Insights into the Nature of Intermolecular Interactions in Low-Energy Conformers of Perindopril Erbumine

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Abstract: The DF-SAPT-DFT approach has been employed to study the contributions to the interaction energy between perindopril and tert-butylamine parts of perindopril erbumine in the four structural arrangements, which have been previously described at the RI-MP2/SVP level of quantum chemical theory. The results are important for proper understanding of the conformational polymorphism of perindopril erbumine.

Key-Words: Perindopril erbumine, *ab initio*, conformation, interaction energy, hydrogen bonds, SAPT, DFT.

1 Introduction

Perindopril erbumine is the complex of tert-butylamine with perindopril molecule ((2S, 3αS, 7αS)-1-[(S)-N-[(S)-1-Carboxybutyl]alanyl]hexahydro-2-inidolinecarboxylic acid, 1-ethyl ester, compound with tert-butylamine (1:1), see Fig. 1), which acts as a potent drug [1]. Consequently, its structure and spectroscopical features have been explored by a variety of techniques. In particular, the polymorphism of perindopril erbumine is being studied experimentally in our Institute, and these investigations have been supplemented by high-level quantum chemical calculations [2].

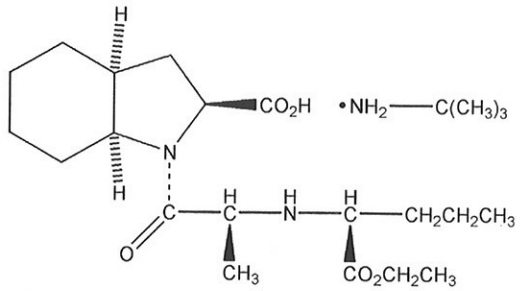

Fig. 1. The structural formula of perindopril erbumine.

Importantly, an extensive search for the low-energy minima on the potential energy hypersurface of perindopril erbumine has been performed (cf. ref. [2] for details). Four conformers have been identified by both the B3LYP/6-31G** and RI-MP2/SVP optimization techniques, and the strength of the interaction between perindopril moiety and tert-butylamine in each of the structures has been evaluated by estimating the stabilization energies, ΔE, at the RI-MP2/aug-cc-pVDZ level of theory [3]. These supermolecular calculations have revealed the differences in stability between the conformers, however, they do not characterize the respective physical mechanisms contributing to the resultant ΔE. Consequently, the symmetry-adapted perturbation-theory treatment is applied here to discern the role played by the first- (electrostatic, exchange), second- (induction, dispersion) and higher-order interaction energies in stabilizing the low-energy forms of perindopril erbumine. These results provide the framework for understanding, modeling and computation of the intermolecular interactions in perindopril erbumine, and can usefully complement the ongoing experimental efforts to describe its conformational polymorphism.

2 Methods

The symmetry-adapted perturbation theory (SAPT) [4] is capable of providing the rigorous decomposition of the interaction energy into its physically meaningful components [5]. It is a double-perturbation theory, where one of the perturbations is the intermolecular interaction investigated, and the other deals with the electron correlation within the interacting subunits. Clearly, for systems as large as perindopril erbumine (74 atoms), the latter treatment needs to be performed using the computationally relatively cheap, density-functional theory (DFT) [6] approach. Here even more efficient technique is adopted, i.e., the combination of the SAPT method with the density-fitting (DF) variant of the DFT representation of monomers, which approximates certain intermediate quantities of calculations through the expansion in an auxiliary basis set [7]. The resulting DF-DFT-SAPT strategy has been succesfully employed to study the interaction in, *e.g.*, sizeable (bio)systems including dimers [8], [9] and even tetramers [10] of DNA nucleobases.

The DF-SAPT-DFT method has been used as implemented in Molpro 2006.1 program package [11]. The PBE0AC asymptotically corrected exchange-correlation functional [7] has been applied together with the standard cc-pVDZ atomic orbitals basis set [12] and the cc-pVTZ auxiliary JK-fitting basis set [13] to describe the monomers, and the adiabatic local density approximation has been adopted in the perturbation treatment of the second-order contributions [14]. The gradient-controlled shift procedure (see ref. [14]) has been employed and the following differences, Δ, between the vertical ionization potential and the energy of the highest molecular orbital have been used (in atomic units): Δ(perindopril)=0.0736, Δ(tert-butylamine) =0.1134.

The total interaction energy, E, has been partitioned into its first-order, $E^{(1)}$, and second-order, $E^{(2)}$, components, and the higher-order contributions to E have been approximated by the $\delta(\mathrm{HF})$ term, which has been obtained by the Hartree–Fock level calculations thoroughly discussed in ref. [7] employing the same basis sets as those used in the DF-DFT procedure. The $E^{(1)}$ value is the sum of the polarization (also called electrostatic or Coulombic), $E^{(1)}_{\mathrm{pol}}$, and exchange, $E^{(1)}_{\mathrm{exch}}$, components, while $E^{(2)}$ collects the induction, E_{I}, and dispersion, E_{D}, contributions. The E_{I} and E_{D} terms contain the second-order induction, $E^{(2)}_{\mathrm{ind}}$, and dispersion, $E^{(2)}_{\mathrm{disp}}$, parts, each of them corrected for the corresponding second-order exchange contributions (i.e., $E^{(2)}_{\mathrm{ind\text{-}exch}}$ and $E^{(2)}_{\mathrm{disp\text{-}exch}}$, respectively). Thus, for four perindopril erbumine structures (*vide infra*), the above-mentioned data are presented together with the results of the resolution-of-the-identity second-order Møller–Plesset perturbation theory (RI-MP2) calculations [15] of the supermolecular interaction energies, ΔE, which have been obtained (TURBOMOLE V5-7-1 [16] program) using the cc-pVDZ atomic orbital and fitting basis sets and employing the counterpoise procedure [17].

3 Results and Discussion

The four RI-MP2/SVP conformers of perindopril erbumine have been characterized in detail in ref. [2]. Briefly, the conformer further referred to as **1** is the most stable one and features fairly strong O–H…N hydrogen bond (H-bond) between the carboxyl group of perindopril and the amino nitrogen, with typical values of the H-bond length and angle (2.62 Å and 168° accordingly). The structure denoted as **2** exhibits a network of bifurcated hydrogen bonds involving the carboxylic carbon and hydrogen of perindopril and the amino nitrogen and the two amino hydrogens of tert-butylamine (*cf.* ref. [2] for the values of geometrical parameters). The conformer which will be designated **3** features rather weak O…H–N hydrogen bond between the carbonyl carbon of the ester group of perindopril and the nitrogen and one of the hydrogens of the amine, with the RI-MP2/SVP H-bond length and angle of 3.26 Å and 166°, respectively. Finally, the structure denoted as **4** is a van der Waals complex containing the intramolecular hydrogen bond within the perindopril moiety (see ref. [2] for details). In what follows, the interaction energies defined in Methods section will be discussed for the conformers **1** – **4**.

3.1 The Carboxyl–Amine H-bonded Conformer

Table 1 presents the absolute and relative values of various types of interaction energies of the structure exhibiting the typical hydrogen bond. The polarization contribution is two times higher than the total interaction energy. However, as expected [8], it is surpassed by the $E^{(1)}_{\mathrm{exch}}$ term, and the first-order energy is destabilizing. The E_{I} and E_{D} results are quite similar and substantially contribute to the overall stabilization. Also the higher-order contributions, at least as estimated from the Hartree–Fock calculations, are significant, constituting almost one half of the E value. Interestingly, the interaction energy obtained from the RI-MP2/cc-pVDZ supermolecular approach differs from its DF-DFT-SAPT/cc-pVDZ counterpart by less than one kcal/mol (see Table 1).

the type of int. energy	magnitude (kJ/mol)	percentage wrt E (%)
$E^{(1)}_{\mathrm{pol}}$	–172.4	200
$E^{(1)}_{\mathrm{exch}}$	228.1	–265
$E^{(1)}$	55.8	–65
$E^{(2)}_{\mathrm{ind}}$	–134.5	156
$E^{(2)}_{\mathrm{ind\text{-}exch}}$	81.5	–95
E_{I}	–53.0	62
$E^{(2)}_{\mathrm{disp}}$	64.2	75
$E^{(2)}_{\mathrm{disp\text{-}exch}}$	–14.7	–17
E_{D}	–49.6	58
$E^{(2)}$	–102.6	119
$\delta(\mathrm{HF})$	–39.3	46
E	–86.1	100
ΔE	–89.9	104

Table 1. Results of *ab initio* calculations on the conformer **1**. See the text for details.

3.2 The Conformer with Bifurcated H-bonds

The interaction energies of the conformer **2** are summarized in Table 2. The most pronounced differences from the results obtained for the more stable structure **1** are the relative unimportance of the induction and of the higher-order contributions, and much higher percentage of the dispersion in **2**. As was the case for **1**, the second-order exchange correction is more important for induction than for dispersion interaction energies. The difference between the supermolecular and SAPT-derived results is again fairly small, but in relative terms the former value is higher by 11% of the DF-DFT-SAPT interaction energy (cf. Table 2).

the type of int. energy	magnitude (kJ/mol)	percentage wrt E (%)
$E_{\mathrm{pol}}^{(1)}$	–46.6	226
$E_{\mathrm{exch}}^{(1)}$	71.9	–350
$E^{(1)}$	25.3	–123
$E_{\mathrm{ind}}^{(2)}$	–23.1	112
$E_{\mathrm{ind\text{-}exch}}^{(2)}$	17.0	–83
E_{I}	–6.1	30
$E_{\mathrm{disp}}^{(2)}$	–40.7	198
$E_{\mathrm{disp\text{-}exch}}^{(2)}$	6.3	–31
E_{D}	–34.4	167
$E^{(2)}$	–40.5	197
$\delta(\mathrm{HF})$	–5.4	26
E	–20.6	100
ΔE	–22.9	111

Table 2. Results of *ab initio* calculations on the conformer **2**. See the text for details.

3.3 The Carbonyl–Amine H-bonded Conformer

The O…H–N hydrogen bond exhibited by the structure **3** is much weaker than both the typical and bifurcated hydrogen bonds found in conformers **1** and **2**, respectively, which involve the contacts between the carboxyl and amino groups. This is predicted by both the total DF-DFT-SAPT and ΔE results (they are almost identical). The interaction energies are collected in Table 3 and show the destabilization brought about by the sum of the first-order terms, which is surpassed mainly by the $E_{\mathrm{disp}}^{(2)}$ contribution constituting 243% of the resultant E value. This is a remarkable example of the importance of the dispersion interaction to the stability of H-bonded systems. It is noted that the importance of the E_{I} and $\delta(\mathrm{HF})$ components is marginal and thus the conformer **3** can be viewed as stabilized by the dispersion energy.

the type of int. energy	magnitude (kJ/mol)	percentage wrt E (%)
$E_{\mathrm{pol}}^{(1)}$	–14.0	127
$E_{\mathrm{exch}}^{(1)}$	30.4	–274
$E^{(1)}$	16.3	–147
$E_{\mathrm{ind}}^{(2)}$	–7.9	72
$E_{\mathrm{ind\text{-}exch}}^{(2)}$	5.6	–51
E_{I}	–2.4	21
$E_{\mathrm{disp}}^{(2)}$	–27.0	243
$E_{\mathrm{disp\text{-}exch}}^{(2)}$	3.0	–27
E_{D}	–24.0	217
$E^{(2)}$	–26.3	237
$\delta(\mathrm{HF})$	–1.1	10
E	–11.1	100
ΔE	–11.5	103

Table 3. Results of *ab initio* calculations on the conformer **3**. See the text for details.

3.4 The Conformer with Intramolecular H-bond

Analogous tendencies as found for **3** hold for the complex **4** as well. In particular, $E_{\mathrm{disp}}^{(2)}$ is the dominating intermolecular interaction. This could be expected on the basis of numerous CH/CH contacts between the tert-butyl group of the amine part and the terminal propyl of perindopril in the RI-MP2/SVP optimized structure [2].

the type of int. energy	magnitude (kJ/mol)	percentage wrt E (%)
$E_{\mathrm{pol}}^{(1)}$	–24.0	244
$E_{\mathrm{exch}}^{(1)}$	46.1	–470
$E^{(1)}$	22.1	–225
$E_{\mathrm{ind}}^{(2)}$	–15.9	162
$E_{\mathrm{ind\text{-}exch}}^{(2)}$	13.1	–133
E_{I}	–2.8	29
$E_{\mathrm{disp}}^{(2)}$	–30.7	313
$E_{\mathrm{disp\text{-}exch}}^{(2)}$	4.5	–46
E_{D}	–26.2	267
$E^{(2)}$	–29.0	295
$\delta(\mathrm{HF})$	–2.9	30
E	–9.8	100
ΔE	–10.8	110

Table 4. Results of *ab initio* calculations on the conformer **4**. See the text for details.

4 Conclusion

Four low-energy structures of perindopril erbumine characterized previously by the RI-MP2/SVP technique [2] have been subjected to the DF-DFT-SAPT/cc-pVDZ treatment to elucidate the role played by the respective types of interactions between the perindopril and tert-butylamine structural units. The corresponding RI-MP2/cc-pVDZ supermolecular interaction energies have been also obtained, which agree very well with their SAPT-based counterparts. Importantly, the structure featuring the O…H–N hydrogen bond has been shown to be predominantly dispersion-bound.

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