

# Ab Initio Calculations on Low-Energy Structures of Perindopril Erbumine

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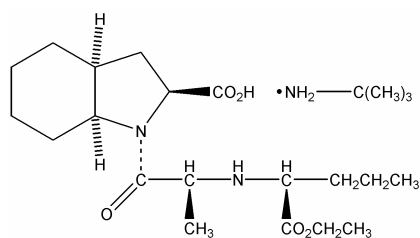
**Abstract:** Four minima on the potential-energy surface of perindopril erbumine, which is the complex of tert-butylamine and perindopril, vastly important from the pharmacological point of view, were located using the B3LYP/6-31G\*\* method and their stabilization energies were estimated at the RI-MP2/aug-cc-pVDZ level of quantum chemical theory. Employing the rigid rotor – harmonic oscillator – ideal gas approximation, the data provided by *ab initio* calculations were combined to obtain the thermodynamic characteristics of the complex formation in different bonding scenarios. The results provide the intrinsic conformational preferences of perindopril erbumine and thus facilitate structural studies of this pro-drug.

**Key-Words:** Perindopril erbumine, perindoprilat, *ab initio*, conformation, complexation, Gibbs energy

## 1 Introduction

Perindopril erbumine, chemically described as (2*S*, 3*αS*, 7*αS*)-1-[(*S*)-N-[(*S*)-1-Carboxybutyl]alanyl]hexahydro-2-indolinecarboxylic acid, 1-ethyl ester, compound with tert-butylamine (1:1), is the complex of tert-butylamine and perindopril (Fig. 1 shows its structural formula). Perindopril, the free acid form of perindopril erbumine, is metabolized *in vivo* by hydrolysis of the ester group to form perindoprilat, the biologically active metabolite which inhibits the angiotensin-converting enzyme (ACE) in human subjects [1]. Perindopril is now a well-established drug that has proven efficacy in a wide range of cardiovascular diseases [2].

Fig. 1. The structural formula of perindopril erbumine.



For the better understanding of the inhibition of ACE by perindopril (and possibly other ACE inhibitors), it is of importance to know the structural and spectroscopical properties of perindopril erbumine. It is an active area of research and such studies are also being carried out in our Institute. To facilitate them, the thermodynamic characteristics of several bonding scenarios of the complex formation between tert-butylamine and perindopril are evaluated on the basis of high-level quantum chemical calculations and thoroughly analyzed here. The following topics are mainly addressed: 1) the

characterization of the mechanisms stabilizing the complex; 2) the description of the magnitudes of the stabilization energy and the Gibbs energy in the respective spatial arrangements; 3) the major structural parameters of the investigated complexes.

## 2 Calculations

Four structural arrangements of perindopril erbumine were generated by using interactive computer graphics (program Insight II (2000), Accelrys Inc., San Diego, California). Two of the arrangements, denoted as **1** and **2** (see Figs. 2 and 3, respectively), contained slightly different hydrogen bonds between the nitrogen atom of tert-butylamine and the carboxylic group of perindopril. The structure **3** featured the hydrogen bond between the carbonyl carbon of the ester group of perindopril and the nitrogen atom of the amine (cf. Fig. 4). Finally the complex **4** (Fig. 5) contained the hydrogen bond between the carboxylic and ester groups of perindopril.

The structures **1** – **4** were then subjected to the full geometrical optimization using the density functional theory (DFT) [3] based method termed MARI-*J* (the multipole accelerated resolution of the identity approximation for Coulomb interaction) [4]; it was applied with the BLYP [5], [6] combination of the DFT functionals and the SVP basis set [7]. The TURBOMOLE V5-7-1 program package [8] was used. The MARI-*J* approach usually predicts reasonably accurate geometries within a fraction of the computational time as compared to the canonical DFT calculation [4]. However, the MARI-*J* structures were used here only as the starting point for the subsequent optimization using the B3LYP (Becke's three parameter exchange [9] and Lee, Yang, Parr [6] correlation)

functional and the standard 6-31G\*\* [10] basis set; the Gaussian 03 suite of quantum chemical programs [11] was employed. Thus located stationary points of the potential-energy surface (PES) of perindopril erbumine were subjected to the calculation of harmonic vibrational frequencies. All frequencies were real for each structure, which confirms that the minima of the PES were found. In addition, the unscaled values of the frequencies were employed to obtain the vibrational-dependent contributions to the thermodynamic characteristics of the system (see below).

For the B3LYP/6-31G\*\* structures, their total energies were calculated using the RI-MP2 (resolution of the identity second order Møller–Plesset perturbation theory) method as implemented [12] in the TURBOMOLE program package and applying the aug-cc-pVDZ (augmented correlation-consistent polarized valence double-zeta) basis set [13]. The total number of basis functions for a given geometry amounted to 1100. The RI-MP2/aug-cc-pVDZ interaction energies were corrected for the basis set superposition error (BSSE) by the counterpoise procedure [14], namely, by performing for each structure the calculations for perindopril and tert-butylamine, respectively, with the ghost atoms in the position corresponding to tert-butylamine and perindopril, respectively. The resulting values,  $\Delta E^{\text{MP2}}$ , are, by definition [10], the sum of the Hartree–Fock,  $\Delta E^{\text{HF}}$ , and the correlation energy,  $\Delta E^{\text{corr}}$ , components ( $\Delta E^{\text{MP2}} = \Delta E^{\text{HF}} + \Delta E^{\text{corr}}$ ).

The thermodynamic characteristics, namely, the standard change in the molar enthalpy, entropy and Gibbs energy of the formation of complexes **1** – **4** at  $T=298$  K (abbreviated as  $\Delta H^0_{298}$ ,  $\Delta S^0_{298}$  and  $\Delta G^0_{298}$  accordingly) were predicted in the rigid rotor – harmonic oscillator – ideal gas approximation [15] employing the  $\Delta E^{\text{MP2}}$  values and the geometrical and vibrational parameters as provided by the B3LYP/6-31G\*\* calculations.

### 3 Results and Discussion

Table 1 summarizes the results of the calculations of the BSSE-corrected interaction energies and the thermodynamic parameters of the perindopril erbumine B3LYP/6-31G\*\* minima **1** – **4**.

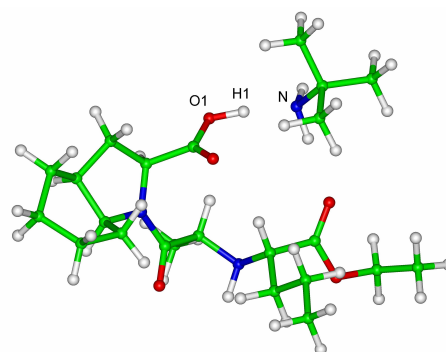
The stabilization energy of the complexes between tert-butylamine and perindopril is governed by a number of factors including hydrogen bonds, London dispersion forces, the changes in the polarity of the subunits upon complexation, and various secondary long-range electrostatic interactions. The relative importance of the respective contributions to the stabilization energy is usually indicated by the amount of the correlation energy

in the total stabilization: the smaller it is, the higher is the role of electrostatic contributions, because they are well-described by the Hartree–Fock interaction energy [16]. This trend is expected to hold also in the case of the structures **1** – **4**. Thus, the most stable structure **1** exhibits one strong hydrogen bond O1–H1...N (see Fig. 2;  $r(\text{N–O1}) = 2.623 \text{ \AA}$ ,  $\alpha(\text{N–H1–O1}) = 166.5^\circ$ ) and the  $\Delta E^{\text{HF}}$  term constitutes ca.  $\frac{2}{3}$  of the total interactions energy of more than  $-90 \text{ kJ/mol}$  (cf. Table 1).

Table 1. Results of the *ab initio* calculations (kJ/mol).

struct.	$\Delta E^{\text{HF}}$	$\Delta E^{\text{MP2}}$	$\Delta H^0_{298}$	$T\Delta S^0_{298}$	$\Delta G^0_{298}$
<b>1</b>	-60.41	-92.09	-86.04	-52.95	-33.09
<b>2</b>	-8.96	-37.70	-30.57	-44.56	+13.99
<b>3</b>	-2.69	-19.28	-13.01	-36.22	+23.21
<b>4</b>	+2.05	-12.55	-5.83	-44.19	+38.36

Fig. 2. The perindopril erbumine optimized structure **1**.



Interestingly, the B3LYP/6-31G\*\* optimization process of **2** yielded the structure with the bifurcated hydrogen bonds (Fig. 3;  $r(\text{N–O1}) = 3.213 \text{ \AA}$ ,  $\alpha(\text{N–H1–O1}) = 52.4^\circ$ ,  $\alpha(\text{N–H3–O1}) = 53.3^\circ$ ;  $r(\text{N–O2}) = 3.170 \text{ \AA}$ ;  $\alpha(\text{N–H2–O2}) = 168.3^\circ$ ). This hydrogen bond network stabilizes the structure much less than the typical hydrogen bond found in **1** (see Table 1). As the majority of the total stabilization of **2** is due to the correlation energy, effects other than the electrostatics play a decisive role in the investigated complex. Among them, the CH/CH interactions [17] (the contacts between alkyl (side)chains bearing C–H bonds) are clearly important in **2**. For example, the distance between the carbon of the methyl group of the alanyl part and the closest carbon of tert-butylamine is  $4.123 \text{ \AA}$  only.

Even less stable is the arrangement **3** featuring the hydrogen bond between the ester group and the amine (see Fig. 3;  $r(\text{N–O2}) = 3.255 \text{ \AA}$ ,  $\alpha(\text{N–H2–O2}) = 165.9^\circ$ ). As was the case for **2**, the correlation energy contribution dominates the interaction energy and there are several significant CH/CH contacts present. For

example, the above-defined intercarbon distance amounts to 4.478 Å in **3**.

Fig. 3. The perindopril erbumine optimized structure **2**.

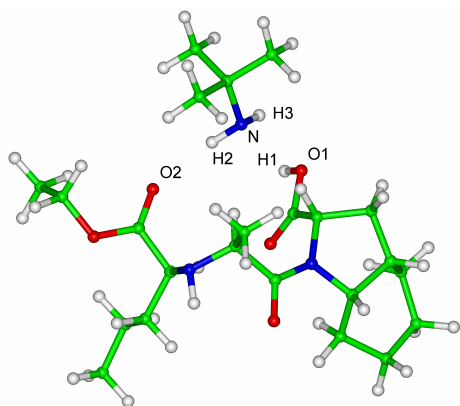
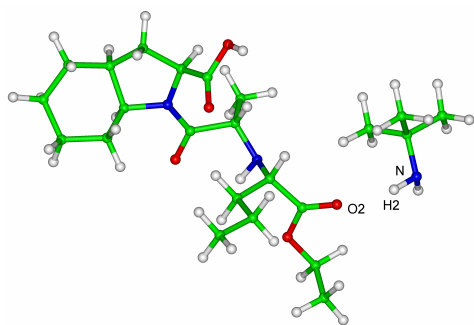
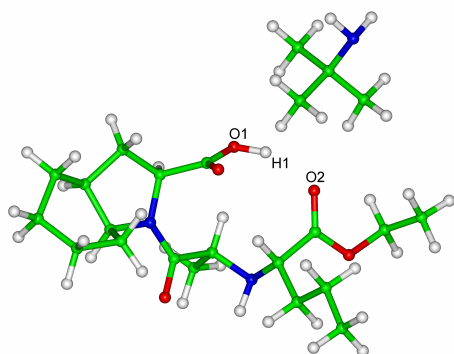


Fig. 4. The perindopril erbumine optimized structure **3**.



The structure **4** is a weak van der Waals complex containing the hydrogen bond within the perindopril part (see Table 1 and Fig. 5;  $r(\text{O1}-\text{O2}) = 2.716 \text{ \AA}$ ,  $\alpha(\text{O1}-\text{H1}-\text{O2}) = 145.2^\circ$ ); its stabilization is due to the correlation energy only.

Fig. 5. The perindopril erbumine optimized structure **4**.



Additional structural details for the perindopril erbumine B3LYP/6-31G\*\* optimized structures **1** – **4**

may be derived from the atomic coordinates, which can be obtained from the author upon request.

The values of the thermodynamic parameters of the structures **1** – **4** follow several trends (cf. Table 1). Thus, the stabilization due to the enthalpy differs considerably (up to one order of magnitude) for the respective complexes, while the differences in the entropic term are much less pronounced. However, the entropic component is crucial for predicting the value of the target quantity, namely,  $\Delta G_{298}^0$ . Importantly, only for the most stable arrangement **1** the negative value of the standard change in the Gibbs energy was obtained (Table 1), implying, within the thermodynamic model adopted, the spontaneous formation of this complex at given conditions.

## 4 Conclusion

The low-energy region of the PES of perindopril erbumine was described using high-level quantum chemical approaches for the first time. Four minima were located using the B3LYP/6-31G\*\* method and the supermolecule RI-MP2/aug-cc-pVDZ calculations of the stabilization energies were performed for them. The results of these calculations were subsequently employed to obtain the thermodynamic characteristics of the structures. The hydrogen-bonding and CH/CH interactions were identified as crucial for the stabilization of perindopril erbumine. The most stable arrangement featured the typical hydrogen bond between the carboxylic group of perindopril and the nitrogen of tert-butylamine, its stabilization energy amounted to  $-92.09 \text{ kJ/mol}$  and the standard change in the Gibbs energy accompanying its formation was predicted to be  $-33.09 \text{ kJ/mol}$ .

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