-1*H*-benzimidazole, at B3LYP/6-311G(d,p): torsion angle around the S-C^{10} bond versus torsion angle around the C^{10}-C^{11} bond. The stationary points of the conformations (GM, GM*-global minima, LMn, LMn*(n=1-5)-local minima, TSn, TSn*(n=1-3)- transition states), the absolute configuration of the stereogenic sulfur atom, and the designators of the pair of the torsion angles O-S-C^{10}-C^{11} and S-C^{10}-C^{11}-C^{16} are indicated. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

optimization were unsuccessful. A possible explanation could be its location at a shallow area of the potential surface, causing the calculation to converge to another stationary point. A full optimization of the missing transition state at a lower basis set, B3LYP/6-31G(d), yielded, indeed, the missing transition state.

The different minima conformations can be classified according to the torsion angle due to rotation around the methylene-sulfur bond, O—S—C^{10}—C^{11}, and around the methylene-pyridine bond, S—C^{10}—C^{11}—C^{16} (See Fig. 2). The first torsion angle is classified as synclinal (+sc or –sc), anticlinal (+ac or –ac), synperiplanar (sp) or antiperiplanar (ap).[37] The second torsion angle is ca. (±) 90°: hence will be marked only as clinal (+c or –c). The absolute configuration of the chiral sulfur center is determined by the dihedral angle χ, 180°-(O—S—C^{10}—C^{2}). $\chi \approx +80°$ matches the absolute configuration *S* of the sulfur center, while $\chi \approx -80°$ matches the absolute configuration *R*. Taking into consideration these two torsion angles and the absolute configuration of the chiral sulfur center, we map the relevant conformations of the pyramidal inversion mechanism: 12 minima conformations and six transition state conformations for the pyramidal inversion. The low energy transition-state conformations for the rotation around the S—C^{10} bond and the C^{10}—C^{11} bond, connecting minima with the same absolute configuration, were not fully optimized.

The twelve minima conformations are divided into six pairs of enantiomers: the global minimum (*S*, −sc, +c) and its enantiomer (*R*, +sc, −c), and the local minima: (*S*, +sc, −c) and its enantiomer (*R*, −sc, +c) (LM1 and LM1*, ΔG° = 1.0 kcal/mol), (*S*, −sc, −c) and its enantiomer (*R*, +sc,+c) (LM2 and LM2*, ΔG° = 1.7 kcal/mol), (*S*, −ac, −c) and its enantiomer (*R*, +ac,+c) (LM3 and LM3*, ΔG° = 1.9 kcal/mol), (*S*,ap,+c) and its enantiomer (*R*, ap, −c) (LM4 and LM4*, ΔG° = 2.4kcal/mol), and (*S*, +sc, +c) and its enantiomer (*R*, −sc, −c) (LM5 and LM5*, ΔG° = 3.8 kcal/mol). The six transition-states for the pyramidal inversion conformations are divided into three pairs of enantiomers; each transition state connects

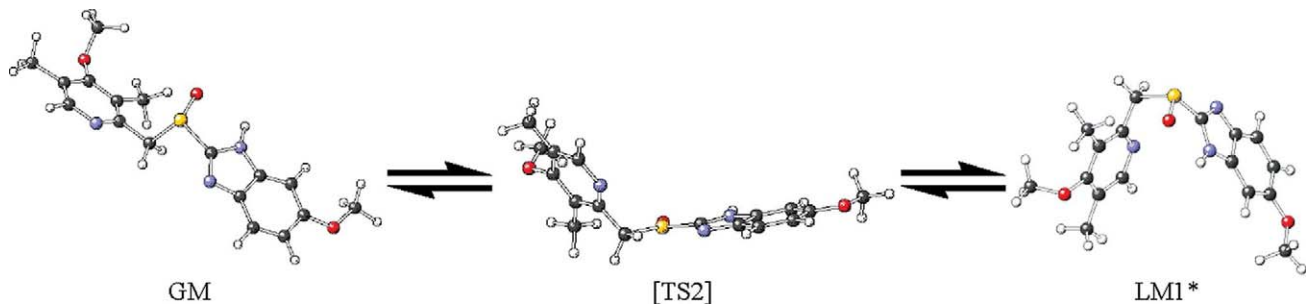

Fig. 4. The global minimum of the 6-methoxy tautomer of (*S*)-omeprazole (GM), the lowest local minimum of the 6-methoxy tautomer of (*R*)-omeprazole (LM1*) and the corresponding transition state for the pyramidal inversion (TS2), at B3LYP/6-311G(d,p). [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

two minima that are similar in their torsion angles but differ in their absolute configurations [TS1 and its enantiomer TS1*, $\Delta G^{\ddagger}$= 40.8 kcal/mol, TS2 and its enantiomer TS2*, $\Delta G^{\ddagger}$= 41.2 kcal/mol, TS3 and its enantiomer TS3*, $\Delta G^{\ddagger}$ = 44.2 kcal/mol. The third transition state and its enantiomer were fully optimized at B3LYP/6-31G(d) only] (Fig. 3).

Six distinct pathways were found for enantiomerization via the pyramidal inversion mechanism for the model molecule. The transition state in which the sulfur, the oxygen and the two carbon atoms connected directly to the sulfur are in one plane, connects two diastereomeric minima, and the enantiomerization is completed by fast rotations around the sulfur- methylene bond, O—S—C^{10}—C^{11}, and around the methylene - pyridine bond, S—C^{10}—C^{11}—C^{16} (vide infra). Examination of the 1D-PES maps showed that the energy barriers for these rotations are no more than 5.5 kcal/mol.

Conformational Space of the Pyramidal Inversion of (S)-Omeprazole

The search for the pyramidal inversion mechanism of (*S*)-omeprazole was based on the results obtained for the model molecule 2-[(3-methyl-2-pyridinyl)methyl]sulfinyl-1*H*-benzimidazole. The tautomers of (*S*)-omeprazole, (*S*)-5-methoxy and (*S*)-6-methoxy-2-[4-methoxy-3,5-dimethyl-(2-pyridinyl)methyl]sulfinyl-1*H*-benzimidazole were calculated (Fig. 1). The missing substituents were added to the model molecule conformations, and full optimizations were held for these conformations. The conformations revealed were similar to the model conformations. There are six minima and two transition states for the pyramidal inversion for each tautomer. Each of these conformations is chiral, and therefore has a paired enantiomer. Figure 4 describes the pyramidal inversion of the global minimum of (*S*)-omeprazole (GM) (6-methoxy tautomer) to the local minimum of (*R*)-omeprazole (LM1*) (6-methoxy tautomer) via the transition state TS2 (at B3LYP/6-311G(d,p)). The missing transition state in the conformational space of the model molecule was also missing in the cases of the (*S*)-omeprazole tautomers, even at B3LYP/6-31G(d) level.

To increase the accuracy of the calculations, the global minimum and the lowest transition-state conformations of the 6-methoxy tautomer of (*S*)-omeprazole were recalculated at higher basis sets, B3LYP/6-311++G(d,p) and B3LYP/6-311G(2df,2pd), and at ab initio MP2 level, MP2/6-311G(d,p).

Energy barriers for the Pyramidal Inversion Mechanism of (S)-Omeprazole

The results of the relative energies ΔE° of the minima conformations of 6-methoxy and 5-methoxy tautomers of (*S*)-omeprazole, and the results of the calculations of the energy barriers for the pyramidal inversion mechanism $\Delta E^{\ddagger}$, the zero point corrected energy barriers $\Delta E^{\ddagger}_{ZPE}$, the enthalpy barriers $\Delta H^{\ddagger}$, and the Gibbs' free energy barriers $\Delta G^{\ddagger}_{298}$ (at T = 298 K) (Fig. 1) of 6-methoxy and 5-methoxy tautomers of (*S*)-omeprazole, calculated at B3LYP/6-311G(d,p), are given in Tables 1 and 2, respectively. The torsion angles D_1, describing the rotation around the methylene-sulfur bond (O—S—C^{12}—C^{13}) and D_2, describing the rotation around the methylene-pyridine ring bond (S—C^{12}— C^{13}—C^{18}), and the dihedral angle χ, representing the pyramidalization degree of the sulfur atom [180°-(O—S—C^{12}—C^{2})] are also included in these Tables, as geometrical characteristics of the different conformations. Table 1 gives also the results of the upgraded calculations at B3LYP/6-311++G(d,p), B3LYP/6-311G(2df,2pd) and

TABLE 1. Relative energies (ΔE°), energy barriers ($\Delta E^{\ddagger}$), ZPE corrected energy barriers ($\Delta E^{\ddagger}_{ZPE}$), enthalpies ($\Delta H^{\ddagger}$, T = 298 K), and Gibbs' free energy barriers of pyramidal inversion ($\Delta G^{\ddagger}_{298}$, T = 298 K) (in kcal/mol), and selected torsion angles[a] (deg) of the 6-methoxy tautomer of (*S*)-omeprazole

Conformation	D_1	D_2	χ	ΔE°	$\Delta E^{\ddagger}$	$\Delta E^{\ddagger}_{ZPE}$	$\Delta H^{\ddagger}$	$\Delta G^{\ddagger}_{298}$
B3LYP/6–311G(d,p)								
GM	−73.5	90.6	79.4	0.00				
LM1	42.0	−87.7	73.1	0.98				
LM2	−83.0	−81.9	79.8	2.44				
LM3	168.3	74.1	73.6	2.51				
LM4	−133.6	−107.4	78.2	2.59				
LM5	62.5	105.4	76.1	3.15				
TS1	59.1	67.9	−0.2		42.25	41.17	41.13	41.22
TS2	−63.3	78.3	0.3		42.86	41.77	41.78	41.30
B3LYP/6–311++G(d,p)								
GM	−75.9	90.9	79.1	0.00				
TS1	58.6	73.2	−0.5		41.18	40.08	40.08	40.01
B3LYP/6–311G(2df,2pd)								
GM	−72.7	92.0	79.2	0.00				
TS1	59.4	69.3	−0.3		42.01	40.93	40.89	40.98
MP2/6–311G(d,p)								
GM	−73.0	90.6	81.0	0.00				
TS1	59.9	63.3	0.2		46.83	45.85	45.81	46.15

GM, global minimum; LM, local minimum; TS, transition state for pyramidal inversion mechanism.
[a]D_1 = O−S−C^{12}−C^{13}, D_2 = S−C^{12}−C^{13}−C^{18}, χ = 180-(O−S−C^{12}−C^{2}).

TABLE 2. Relative energies (ΔE°), energy barriers ($\Delta E^{\ddagger}$), ZPE corrected energy barriers ($\Delta E^{\ddagger}_{ZPE}$), enthalpies ($\Delta H^{\ddagger}$, $T = 298$ K), and Gibbs' free energy barriers of pyramidal inversion ($\Delta G^{\ddagger}_{298}$, $T = 298$ K) (in kcal/mol), and selected torsion angles[a] (deg) of the 5-methoxy tautomer of (*S*)-omeprazole

Conformation	D_1	D_2	χ	ΔE°	$\Delta E^{\ddagger}$	$\Delta E^{\ddagger}_{ZPE}$	$\Delta H^{\ddagger}$	$\Delta G^{\ddagger}_{298}$
B3LYP/6–311G(d,p)								
GM	−73.3	90.5	74.6	0.00				
LM1	41.3	−87.6	77.0	0.97				
LM2	−87.1	−82.4	79.8	2.53				
LM3	167.0	73.6	73.5	2.73				
LM4	−131.6	−106.7	78.3	2.63				
LM5	59.8	105.7	76.1	3.20				
TS1	58.4	67.7	−0.2		41.88	40.85	40.78	41.13
TS2	−63.3	78.3	0.3		42.43	41.40	41.41	40.88

GM, global minimum; LM, local minimum; TS, transition state for pyramidal inversion mechanism.
[a]$D_1 = O-S-C^{12}-C^{13}$, $D_2 = S-C^{12}-C^{13}-C^{18}$, $\chi = 180-(O-S-C^{12}-C^{2})$.

MP2/6-311G(d,p) levels for the global minimum and the lowest transition-state conformations of the 6-methoxy tautomer of (*S*)-omeprazole. Upgrading the basis set of the B3LYP method did not change the energy barrier dramatically. Using the MP2/6-311G(d,p) method yielded a higher energy barrier (46.8 kcal/mol for the first transition state). The dependence of the energy barriers of simple sulfoxides on the method of calculation and on the basis set have been previously analyzed in detail. The convergence of the energetic results of simple sulfoxides matches the current results.[29]

The following points should be noted in the comparison between the calculated and experimental results:

(i) When several enantiomeric and/or diastereomeric transition states for the pyramidal inversion exist, each pathway contributes to the enantiomerization rate. Four distinct pathways were found for enantiomerization via the pyramidal inversion mechanism for each of the tautomers of (*S*)-omeprazole. The four transition states of these pathways are two enantiomeric pairs of transition states. The transition state in which the sulfur, the oxygen and the two carbon atoms connected directly to the sulfur are in one plane, connects two diastereomeric minima, and the enantiomerization is completed by a free rotation around the sulfur-methylene bond, $O—S—C^{12}—C^{13}$, and around the methylene–pyridine ring bond, $S—C^{12}—C^{13}—C^{18}$ (vide infra). The rate constant of each individual pathway was calculated from its free energy barrier and summed up, resulting in the combined rate constant of the enantiomerization of (*S*)-omeprazole, $k = 2k_1 + 2k_2$. The effective Gibbs' free energy barrier calculated from the combined rate constant, $\Delta G^{\ddagger}_{ena}$, of the two tautomers of (*S*)-omeprazole at B3LYP/6-311G(d,p), are shown at Table 3. Although the missing transition state for the pyramidal inversion at this level was not found, we assumed that there is an additional enantiomeric pair of transition state conformations. Taking into account the results obtained for the model molecule of (*S*)-omeprazole, we expect that the effective Gibbs' free energy barrier will be 0.5 kcal/mol lower, at the most.

(ii) The experimental energy barriers were derived from the rate constants of loss of optical activity, i.e., racemization rate constants. Racemization describes a process that transforms molecules of a single enantiomer of a compound into an equimolar mixture of the two paired enantiomers of this compound. On the other hand, the process examined in the quantum-mechanical calculations is the enantiomerization process, a process that transforms a single enantiomer into its paired enantiomer. The rate constant for the racemization process is twice the rate constant for the enantiomerization process. Therefore, the calculated free energy barriers for the enantiomerization process $\Delta G^{\ddagger}_{ena}$ were adjusted to the corresponding energy barrier for the racemization process $\Delta G^{\ddagger}_{rac}$, using the equation $\Delta G^{\ddagger}_{rac} = \Delta G^{\ddagger}_{ena} - RT \ln 2$. The effective Gibbs' free energy barriers for the racemization process of the two tautomers of (*S*)-omeprazole, $\Delta G^{\ddagger}_{rac}$, are also given in Table 3.

(iii) Since the published experimental data of the racemization barrier of (*S*)-omeprazole were obtained at temperatures different from room temperature, another correction was made. The calculated free energy barrier results (calculated at room temperature) $\Delta G^{\ddagger}_{298}$ were recalculated at the experimental temperatures, 37, 50, 75°C. However, no significant differences were found in the results of the free energy barriers matching the room temperature and those temperatures. For example, the free energy barrier for the

TABLE 3. The effective Gibbs' free energy barrier for enantiomerization calculated from the combined rate constant ($\Delta G^{\ddagger}_{ena}$) and the effective Gibbs' free energy barrier for racemization ($\Delta G^{\ddagger}_{rac}$) of the two tautomers of omeprazole at B3LYP/6–311G(d,p), and the experimental barrier (at 75°C) for the racemization of omeprazole[15] (in kcal/mol)

B3LYP/6–311G(d,p)				
6-methoxy		5-methoxy		Previous experimental data
$\Delta G^{\ddagger}_{ena}$	$\Delta G^{\ddagger}_{rac}$	$\Delta G^{\ddagger}_{ena}$	$\Delta G^{\ddagger}_{rac}$	$\Delta G^{\ddagger}_{rac}$
40.44	40.03	40.17	39.76	26.43

TABLE 4. Selected bond lengths (pm), bond angles[a] and torsion angles[b] (deg) of optimized conformations of 6-methoxy tautomer of (*S*)-omeprazole and of X-ray molecular structure of omeprazole[19]

Conformation	S—O	S—C^{12}	S—C^{2}	A_1	A_2	A_3	χ	D_1	D_2	D_3	D_4	D_5
B3LYP/6–311G(d,p)												
GM	152.3	187.4	180.8	95.9	107.9	102.7	79.4	−73.5	90.6	180.1	180.2	92.6
LM1	152.1	188.3	180.2	98.1	107.9	103.3	73.1	42.0	−87.7	172.5	180.1	96.0
TS1	154.1	184.2	173.8	111.5	129.5	118.9	−0.2	59.1	67.9	184.2	180.5	98.2
TS2	154.6	184.3	174.2	112.5	128.1	119.4	0.3	−63.3	78.3	186.1	179.8	96.4
B3LYP/6–311++G(d,p)												
GM	152.5	187.5	181.0	96.0	108.1	102.9	79.1	−75.9	90.9	182.3	180.0	95.9
TS1	154.3	185.2	174.1	112.8	129.1	118.1	−0.5	58.6	73.2	181.4	180.9	99.7
B3LYP/6–311G(2df,2pd)												
GM	150.2	186.2	179.9	95.7	108.1	103.4	79.2	−72.7	92.0	180.6	180.2	92.8
TS1	151.5	182.6	172.6	112.7	128.0	119.3	−0.3	59.4	69.3	182.6	180.6	98.6
MP2/6–311G(d,p)												
GM	151.6	183.1	178.6	94.6	107.0	102.9	81.0	−70.3	90.6	179.7	180.2	97.4
TS1	152.9	179.7	172.2	111.3	129.1	119.7	0.2	59.9	63.3	185.2	180.1	100.4
X-ray	148.7	181.5	176.8	96.6	105.9	108.6	69.1	−70.0	148.3	129.5	184.6	89.4

GM, global minimum; LM, local minimum; TS, transition state for pyramidal inversion mechanism.
[a]$A_1 = C^2–S–C^{12}$, $A_2 = O–S–C^{12}$, $A_3 = O–S–C^2$, $\chi = 180\text{-}(O–S–C^{12}–C^2)$.
[b]$D_1 = O–S–C^{12}–C^{13}$, $D_2 = S–C^{12}–C^{13}–C^{18}$, $D_3 = O–S–C^2–N^3$, $D_4 = C^9–O^8–C^6–C^5$, $D_5 = C^{20}–O^{19}–C^{17}–C^{16}$.

first transition state was 41.2 kcal/mol at room temperature, and 41.3 kcal/mol at 75°C, both at B3LYP/6-311G(d,p) level.

Table 3 also shows the experimental barrier for the racemization of (*S*)-omeprazole, calculated from the published experimental racemization data for (*S*)-omeprazole.[15]

The results obtained for the racemization barrier via the pyramidal inversion mechanism of (*S*)-omeprazole are 40.0 kcal/mol for the 6-methoxy tautomer and 39.8 for the 5-methoxy tautomer. These results differ considerably from the published experimental data, 26.4 kcal/mol.[15] MP2/6-311G(d,p) gave even higher energy barrier: 46.1 kcal/mol versus 41.2 kcal/mol at B3LYP/6-311G(d,p), for the first transition state of the 6-methoxy tautomer. The discrepancies raise doubt whether the pyramidal inversion is the principal mechanism of the racemization of (*S*)-omeprazole, under the experimental conditions applied (although the authors state that (*S*)-omeprazole undergoes racemization via the pyramidal inversion mechanism[15]). It should be noted that the data reported contain only one value at one temperature, a single point of $t_{1/2}$ at 75°C. The corresponding values of the other temperatures measured, were not reported. Such a representation may have led to inaccuracies.

The energy barrier found for the 6-methoxy tautomer of (*S*)-omeprazole, 40.0 kcal/mol, is 1 kcal/mol lower than the one calculated for the simple molecule benzyl phenyl sulfoxide, 41.4 kcal/mol.[29] (*S*)-omeprazole and (*S*)-benzyl phenyl sulfoxide have similar substituents directly connected to the sulfur atom (benzyl versus 2-pyridinyl methyl, and phenyl versus 2-benzimidazolyl). As in the case of (*S*)-omeprazole, the results obtained for benzyl phenyl sulfoxide do not match previous experimental data (32.8 kcal/mol), suggesting that the pyramidal inversion mechanism may not necessarily apply to the racemization of this compound as well.[29]

A theoretical study of the racemization barrier of (*S*)-omeprazole, using the PM3 semiempirical method, has very recently been reported.[30] The Principal Component Analysis (PCA) chemometric method was used to find all minimum energy structures. In addition, single point calculations were carried out using HF/6-31G(d,p) and B3LYP/6-31G(d,p). The authors state that the racemization barrier was not calculated from the differences between the ground state and the transition state for pyramidal inversion. The calculated (average) racemization barrier was 43.6 kcal/mol.

The $(S,M) \rightleftharpoons (S,P)$ and $(R,M) \rightleftharpoons (R,P)$ diastereomerizations of (*S*)-omeprazole and (*R*)-omeprazole, respectively, due to the rotation around the chiral axis in the pyridine ring deserve special attention. The 4-methoxy substituent of the pyridine ring is not coplanar with the pyridine ring, due to the presence of the two ortho-methyl substituents (at positions 3 and 5). This spatial orientation introduces a chiral axis and may in principle, lead to atropisomers.[38] The challenge of atropisomerism in the drug industry has recently been highlighted.[39] In the present study, the effective energy barrier ($\Delta G^{\ddagger}$) for the $(S,M) \rightleftharpoons (S,P)$ diastereomerization of esomeprazole (6-methoxy tautomer) proved to be very low, 5.8 kcal/mole at B3LYP/6-311G(d,p). The torsion angle D_5 ($C^{20}—O^{19}—C^{17}—C^{16}$) in the transition state for the rotation around the chiral axis is 170.3°. The (S,M) and (S,P) diastereomers should not be considered atropisomers (conformers which owing to steric or electronic constrained, interconvert slowly enough that they can be isolated[38,39]).

Geometrical Parameters

Selected geometrical parameters of the two lowest minima and the transition states of 6-methoxy and 5-methoxy tautomers of (*S*)-omeprazole, calculated at B3LYP/6-311G(d,p), are listed in Tables 4 and 5, respectively. The

TABLE 5. Selected bond lengths (pm), bond angles[a] and torsion angles[b] (deg) of optimized conformations of 5-methoxy tautomer of (*S*)-omeprazole

Conformation	S—O	S—C^{12}	S—C^{2}	A_1	A_2	A_3	χ	D_1	D_2	D_3	D_4	D_5
B3LYP/6–311G(d,p)												
GM	152.2	187.4	180.9	95.7	108.0	102.8	74.6	−73.3	90.5	180.7	179.8	92.6
LM1	152.0	188.3	180.3	97.8	108.0	103.6	77.0	41.3	−87.6	173.1	179.8	95.9
TS1	154.0	184.2	173.6	111.5	129.3	119.2	−0.2	58.4	67.7	183.8	179.8	98.1
TS2	154.4	184.6	173.9	112.6	127.5	119.9	−0.6	−51.6	79.7	183.7	179.8	96.9

GM, global minimum; LM, local minimum; TS, transition state for pyramidal inversion mechanism.
[a]A_1 = C^2–S–C^{12}, A_2 = O–S–C^{12}, A_3 = O–S–C^2, χ = 180-(O–S–C^{12}–C^2).
[b]D_1 = O–S–C^{12}–C^{13}, D_2 = S–C^{12}–C^{13}–C^{18}, D_3 = O–S–C^2–N^3, D_4 = C^9–O^8–C^5–C^6, D_5 = C^{20}–O^{19}–C^{17}–C^{16}.

following geometrical parameters were considered: bond length between the sulfur and the oxygen (S-O), between the sulfur and the methylene (S—C^{12}), and between the sulfur and the benzimidazole moiety (S—C^2); bond angles around the sulfinyl group: C^2—S—C^{12} (A_1 angle), O—S—C^{12} (A_2 angle), and O—S—C^2 (A_3 angle); the pyramidalization angle χ, 180°-(O—S—C^{12}—C^2), torsion angle D_1, describing the rotation around the sulfur-methylene bond (O—S—C^{12}—C^{13}), torsion angle D_2, describing the rotation around the methylene-pyridine ring bond (S—C^{12}—C^{13}—C^{18}), torsion angle D_3, describing the rotation of the benzimidazole ring (O—S—C^2—N^3), torsion angle D_4, describing the rotation of the 6-methoxy/5-methoxy substituents at the benzimidazole ring system (C^9—O^8—C^6—C^5/ C^9—O^8—C^5—C^6), and torsion angle D_5, describing the rotation of the 4-methoxy substituent at the pyridine ring (C^{20}—O^{19}—C^{17}—C^{16}).

Table 4 gives also the results of the upgraded calculations to B3LYP/6-311++G(d,p), B3LYP/6-311G(2df,2pd) and MP2/6-311G(d,p) levels for the global minimum and the lowest transition state conformations of the 6-methoxy tautomer of (*S*)-omeprazole.

Geometrical parameters derived from the X-ray crystal structures of the 6-methoxy tautomer of omeprazole[19] are also included in Table 4. The crystallographic data were compared to the corresponding calculated parameters of the global minimum of the 6-methoxy tautomer of (*S*)-omeprazole.

The experimental data and the calculated results are generally in agreement. The discrepancies may be caused by the fact that the calculations are carried out on a molecule in the gas phase, while the X-ray results pertain to crystals in the solid state. Exceptions are the differences in the torsion angles D_2 and D_3 (90.6° and 180.1° for the calculated global minimum at B3LYP/6-311G(d,p) level versus 148.3° and 129.5° for the X-ray results, respectively), which may be attributed to packing effects, since the unit cell at the crystallographic data contains a C_i-dimer of omeprazole, the racemate, in which the enantiomers are held together by two hydrogen bonds $N^{1}\cdots H^{1}\cdots O^{11}$, between the benzimidazole nitrogen N^1 and the corresponding hydrogen H^1 of one enantiomer, and the sulfinyl oxygen O^{11} of the paired enantiomer.

The bond between the sulfur atom and the benzimidazole ring is shortened in the transition state for pyramidal inversion conformations, compared to the corresponding bonds in the minima conformations. At the global minimum of the 6-methoxy tautomer of (S)-omeprazole, the S—C^2 bond is 180.8 pm, while at the first transition-state, the S—C^2 bond is 173.8 pm (at B3LYP/6-311G(d,p) level). This indicates stabilizing resonance effects in the transition states (compared with the minima). A similar effect was found for simple sulfoxides.[29]

Upgrading the calculation level to B3LYP/6-311++G(d,p), B3LYP/6-311G(2df,2pd) and MP2/6-311G(d,p), results in more accurate geometrical parameters (as compared to the crystallographic data). For example, the S-O bond at the global minimum of the 6-methoxy tautomer of (*S*)-omeprazole is shortened from 152.3 pm at B3LYP/6-311G(d,p) to 150.2 pm at B3LYP/6-311G(2df,2pd) and to 151.6 pm at MP2/6-311G(d,p) (compared to 148.7 pm in the crystallographic data), and the S—C^2 bond at the same conformation is shortened from 180.8 pm at B3LYP/6-311G(d,p) to 179.9 pm at B3LYP/6-311G(2df,2pd) and to 178.6 pm at MP2/6-311G(d,p) (compared to 176.8 pm at the crystallographic data).

6-Methoxy Tautomer Versus 5-Methoxy Tautomer

The drug omeprazole is defined as the 5-methoxy tautomer 5-methoxy-2-[4-methoxy-3,5-dimethyl-(2-pyridinyl)methyl]sulfinyl-1*H*-benimidazole. However, the 5-methoxy tautomer readily converts in solution to the 6-methoxy tautomer, and vice versa. The same holds true also in the case of esomeprazole, which gives rise to the 5-methoxy tautomer and the 6-methoxy tautomer.

The crystal structure of omeprazole, the racemate, published in 1989, was that of the 6-methoxy tautomer [even though the publication had the title of "Structure of 5-methoxy-2-[4-methoxy-3,5-dimethyl-(2-pyridinyl)methyl]-sulfinyl-1*H*-benzimidazole (omeprazole)"].[19] A 2000 publication gave an X-ray ORTEP drawing of omeprazole as a dimer consisting of the (*R*)- and (*S*)-enantiomers of the 6-methoxy tautomer.[20]

The tautomerism of omeprazole in solution was established by ^{1}H- and ^{13}C NMR spectroscopy: K_T=0.59 in THF at 195K. The 6-methoxy was found to be more stable than the 5-methoxy tautomer by 0.31kcal/mol (ratio of 63:37 in favor of the 6-methoxy).[18] A theoretical calculation of the absolute shieldings (GIAO/DFT/6-311G**) of the tautomers in the gas phase was also reported.[18] The 5-methoxy tautomer was found to be only slightly more stable

TABLE 6. Relative energies (ΔE°), zero point corrected relative energy (ΔE^{0}_{ZPE}), relative enthalpy (ΔH°), and Gibbs' free energy (ΔG^{0}_{298}, at $T = 298$ K), of the minima conformations of the 6-methoxy and 5-methoxy tautomers of omeprazole, calculated at B3LYP/6–311G(d,p) (in kcal/mol)

	ΔE°	ΔE^{0}_{ZPE}	ΔH°	ΔG^{0}_{298}
6-Methoxy	0.00	0.00	0.00	0.00
5-Methoxy	0.16	0.02	0.09	−0.32

than the 6-methoxy tautomer, ΔE = 0.07kcal/mol. A recent ^{13}C- and ^{15}N NMR study of omeprazole in the solid state showed that omeprazole consists uniquely of the 6-methoxy tautomer.[17] A theoretical study of the conformational space of omeprazole by semiempirical, ab initio and DFT methods found that the 6-methoxy tautomer was more stable than the 5-methoxy tautomer, by 0.07kcal/mol (at B3LYP/TZ2P).[16]

In 2001 and 2002, aaiPharma, Inc. received U.S. patent protection over the pharmaceutically active compounds of the benzimidazole family, including omeprazole.[40–47] The patents described the complex nature of this family of compounds. These patents claim, inter alia, that the 5-methoxy- and the 6-methoxy-1*H*-benzimidazole derivatives are present in the solid state, and their ratios vary with the method of manufacture. A method of preparing the pure 6-methoxy-1*H*-benzimidazole tautomer was also claimed.

The results of the relative energies ΔE°, the zero point corrected relative energy ΔE^{0}_{ZPE}, the relative enthalpy ΔH°, and the Gibbs' free energy ΔG^{0}_{298} (at T = 298 K), of the global minima conformations of the 6-methoxy and the 5-methoxy tautomers of (*S*)-omeprazole, calculated at B3LYP/6-311G(d,p), are given in Table 6.

An examination of the Gibbs' free energies ΔG^{0}_{298} shows that the 5-methoxy tautomer of (*S*)-omeprazole is 0.32kcal/mol more stable than the 6-methoxy tautomer. This result is consistent with previous results of the theoretical calculations of the absolute shieldings (GIAO/DFT/6-311G**).[18] A consideration of the corresponding relative energies ΔE° shows that the 6-methoxy tautomer of (*S*)-omeprazole is 0.16kcal/mol more stable than the 5-methoxy tautomer. This result closely resembles previous results of theoretical calculations at B3LYP/TZ2P.[16]

The racemization barrier via the pyramidal inversion mechanism of the 6-methoxy tautomer of (*S*)-omeprazole is 0.27kcal/mol higher than that of the 5-methoxy tautomer (vide supra).

In conclusion, the pyramidal inversion mechanism of (*S*)-omeprazole results in diastereomerization: (*S*,*M*) $\rightleftharpoons$ (*R*,*M*). Taking into account only the chiral element resulting from the chiral center of (*S*)-omeprazole, and ignoring the chiral element resulting from the chiral axis of (*S*)-omeprazole, the pyramidal inversion mechanism results in enantiomerization: (*S*) $\rightleftharpoons$ (*R*).

The energy barrier for the pyramidal inversion mechanism of (*S*)-omeprazole is about 40 kcal/mol at B3LYP/6-311G(d,p). The results indicate that the enantiomers of omeprazole are stable at room temperature, in the gas phase, assuming the pyramidal inversion mechanism. However, racemization occurring via different mechanisms, thermally, photochemically, or involving the chemical environment, with a lower energy barrier, cannot be ruled out. The results obtained for the racemization barrier via the pyramidal inversion mechanism of omeprazole differ from the reported experimental results[15] (about 27 kcal/mol). This discrepancy may suggest an alternative mechanism to the pyramidal inversion mechanism for the racemization of omeprazole, under the reported experimental conditions. The effect of the medium (e.g., solvent), and possible inaccuracies in the experimental results should not be overlooked.

ACKNOWLEDGMENT

The authors thank Dr. P.U. Biedermann (Max-Planck-Institut für Eisenforschung GmbH, Düsseldorf, Germany) for fruitful discussions.

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