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Original article

Molecular structure and stability of perindopril erbumine and perindopril L-arginine complexes

Milan Remko*

Comenius University, Faculty of Pharmacy, Department of Pharmaceutical Chemistry, Odbojarov 10, SK-832 32 Bratislava, Slovakia

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Abstract

The methods of theoretical chemistry have been used to elucidate molecular properties of the antihypertensive, cardiovascular protective and antithrombotic perindopril ((2*S*,3a*S*,7a*S*)-1-[(2*S*)-2-[[(2*S*)-1-ethoxy-1-oxopentan-2-yl]amino]propanoyl]-2,3,3a,4,5,6,7,7a-octahydroindole-2-carboxylic acid). The geometries and energies of various neutral and ionized complexes of perindopril erbumine and perindopril L-arginine have been computed using HF/6-31G(d) and Becke3LYP/6-31G(d) methods. The calculations showed that in both, the isolated state and water solution perindopril erbumine exists as a neutral complex. In the gas-phase perindopril L-arginine both neutral and ionic complexes are, at the HF level of theory, almost equally stable. The B3LYP level of theory slightly favors single proton transfer complex perindopril L-arginine (by about 14 kJ mol^{-1}). In polar solvents like water, the ionized form of perindopril L-arginine becomes much more favored. According to our calculations L-arginine is bound to perindopril more strongly (by about 25 kJ mol^{-1}) than erbumine.

Keywords: ACE inhibitor; Perindopril complexes; *Ab initio* SCF, DFT; Interaction energy; Solvent effect

1. Introduction

Perindopril ((2*S*,3a*S*,7a*S*)-1-[(2*S*)-2-[[(2*S*)-1-ethoxy-1-oxopentan-2-yl]amino]propanoyl]-2,3,3a,4,5,6,7,7a-octahydroindole-2-carboxylic acid) belongs to the class of antihypertensive drugs, acting through the inhibition of angiotensin converting enzyme (ACE), a zinc metalloenzyme involved in the control of blood pressure [1]. Besides this antihypertensive effect, the ACE inhibitors possess some additional properties (such as vasculoprotective and antithrombotic effects) that can play a favorable role in terms of cardiovascular morbility [2–4]. The concentration of an ACE inhibitor in a particular tissue depends on the physicochemical characteristics of its molecule, e.g. molecular size, dissociation constant, lipophilicity, as well as the presence of blood–tissue barriers and the ability of the tissue to transform inactive prodrugs into active form [1]. Perindopril is a prodrug ester that, after oral administration, is converted to the active diacid perindoprilat by hydrolysis [5,6]. Perindopril is orally administered in the form of tablets containing its salts (1:1) with erbumine (*tert*-butylamine) and L-arginine (perindopril erbumine and perindopril L-arginine). The perindopril L-arginine salt is equivalent to perindopril erbumine and more stable, and can be distributed to climatic zones III and IV without the need for specific packaging [7].

Pharmaceutical cocrystals are crystalline molecular complexes that often rely on intermolecular hydrogen bonds formed between neutral molecules of an active pharmaceutical ingredient (API) and other components with well-defined stoichiometries. Cocrystals have been known at least since the late 19th century, but have only recently gained attention as an additional tool in the pharmaceutical field [8]. Cocrystals and pharmaceutical salts are multicomponent crystals that can be distinguished by the location of the proton between an acid and a base [8,9]. Many cocrystals have been prepared through strong hydrogen bonds. However, the reaction between such components can also result in the formation of a salt if the proton is transferred from the acid to the base [10]. Understanding of the structural and functional roles played by salt bridges in

* Tel.: +421 2 50117225; fax: +421 2 50117100.
E-mail address: remko@fpharm.uniba.sk

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pharmaceutical cocrystals cannot be achieved without knowledge of the energetics of this interaction. Most of the clinically useful ACE inhibitors are in pharmaceutical formulations present in the form of cocrystals with Lewis bases and acids. To answer the question of how proton transfer affects the stability of individual salts of the ACE inhibitor perindopril we examined molecular structure of two clinically useful dosage forms of API – perindopril erbumine and perindopril L-arginine. Of particular interest are equilibrium geometries and interaction energies of perindopril erbumine and perindopril L-arginine, and how the shape of perindopril is changed upon complexation and/or in water solution.

2. Computational details

Ab initio calculations of the perindopril erbumine and perindopril L-arginine were carried out with the Gaussian 98 computer code [11] at the *ab initio* SCF (HF [12]) and density functional theory (DFT, Becke3LYP [13,14]) levels of theory using the 6-31G(d) basis set [15–17]. The perindopril erbumine and perindopril L-arginine complexes were considered in two sets of neutral and ionic hydrogen bonded complexes (Fig. 1). In order to evaluate the conformational behavior of these systems in solvent, we carried out optimization calculations in the presence of water. The methodology used in this work is centered on two solvation methods, CPCM [18,19] and Onsager [20] models. Since the initial geometry optimizations of the individual species using the much more computationally expensive conductor polarized continuum model (CPCM) did not converge, in further studies we decided to utilize the self-consistent reaction field method using the Onsager solvent reaction field (SCRF) model. This model has been implemented and successfully used by Wong et al. [21–24].

The interaction energy, ΔE, for the reaction of an acid perindopril (P) with Lewis bases (LB) erbumine and L-arginine is given by the following equation:

$$\Delta E = E[\mathrm{P}\cdots\mathrm{LB}] - \{E[\mathrm{P}] + E[\mathrm{LB}]\} \quad (1)$$

where E[P] and E[LB] are the energies of the perindopril and Lewis base molecules, respectively, and E[P···LB] is the energy of the complex. Basis set superposition error (BSSE) was corrected following Boys and Bernardi [25]. The structures of all gas-phase species were fully optimized at the HF/6-31G(d) and Becke3LYP/6-31G(d) levels of theory without any geometrical constraint. It has been shown [26] that the density functional theory method yields binding energies and geometries of hydrogen bonded complexes, which compare favorably with the corresponding results obtained using high level, *ab initio*, coupled-cluster method. Hence, DFT is suitable as an alternative to traditional *ab initio* methods for studying larger hydrogen bonded systems. In order to check the correctness of the B3LYP calculated relative energies using the double-ζ basis set, we also performed single-point calculations of the perindopril species, using the basis set of the triple-ζ quality (B3LYP/6-31++G(d,p) level of theory) implemented in the Gaussian 98 package of computer codes [11]. The structures of all condensed phase (SCRF) species were fully optimized without any geometrical constraint at the HF/6-31G(d) level of theory.

The calculations of the macroscopic pK_a of perindopril, arginine and erbumine were performed using the program SPARC [27]. The computer program SPARC, developed by Carreira et al. [28–30], uses computational algorithms based on fundamental chemical structure theory to estimate a variety of chemical reactivity parameters (such as ionization pK_a, kinetics, heat of vaporization, boiling point, diffusion coefficient…). SPARC costs the user only a few minutes of computer time and provides greater accuracy than is possible with other conventional methods [30].

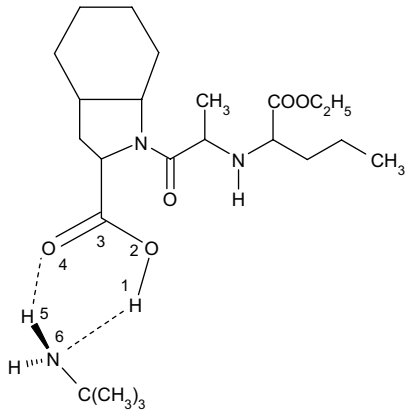
3. Results and discussion

3.1. Geometry

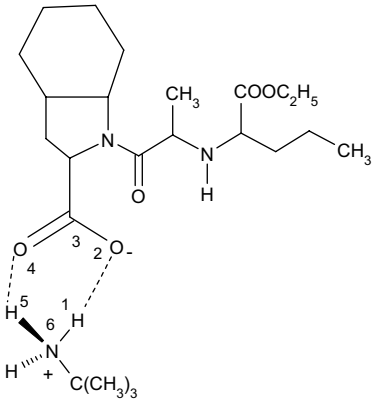
Initial conformations to use in the calculations of the perindopril salts studied were constructed by means of the Gauss View graphical interface of Gaussian. The starting conformation of perindopril was set to the all-*S* absolute configuration. This conformation was taken as it was confirmed by crystallographic studies and stereospecific synthesis of the biologically active perindoprilate [5]. Arginine was taken in the more stable L-form. The complex perindopril erbumine is considered to exist in three stable conformations: one neutral hydrogen bonded complex and two complexes involving charged (ionic) hydrogen bonds (Fig. 1). The two ionic hydrogen bonded complexes of the perindopril erbumine system differ by the position of the *tert*-butyl group of the erbumine with respect to the perhydroindole ring of the perindopril (*cis* or *trans* orientation). Perindopril L-arginine system was considered in two forms. One is the complex stabilized by neutral hydrogen bond between the carboxyl group of perindopril and guanidine moiety of L-arginine. A second complex studied involves ionic guanidinium–carboxylate interaction (Fig. 1). The Cartesian coordinates (Å) of all gas-phase perindopril arginine and perindopril erbumine species investigated, optimized at the B3LYP/6-31G(d) level of theory, are given in Table A of the electronic Supporting information. For an illustration of the geometric structure of these complexes the optimized systems are shown in Fig. 2.

3.1.1. Gas phase

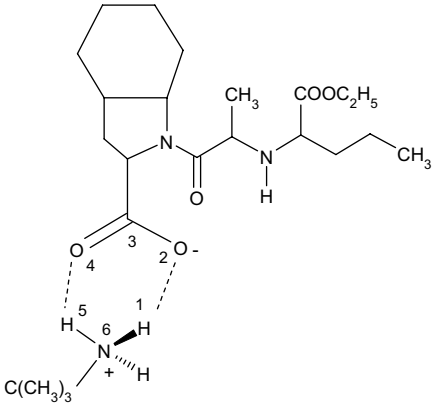
Important geometric parameters of the hydrogen bonded moieties of the complexes investigated are given in Table 1. The following trends are apparent. (i) The calculated rotamer around proline in perindopril is *trans* (C–N–C=O dihedral angle). This orientation of this group is also preserved in the complexes of perindopril with erbumine and arginine. (ii) The conformation of the proline moiety of the perhydroindole ring is an envelope. (iii) The carboxyl group of perindopril and the proline part of drug are in mutual anti-clinal conformation (dihedral angle Φ[N–C–C(3)–O(4)], Table 1). (iv) The methyl group of alanine is perpendicularly oriented to the amide plane and parallel to the ester group. (v) The alkyl chains



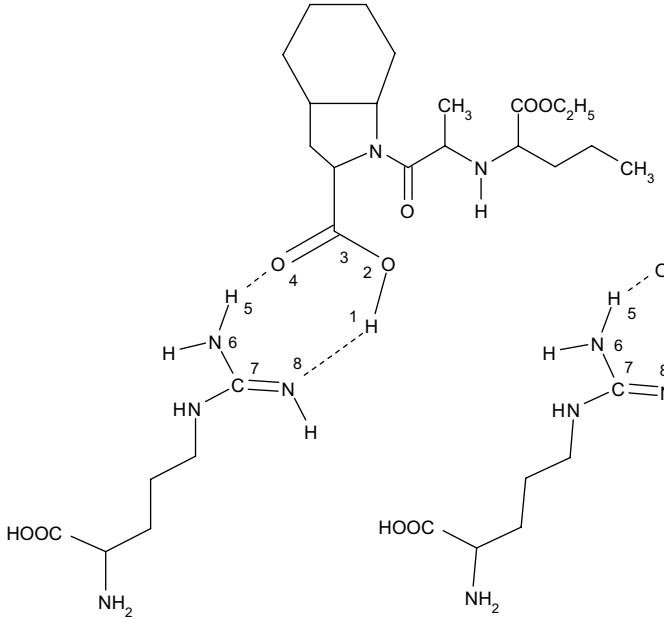
Perindopril erbumine, neutral complex I



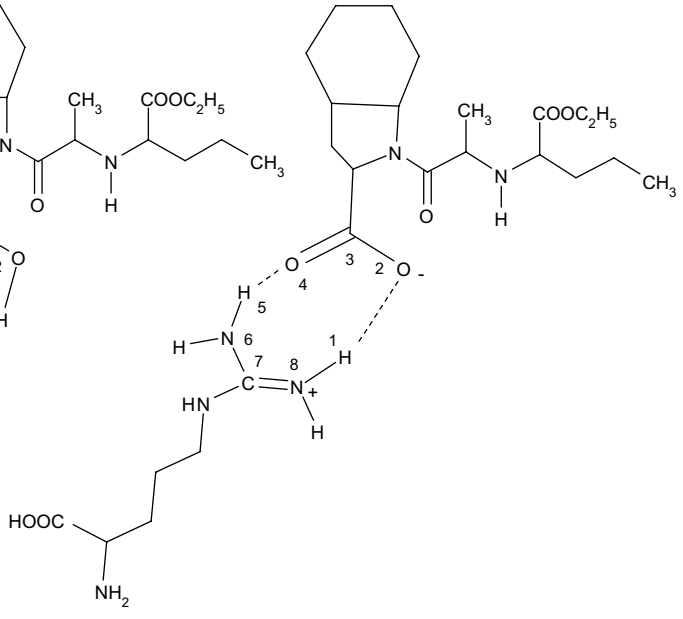
Perindopril erbumine, ionized complex IIa



Perindopril erbumine, ionized complex IIb



Perindopril arginine, neutral complex III



Perindopril arginine, ionized complex IV

Fig. 1. Structure and numbering of atoms of the perindopril erbumine and perindopril L-arginine complexes.

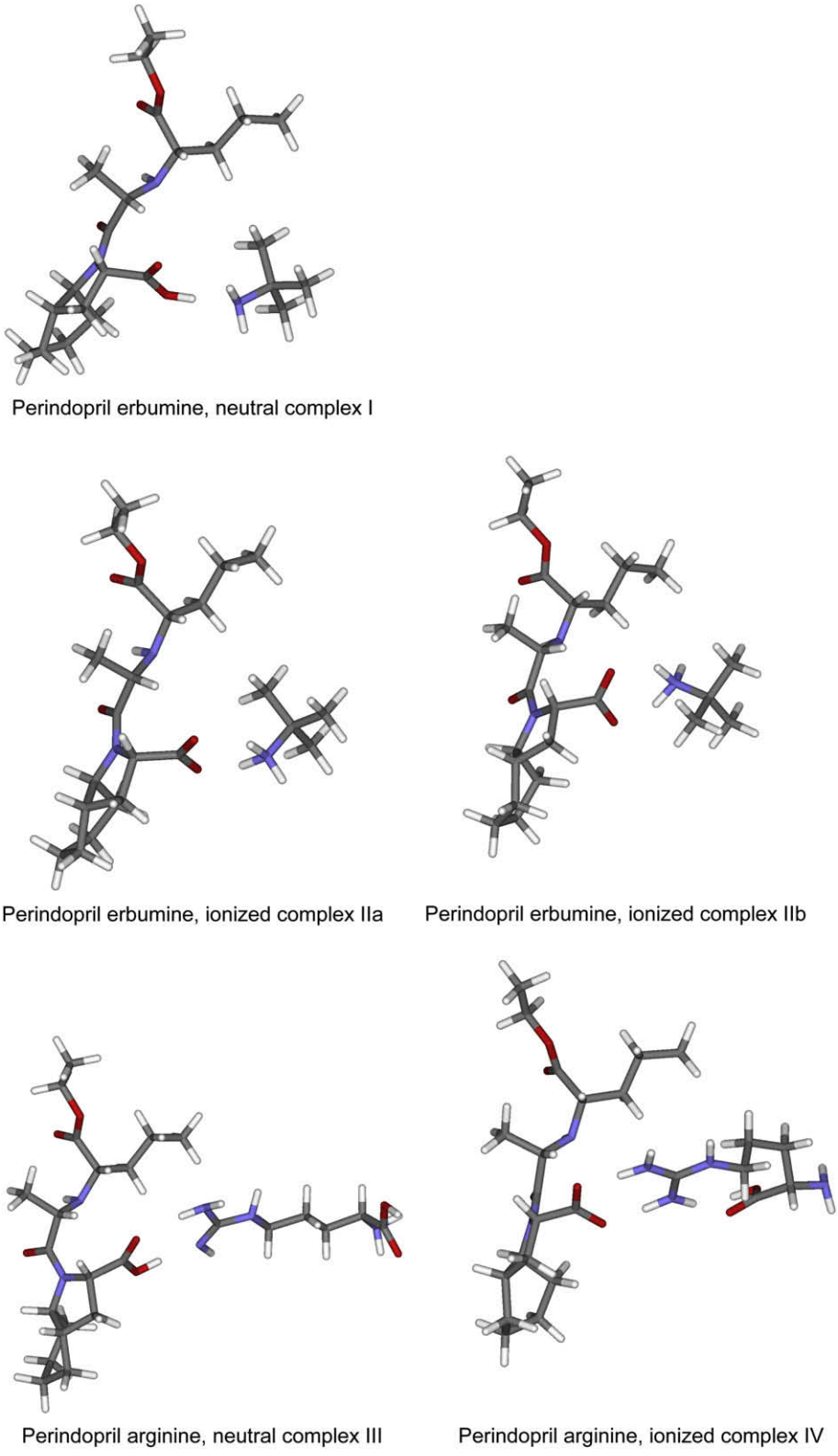


Fig. 2. Lowest energy structures of the perindopril erbumine and perindopril arginine complexes.

exist in fully extended conformation. (vi) Single proton transfer between electronegative atoms oxygen and nitrogen of the perindopril erbumine and perindopril arginine systems requires heavy atom reorganization (Table 1). This structural arrangement of perindopril is also observed in the solvated systems.

The nature of the perindopril erbumine and perindopril arginine interaction may be explained on the basis of the

Table 1
HF/6-31G(d) optimized geometry of the hydrogen bonded moiety in the perindopril erbumine and perindopril L-arginine complexes

Parameter[a]	Perindopril erbumine						Perindopril L-arginine			
	Neutral complex		Ionic complex 1		Ionic complex 2		Neutral complex		Ionic complex	
	Gas	Water	Gas	Water	Gas	Water	Gas	Water	Gas	Water
d[H(1)–O(2)]	0.975	0.977	1.606	1.829	1.683	1.902	0.981	0.986	1.701	1.837
d[H(1)–N(8)]							1.810	1.778	1.029	1.017
d[H(1)–N(6)]	1.853	1.847	1.055	1.027	1.042	1.022				
d[O(2)–C(3)]	1.308	1.309	1.249	1.238	1.244	1.237	1.298	1.298	1.235	1.233
d[C(3)–O(4)]	1.196	1.195	1.236	1.242	1.242	1.245	1.201	1.200	1.241	1.239
d[O(4)–H(5)]	2.689	2.681	1.943	1.790	1.831	1.745	2.060	2.087	1.704	1.770
d[H(5)–N(6)]	1.005	1.005	1.019	1.030	1.027	1.034	1.002	1.001	1.031	1.021
d[N(6)–C(7)]							1.369	1.367	1.320	1.327
d[C(7)–N(8)]							1.274	1.279	1.309	1.313
Θ[C(3)–O(2)–H(1)]	110.2	110.1	104.8	105.5	105.6	106.4	111.9	111.9	119.7	118.0
Θ[O(2)–H(1)–N(8)]							175.7	174.1	176.7	173.7
Θ[O(2)–H(1)–N(6)]	172.5	171.8	154.7	140.7	147.4	135.5				
Θ[H(1)–N(8)–C(7)]							128.3	128.1	119.3	119.5
Θ[O(2)–C(3)–O(4)]	124.3	124.4	126.0	126.8	126.1	126.7	124.7	125.0	127.0	127.3
Θ[C(3)–O(4)–H(5)]	104.6	104.5	106.6	106.0	105.6	105.5	125.0	124.5	114.8	114.5
Θ[O(4)–H(5)–N(6)]	114.2	114.0	130.0	142.4	137.5	147.2	170.9	168.6	179.9	172.0
Φ[O(2)–H(1)–N(8)–C(7)]							−137.6	−114.4	25.7	−49.7
Φ[C(3)–O(4)–H(5)–N(6)]	−0.2	3.7	3.4	5.8	−6.5	−3.3	−17.6	−22.3	86.4	−102.1
Φ[N–C–C(3)–O(4)]	142.9	140.3	140.6	137.5	133.4	130.9	131.4	128.8	139.4	120.2

[a] Bond lengths in Å, bond angles and dihedral angles in degree.

hydrogen bonded interaction between neutral moieties and/or on the consequence of the ion pair nature of the two intermolecular hydrogen bonds, which are much stronger than those between neutral molecules [31,32]. In the absence of experimental structural data for perindopril and its salts we used for initial calculations neutral molecule of perindopril. This structure was adopted according to the recent X-ray study of structurally closely related ramipril, which in the crystal exists in the neutral form [33]. The relative energies of various perindopril species with respect to the most stable complexes of perindopril are reported in Table 2. Table 2 also presents the relative energies by performing single-point B3LYP calculations with a 6-31++G(d,p) basis set at the B3LYP/6-31G(d) geometries. The B3LYP/6-31G(d) values are close to the B3LYP/6-31++G(d,p) results and do not change the relative stability of individual systems. The B3LYP/6-31++G(d,p) formalism approximates a higher-level calculation with larger basis set. The comparison of the B3LYP/6-31G(d) results with this method shows that density functional theory in combination with the double-ζ quality performs quite well and can be used as a relatively inexpensive alternative for investigations of larger complexes.

In the isolated perindopril erbumine complex (**I**) the absolute minimum is stabilized by intermolecular O–H···N hydrogen bond. Both, HF and DFT methods predict that the neutral complex (**I**) is substantially more stable than the ionic ones (**IIa** and **IIb**). Thus, in the isolated state perindopril erbumine will exist as a neutral complex. The two ionic $O^{-}\cdots{}^{+}H$–N complexes (**IIa** and **IIb**) of perindopril erbumine are approximately equally stable, and the orientation of the *tert*-butyl group of erbumine with respect to the proline moiety does not play any crucial part in the energetic stabilization of ionic complex.

More interesting situation is with the perindopril L-arginine system. Our HF calculations showed that both neutral and ionic complexes are almost equally stable. However, the

Table 2
Relative energy and interaction energy (in kJ mol^{-1}) of the systems studied

No.	System	Relative energy			Interaction energy	
		Gas phase	Solvated system	Gas phase	Δ*E*, HF[a]	Δ*E*, B3LYP[b]
Perindopril erbumine						
I	Neutral complex	0[a]	0[a]	0[b]; 0[c]	−41.7	−67.8
IIa	Ionic complex	46.6	32.5	18.5; 23.7	−487.2	−526.9
IIb	Ionic complex	46.8	30.0	20.7; 24.8	−485.0	−518.5
Perindopril L-arginine						
III	Neutral complex	0	0	0; 0[c]	−65.3	−93.5
IV	Ionic complex	1.7	−18.7	−14.0; −14.7	−426.8	−473.3

[a] HF/6-31G(d)//HF/6-31G(d) method.
[b] B3LYP/6-31G(d)//B3LYP/6-31G(d) method.
[c] B3LYP/6-31++G(d,p)//B3LYP/6-31G(d) method.

B3LYP method prefers the existence of single proton transfer complex of perindopril L-arginine as the most stable one (Table 2). L-Arginine has a guanide group and is the strongest basic amino acid. Experimental spectroscopic studies on gas-phase arginine demonstrate that it exists in a neutral form [34]. Other experiments suggest that protonated dimers of arginine are bound by a salt bridge in the gas phase, and the most stable form of arginine itself is a zwitterion [35]. Calculations predict that, in the absence of other stabilizing forces, the arginine zwitterion is not a stable species in the gas phase [36–38]. Melo et al. [39] have investigated guanidinium–carboxylate interaction at the HF and MP2 levels of the *ab initio* theory. In the solvent-free environment the neutral form of the complex has been found to be more stable than the zwitterionic (ionized) one [39]. Recent DFT calculations indicate that arginine prefers the zwitterionic form when clustered together with at least one other arginine even in the absence of solvent or net charge [40]. The zwitterionic form of arginine can also be stabilized by the presence of counterions and/or water molecules [41,42]. In the complex perindopril L-arginine the ionic hydrogen bonded complex **IV** is, besides strong electrostatic attraction of the negatively charged perindoprilate and the positively charged guanidinium moieties, energetically stabilized via intramolecular hydrogen bond C=O···H–N formed by the carbonyl oxygen atom and the $=NH_2^+$ group of the guanidinium part of arginine.

3.1.2. In water

In order to study the influence of the surrounding medium on the relative stability of the complexes studied we also investigated the environmental effects. The calculations were carried out using the SCRF formalism of Wong et al. [21–24] in combination with the HF/6-31G(d) method. The placing of the isolated molecules into a spherical cavity within a dielectric medium of the Onsager model of solvation does not represent the realistic situation in the biological medium; it seems helpful in revealing the main role of the solvent in intermolecular electrostatic interactions. Water ($\varepsilon = 78.5$) has a remarkable effect on the geometry and stability of the individual complexes studied, especially ionic complexes, Tables 1 and 2. The calculated hydrogen bond geometries of the ionic complexes (Table 1) in H_2O are quite different. The difference in O···H bond lengths is about 0.1–0.2 Å, and the difference in bond angles can be as large as 10°. However, the largest changes upon solvent are observed in the stereochemical arrangement of the salt bridges, especially in the ionized complex of perindopril L-arginine (dihedral angles [O(2)–H(1)–N(8)–C(7)], [C(3)–O(4)–H(5)–N(6)]). The solvent effect causes substantial structural rearrangement of the guanidinium group of arginine (Table 1). Energetic stability of the solvated complexes of perindopril is also considerably changed. However, in the case of the perindopril erbumine complex the solvent effect is not able to reverse the absolute stability of neutral and ionic complexes. Neutral complex of perindopril erbumine is also substantially more stable (by about 30 kJ mol^{-1}) in water solution. A different situation exists with the perindopril L-arginine system. The ionic complex is by 19 kJ mol^{-1} more stable, thus in water the zwitterionic H-bonded complex becomes much more favored.

3.2. Interaction energies

3.2.1. Gas phase

The interaction energies corrected to the basis set superposition error of the complexes are given in Table 2. The correction of the interaction energy for the superposition error (BSSE) determined at the potential minimum does not alter the relative stability order of the complexes studied. At the B3LYP level of theory computed interaction energy is slightly higher. Complexes **I** and **III** pair the neutral perindopril with erbumine and L-arginine. According to our calculations neutral arginine is bound to perindopril more strongly (by about 25 kJ mol^{-1}) than the neutral erbumine. The higher stabilization of the perindopril arginine complex by means of two neutral (O–H···N and N–H···O) hydrogen bonds is mainly responsible for this increase in interaction energy. On the other hand, the neutral complex perindopril erbumine is stabilized by means of just one intermolecular O–H···N hydrogen bond (Table 1).

Single proton transfer from perindopril to erbumine and/or arginine results in the formation of two intermolecular hydrogen bonds (ionized complexes **IIa**, **IIb** and **IV**). The proton transfer in the perindopril erbumine complex is accompanied by the structural rearrangement of proton acceptor erbumine and formation of a second hydrogen bond O(4)···H(5) with the computed length of about 1.8–1.9 Å, Table 1. The binding energy of the gas-phase ionized complexes is very high and varies from −470 to −520 kJ mol^{-1} (B3LYP method), Table 2. Greater interaction energy was found for the ionized complexes **IIa** and **IIb** of perindopril erbumine. The difference in stability of these complexes is very small (around 2 kJ mol^{-1}), but ionized structures (**IIa**, **IIb**) are disfavored by around 20 kJ mol^{-1} (B3LYP calculation) from the most stable neutral complex **I**, and in both gas phase and water solution perindopril erbumine exists in the form of neutral complex **I** (Table 2).

3.2.2. Solution phase

The preference for proton transfer in solution can be deduced from the known pK_a values of the reactants in water. It is generally accepted that reaction of an acid with a base will be expected to form a salt (ionized complex) if $\Delta pK_a = pK_a(\text{base}) - pK_a(\text{acid})$ is greater than 2 or 3 [8]. This criterion is frequently used in pharmaceutical research for selection of appropriate counterions in a salt selection. We used software SPARC to compute the theoretical pK_a values of studied structures in condensed phase (water). The calculated macroscopic pK_a values are listed in Table 3. The computed pK_a values correlate well with the available experimental pK_a values found in the literature. The guanine group of arginine with the computed $pK_a = 13.6$ is a stronger base than erbumine ($pK_a = 10.3$). However, at physiological pH = 7.4 both compounds are completely protonated. Similarly, perindopril is at this pH also completely ionized ($pK_a = 3.0$). For the system perindopril arginine the computed ΔpK_a difference is very

Table 3
The pK_a values of the species investigated (pH = 7.0)

Compound	pK_a, calc		pK_a, exp	
	Acidic function	Basic function	Acidic function	Basic function
Perindopril	3.78	5.33	3.0[a]	5.7[a]
Arginine	1.77	13.62	2.18[b]	13.2[b]
			1.82[c]	12.5[c]
Erbumine		10.37	10.7[d]	

[a] Ref. [43].
[b] Ref. [44].
[c] Ref. [45].
[d] Ref. [46].

high (9.85), indicating the existence of this system in solution in the form of ionized complex (salt). The complex perindopril erbumine has also a ΔpK_a value much greater than 3 ($\Delta pK_a = 6.60$) and falls into salt category. Based on the pK_a values of the separation between perindopril and erbumine (6.60) and perindopril and arginine systems (9.85) and on mixing equimolar quantities in water the concentration of the ionized species will be about 4×10^6 (perindopril erbumine) and 7×10^9 (perindopril arginine), respectively. Therefore the concentration of the ionized species will be about 6 times (perindopril erbumine) and 9 times (perindopril arginine) greater than the concentration of the un-ionized (neutral) species.

Ionic hydrogen bonds in solution have been experimentally investigated using IR continuum absorption [47]. These studies show that many ionized hydrogen bond effects in the gas phase have analogies in solution [32,48]. The favorable existence of an ion pair complex perindopril L-arginine in solution is also supported by our theoretical quantum chemical calculations. On the other hand, the calculated lower stability of the perindopril erbumine complex in water solution in comparison with the isolated system may be partly attributed to solvation effects. It is well known that different base types will not respond the same way to hydrogen bonding and proton transfer with a reference acid [48]. The number of hydrogen bond donors and acceptors in erbumine is much lower (3) than in arginine (13), thus erbumine in comparison with arginine cannot establish proper hydrogen bond interactions.

Due to the experimental difficulties attempts to determine the crystal structure of perindopril erbumine and perindopril L-arginine were until now unsuccessful. The surrounding may bias molecules in the solid state. The so-called packing effect makes the molecules in solid state to exist in local minimum conformation. Thus, the computational methods can calculate geometries, which are not observed in the crystalline state. For both perindopril complexes studied the calculated ΔpK_a value is much greater than 3, indicating the existence of these systems in solution in the form of ionized complexes. pK_a values are also being used to characterize a system to which they do not apply, but despite the problems with using pK_a values to predict the ionization state in crystals, the cutoff values suggested for solution is a useful and accessible method for prediction of extents of proton transfer also in solids [8]. It is therefore probable that in the solid state the molecular structure held together by means of a system of intermolecular hydrogen bonds of the neighboring molecules of the crystal, and/or water coordination may stabilize ionized salt-bridge perindopril arginine and perindopril erbumine complexes. Moreover, in solid state charge separation is increasingly favored by the presence of other charges. Due to this stabilization effect both the erbumine and arginine complexes may be ionized in the solid phase.

4. Conclusions

This theoretical study set out to determine geometries and energies of various neutral and ionized complexes of perindopril erbumine and perindopril L-arginine for which a relatively small amount of structural data exist, considering their pharmacological importance. Using the theoretical methods the following conclusions can be drawn.

1. The overall shape of molecular structure of neutral erbumine and L-arginine complexes of perindopril is stabilized via intermolecular O–H···N hydrogen bonds. The calculations showed that in both, the isolated state and water solution perindopril erbumine exists as a neutral complex.
2. In the gas-phase perindopril L-arginine both neutral and ionic complexes are, at the HF level of theory, almost equally stable. The B3LYP level of theory slightly favors single proton transfer complex perindopril L-arginine (by about 14.0 kJ mol^{-1}).
3. In polar solvents like water, the ionized form of perindopril L-arginine becomes much more favored. According to our calculations L-arginine is bound to perindopril more strongly (by about 25 kJ mol^{-1}) than erbumine.

This work yields quantities that may be inaccessible or complementary to experiments and represents the first quantum mechanical approach in which both the gas-phase and solvated-phase complexations between ACE inhibitor and pharmaceutically useful Lewis bases were evaluated. Such investigations may be, due to the present recognition of the important potential commercial value of generating new crystal forms of drugs, useful in design of new dose forms with improved properties and intellectual property value.

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Appendix. Supporting information

Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.ejmech.2008.03.012.

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