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Crystal and molecular structure of perindopril erbumine salt

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ABSTRACT

The crystal structure of perindopril (2S,3aS,7aS)-1-[(2S)-2-[[(2S)-1-ethoxy-1-oxopentan-2-yl]amino]propanoyl]-2,3,3a,4,5,6,7,7a-octahydroindole-2-carboxylic acid) erbumine salt $C_{23}H_{43}N_3O_5$, angiotensin-converting enzyme inhibitor, was determined from single-crystal X-ray diffraction data. The compound crystallizes in the triclinic, non-centrosymetric space group P1, with unit cell dimensions $a = 6.575(3)$, $b = 12.165(5)$, $c = 16.988(8)$ Å and $\alpha = 97.153(4)$, $\beta = 94.417(4)$, $\gamma = 90.349(4)^\circ$, $Z = 2$. The structure was refined by full matrix least squares methods to $R = 0.037$. In the solid state ionized molecules of perindopril and erbumine are linked together forming a complex via O···HN$^+$ hydrogen bonds between the positively charged amino groups of the erbuminium cations and oxygen atoms of the perindopril carboxylate groups. Intermolecular N—H···O and C—H···O contacts seem to be effective in the stabilization of the structure, resulting in the formation of a three-dimensional network.

The gas-phase structure of perindopril–erbumine complex was optimized by the HF/6-31G(d) and Becke3LYP/6-31G(d) methods. The conformational behavior of this salt in water was examined using the CPCM and Onsager models. In both the gas phase and water solution the perindopril erbumine will exist in prevailing triclinic form.

1. Introduction

Perindopril (2S,3aS,7aS)-1-[(2S)-2-[[(2S)-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 long acting angiotensin-converting enzyme (ACE) inhibitors, which are effective in the treatment and prevention of several medical conditions (such as reducing blood pressure, reversing abnormalities of vascular structure and function in patients with essential hypertension, congestive heart failure, post-myocardial infarction, diabetic nephropathy) [1–4]. Besides antihypertensive effect, ACE inhibitors exhibit also vasculoprotective and antithrombotic activities that play a favorable role in terms of cardiovascular morbidity [5–7]. Perindopril is an acid-ester prodrug, which is deesterified in the liver by esterases. The active form of perindopril—perindoprilat is diacid. Pascard et al. [8] determined configuration and preferential solid-state conformation of perindoprilat, and more recently theoretical calculations of molecular structure and stability of the arginine and erbumine salts of perindopril were also carried out [9]. The physicochemical and pharmacokinetic properties of ACE inhibitors and their active metabolites were also theoretically examined [10]. Perindopril is observed to be chemically unstable and undergoes degradation in dosage forms to form diketopiperazines and diacids [11]. Therefore in the therapeutical praxis perindopril is orally administered in the form of tablets containing physiologically acceptable salts (1:1) with erbumine (tert-butylamine) and L-arginine (perindopril erbumine and perindopril L-arginine).

The existence of different solid forms of perindopril erbumine salts was described in several patents [12–14]. However, a problem associated with various known polymorphic (and pseudopolymorphic) forms of perindopril erbumine is that they can be relatively unstable over an appreciable period of time thereby resulting in the polymorphs (pseudopolymorphs) being difficult to handle and formulate. Many attempts to crystallize perindopril erbumine in order to prepare suitable stable crystals for X-ray analysis were unsuccessful. Thus, the phenomenon of polymorphism (pseudopolymorphism) of perindopril erbumine was investigated only qualitatively using a powder X-ray diffraction pattern comprising characteristic peaks [12–14].

So far only the crystal structure of perindoprilat (pharmacologically active compound) has been known (see SIWBUV refcode in the CSD, ver. 2010), determined in the 1991. Nevertheless, the perindopril plays an important role in drug formulation and its bioavailability. Therefore it can be surprising that three-dimensional structure of so popular substance was unknown so long.

Understanding of the structural and functional roles played by salt bridges in pharmaceutical cocrystals of perindopril cannot be achieved without knowledge of the energetics of this interaction. To answer the question of how proton transfer affects the stability

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of individual salts of ACE inhibitor perindopril we report the structural analysis of triclinic structure of perindopril erbumine. The solid-state structure of perindopril erbumine was examined by X-ray crystallography. Theoretical quantum chemical methods were used for determination of equilibrium geometries in the isolated state and in aqueous solution.

2. Experimental

2.1. X-ray data collection, structure solution and refinement

Crystallization of perindopril erbumine was not an easy task. After several weeks of growth, a few rather big crystals were formed by slow evaporation of water or methanol-ethanol solution at room temperature. The crystals grown from an aqueous solution have the shape of elongated prisms, whereas those crystallized from the methanol–ethanol solution are the shape of needles. Two monocrystals representative for the two observed habits were chosen for the X-ray experiment. The selected crystals turned out to be polymorphic forms of the perindopril erbumine salt. The prismatic one had triclinic P1 symmetry, while the needle-like one had monoclinic $P2_1$ symmetry.

The X-ray diffraction measurement of triclinic structure was performed on KM4CCD diffractometer using graphite-monochromatized Mo Kα radiation (λ = 0.71073 Å) at 293 K. Data reduction was carried out with the CrysAlis software [15]. The structure was solved by direct methods by using the SHELXS-97 program.

Because of the presence of only very weak anomalous scattering atoms, the absolute structure cannot be determined reliably and the Friedel opposite reflections have been merged.

All non-hydrogen atoms were refined anisotropically by full-matrix least-squares based on F^2 using the SHELXL-97 program [16]. All C-bound H-atoms were placed in idealized locations and refined using a riding model, with C—H = 0.97 Å and U_{iso}(-H) = 1.2 U_{eq}(C). The H-atoms attached to nitrogens were located in difference Fourier map and refined with the constraints N—H = 0.86 Å and U_{iso} = 1.2 U_{eq}(N). Hydrogen atoms of the water molecules were not found in $\Delta\rho$ map. In the case of one water molecule oxygen atom (O2w) is disordered with occupancy factors of 0.7 and 0.3. Crystallographic data and experimental details are gathered in Table 1. Figures were drawn using ORTEP3 [17] and MERCURY [18] programs.

Table 1
Crystal data and structure refinement details of triclinic structure of perindopril erbumine.

Empirical formula	$C_{23}H_{43}N_3O_5$
Formula weight	457.60
Radiation	Mo(Kα) = 0.71073 Å
Space group	*P*1
Unit cell	
a (Å)	6.5746 (3)
b (Å)	12.1652 (5)
c (Å)	16.9885 (8)
α (°)	97.153 (4)
β (°)	94.417 (4)
γ (°)	90.349 (4)
Volume (Å^3)	1344.02 (10)
Z	2
Calculated density (g/cm^{-3})	1.131
Absorption coefficient (mm^{-1})	0.081
F (0 0 0)	500
Diffractometer	KM4CCD
Refinement method	Full-matrix least-squares on F^2
Index ranges	$-8 \leqslant h \leqslant 7$ $-15 \leqslant k \leqslant 14$ $-20 \leqslant l \leqslant 20$
Reflections collected	19718
Data/parameters	5244/601
Goodness-of-fit on F^2	0.996
Final *R* indices [$I > 2\sigma(I)$]	*R*1 = 0.0373
wR^2	0.0715
R_{int}	0.0398
$\Delta\rho$ min/max (e Å^{-3})	0.16 and −0.18

Crystallographic data of monoclinic structure were recorded on the Bruker SMART APEXII CCD [19] diffractometer using Mo Kα radiation up to a resolution limit of 1.17 Å. The absorption correction was applied using semi-empirical methods by SADABS program [20]. The structure was solved by direct methods. E-map provided positions for all non-H-atoms. The unit cell was determined using 1848 reflections (*theta min* = 2.18, *theta max* = 17.51). The structure has $P2_1$ symmetry, with the following cell constants: *a* = 12.400(3), *b* = 6.4313(17), *c* = 16.656(4) Å and

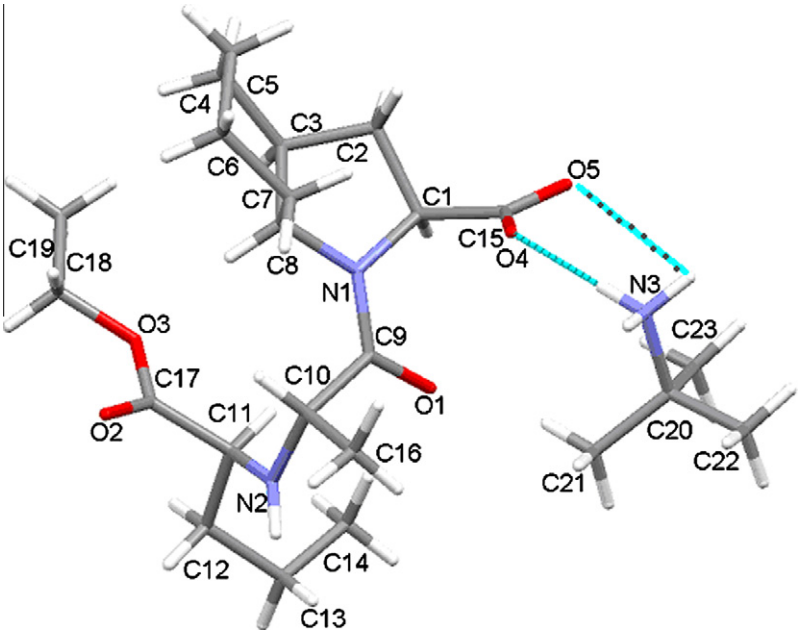

Fig. 1. Example of structural motif in the crystal of triclinic form with numbering of the non-hydrogen atoms (hydrogen bonds are indicated by dashed line).

β = 97.013(3)°. The structure was refined to relatively high R = 0.076 using 970 reflections (R_{int} = 0.0432 for 7118 reflections). The Friedel opposite reflections have been merged. The X-ray structure analysis of monoclinic form revealed, that the asymmetric part of the unit cell contains one independent molecule. The alkyl chains were treated as disordered over two sets of positions using restraints on the isotropic displacement, with the occupancies fixed to 0.60 and 0.40 respectively. Due to poor quality of monoclinic structure, we are not presented structural details here. On the other hand, from computational point of view it can be used as a starting model and therefore we calculated also geometry of this structure.

Crystallographic data of the both complexes of the title salt has been deposited with the Cambridge Crystallographic Data Centre as supplementary publication Nos.: 818604 and 818605.

Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44 1223 336 033; e-mail: deposit@ccdc.cam.ac.uk, www: http://www.ccdc.cam.ac.uk).

2.2. Computational procedure

Ab initio calculations of the perindopril erbumine were carried out with the Gaussian 03 computer code [21] at the *ab initio* SCF (HF [22]) and density functional theory (DFT, Becke3LYP [23–27]) levels of theory using the 6-31G(d) basis set [22]. The perindopril erbumine structures 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 [28,29] and Onsager [30] 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. [31,32]. The structures of all gas-phase species were fully optimized at the HF/6-31G(d) and Becke3-LYP/6-31G(d) levels of theory without any geometrical constraint. The structures of all condensed-phase (SCRF) species were fully optimized without any geometrical constraint at the Becke3LYP/6-31G(d) level of theory.

3. Results and discussion

3.1. Crystal structure analysis

Single-crystal XRD analysis showed that the title compound crystallizes in the non-centrosymmetric $P1$ space group with perindopril anion $(C_{19}H_{32}N_2O_5)^-$ and erbumine cation $(C_4H_9N)^+$, Z = 2. The carboxylate groups of the both perindopril molecules are deprotonated, while amino groups of the erbumine molecules are positively charged. Ions are linked together forming a

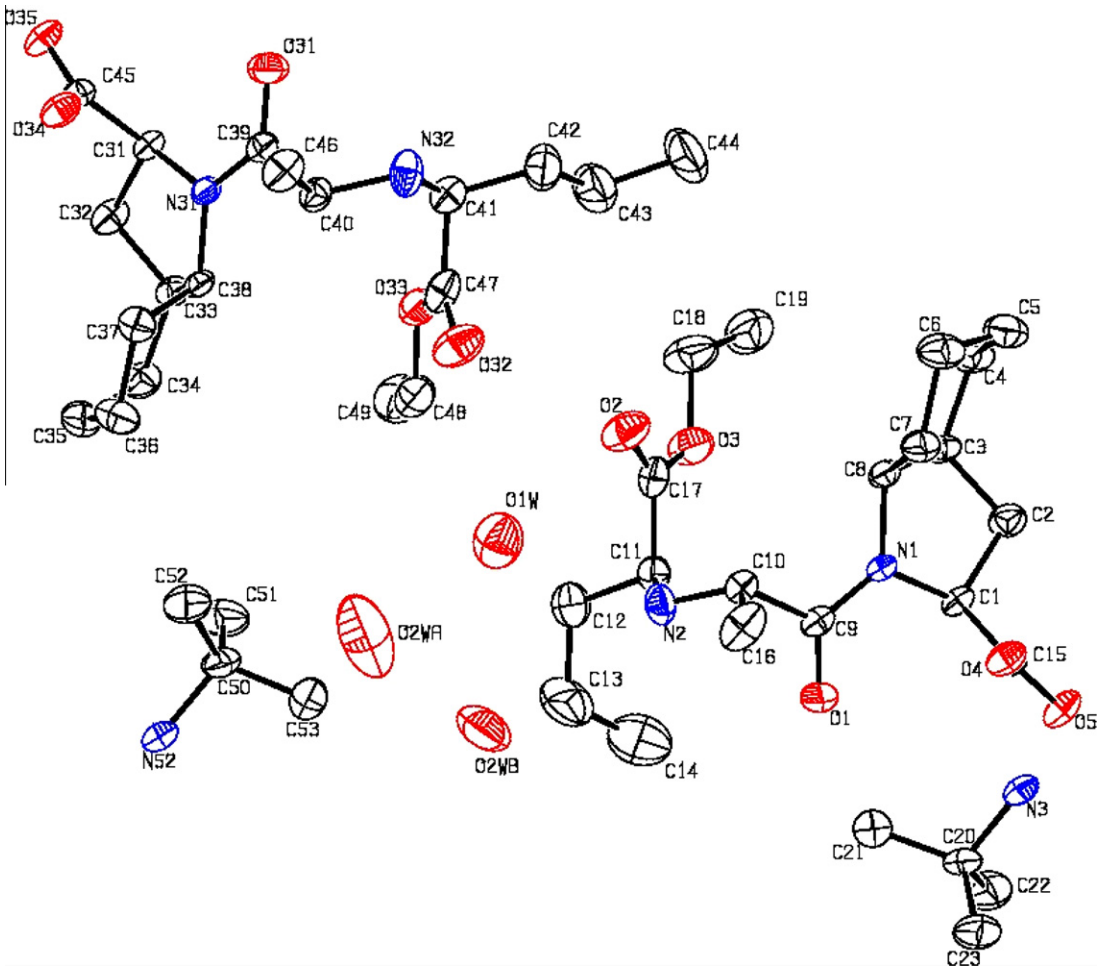

Fig. 2. ORTEP drawing of triclinic structure. Displacement ellipsoids are drawn at the 30% probability level. Hydrogen atoms are omitted for clarity.

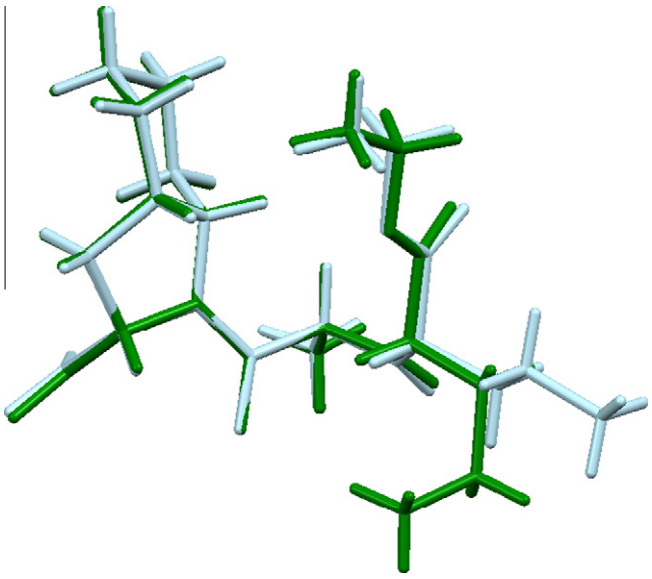

Fig. 3. Superimposition of two conformers of triclinic form (perinropril anions), with respect to the amide plane.

complexes *via* $COO^{-}\cdots H_3N^{+}$ hydrogen bonds. The values of these contacts are within a normal range and comparable in the both triclinic and monoclinic complexes (2.793, 2.814 and 2.791, 2.811 Å, respectively). The example of structure motif for studied object is presented in Fig. 1. It should be mentioned that beside of two independent molecules (erbumine salts of perindopril) two water molecules were also found in the crystal lattice. The O2w oxygen atom of the water molecule is disordered with occupancy parameters of 0.7 and 0.3 for O2wA and O2wB, respectively. The ORTEP plot, with the atom-numbering scheme, is depicted in Fig. 2. The distances between oxygen atoms O1w···O2wA = 2.874(8), O1w···O2wB = 2.982(10) and O2wB···O31 = 2.767(10) Å suggest the creation of hydrogen bond interactions. One of the anionic molecule exhibits the existence of N2—H2···O1w = 2.53 and N2—H2···O2wB = 2.63 Å hydrogen bonds, while at the other one they are made impossible by the presence of methyl aliphatic groups (C14). Both molecules have the same configuration most likely the known S-configuration of the five chiral carbon atoms [33]. It is worth to notice, in spite that two independent molecules in the unit cell are geometrically similar, they have different conformation of one alkyl chain. The ϕ (N2—C11—C12—C13 and N5—C34—C35—C36) torsion angles are −63° and 178° respectively. This difference is clearly visible from superimposition of molecules, with respect to amide plane (Fig. 3). A ring puckering analysis of the proline rings in both perindopril anions shows a slightly deformed envelope conformation with the C3 and C33 atoms in the flap position, with the puckering defined by Q(2) = 0.384(3) and 0.392(3) Å, and $\varphi(2) = 291.5(4)$ and 293.0(4)° for the N1/C1/C2/C3/C8 and N31/C31/C32/C33/C38 rings, respectively. The six-membered C3/C4/C5/C6/C7/C8 and C33/C34/C35/C36/C37/C38 rings adopt a chair conformation with $\varphi(2) = 4(2)$ and 3(2)°, respectively [34]. Moreover, the methyl groups of the alanines are in a direction nearly perpendicular to the amide plane.

Due to the presence of several H-donor and acceptor atoms, hydrogen bonding is the main directing force that rules the solid-state assembly of compound, giving rise to interesting supramolecular network. Perindopril anions and erbuminium cations are joined together by $N—H\cdots O_{(carboxy)}$ hydrogen bonds and shape a 10-membered edge-fused rings with the graph-set motif of $R_4^3(10)$ [35,36] to give an infinite "ladder" running along the [0 1 0] direction. The hydrogen-bonding pattern in the crystal

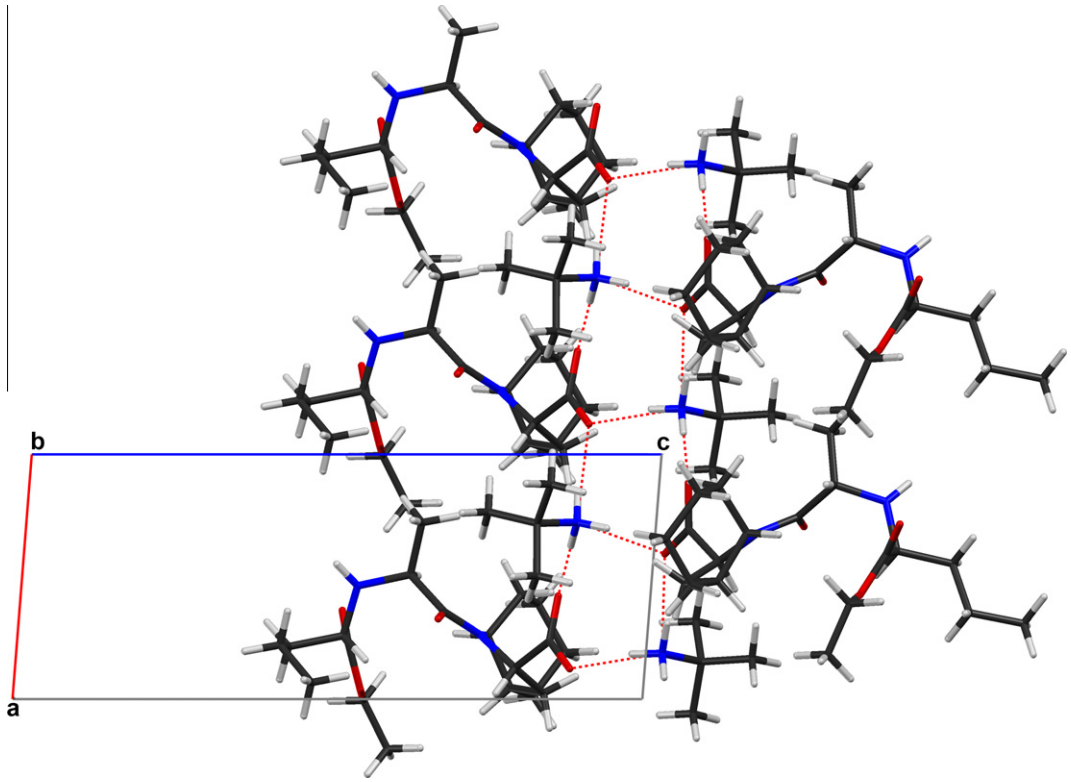

Fig. 4. Crystal packing of triclinic structure, showing hydrogen bonds as dashed lines. Hydrogen bonds N—H···O generate infinite rings $R_4^3(10)$ along [0 1 0] direction. Water molecules were omitted for clarity.

Table 2
Hydrogen bonds geometry.

D—H···A	H···A	D···A	D—H···A
N2—H2···O1w	2.53	3.022	117
N3—H3A···O5 (−1 + *x*, *y*, *z*)	1.94	2.814	168
N3—H3B···O4	1.90	2.793	179
N3—H3C···O35 (*x*, −1 + *y*, 1 + *z*)	1.90	2.779	169
N52—H52A···O35 (*x*, −1 + *y*, *z*)	1.94	2.811	166
N52—H52B···O34 (1 + ×, −1 + *y*, *z*)	1.90	2.791	179
N52—H52C···O5 (*x*, *y*, −1 + *z*)	1.90	2.784	169
C12—H12B···O1w (1 + *x*, *y*, *z*)	2.53	3.499	175
C16—H16B···O3 (−1 + *x*, *y*, *z*)	2.60	3.505	157
C19—H19A···O2 (1 + *x*, *y*, *z*)	2.57	3.513	166
C48—H48B···O2	2.48	3.384	155
O1w···O2wA		2.98	
O1w···O2wB		2.86	

lattice is illustrated in Fig. 4. Furthermore, the compound presents contacts of type C—H···O involving the carbonyl and the methoxy or ethoxy groups. The geometric parameters associated with intra and intermolecular D—H···A interactions are listed in Table 2. The length of these hydrogen bonds ranges from 2.779 to 3.513 Å.

3.2. Theoretical calculations

The structure of the perindopril erbumine salt undergoing restricted thermal motion in a crystal field and measured by single-crystal X-ray diffraction is discussed in previous section. The structure of the isolated perindopril erbumine salt is the definitive structure from the point of view of the *ab initio* theoretical chemist. The initial conformations for use in the *ab initio* calculations were previously analyzed experimental structural data obtained from X-ray crystallography. The important geometric parameters are given in Table 3. The HF and B3LYP DFT bond lengths and bond angles of salt studied fit one another to within about 0.02 Å for bond lengths and about 3° for bond angles. Larger differences (about 5–9°) were observed for dihedral angles. The geometry of the hydrogen bonding moiety $COO^{-}\cdots H_3N^{+}$ is described by both *ab initio* methods by the same way. The initial calculations of the perindopril erbumine were carried out for the complexes involving charged (ionic) hydrogen bonds. In these complexes the proton is transferred from the perindopril to the erbumine (Fig. 1). According to our calculations both, HF and DFT methods suggest that the most stable structure is stabilized via neutral hydrogen bond of the COOH···N type. It means that in the isolated state perindopril erbumine will exist as neutral hydrogen bonded complex.

Important structural parameters of the perindopril erbumine are given in Table 3 together with the experimental X-ray data for its triclinic form and the X-ray data for perindoprilat in the bound state at the angiotensin converting enzyme (ACE) homolog from *Drosophila melanogaster* (AnCE) (PDB file 2X94) [37]. The computed rotamer around the proline carboxyl group in perindopril erbumine is syn-periplanar (dihedral angle Φ[N(1)—C(1)—C(15)—O(4)] is about −30°). The perhydroindole ring of the proline moiety is an envelope. The cyclohexane ring exists in more stable chair conformation. The carboxyl group of perindopril and the proline part of drug are in mutual anti-clinal arrangement. The ethyl of the ester group exists in fully extended

Table 3
Experimental and theoretically optimized relevant bond lengths (Å), bond angles (°) and dihedral angles (°) of the triclinic form of perindopril erbumine.

Parameter	X-ray	HF	DFT	HF-SCRF	X-ray (PDB 2X94) Perindoprilat
d[C(1)—C(15)]	1.519	1.517	1.527	1.529	1.547
d[C(15)—O(4)]	1.232	1.312	1.331	1.241	1.245
d[C(15)—O(5)]	1.272	1.193	1.220	1.243	1.252
d[N(3)—C(20)]	1.492	1.472	1.489	1.498	
d[N(1)—C(9)]	1.336	1.354	1.365	1.347	1.350
d[C(9)—O(1)]	1.228	1.205	1.233	1.207	1.231
d[C(9)—C(10)]	1.529	1.531	1.538	1.534	1.543
d[C(10)—N(2)]	1.449	1.453	1.469	1.456	1.477
d[N(2)—C(11)]	1.441	1.442	1.453	1.441	1.476
d[C(11)—C(17)]	1.511	1.526	1.534	1.525	1.532
d[O(4) · · · N(3)]	2.793	2.827	2.687	2.655	
d[O(5) · · · N(3)]	4.022	3.192	3.026	2.654	
Θ[C(1)—C(15)—O(4)]	120.43	114.25	113.69	115.2	116.9
Θ[C(1)—C(15)—O(5)]	114.29	121.44	121.33	118.2	117.8
Θ[C(1)—O(4)—N(3)]	129.71	103.61	100.63	91.5	
Θ[C(1)—O(5)—N(3)]	66.52	88.83	87.43	91.5	
Θ[N(1)—C(9)—O(1)]	121.98	120.33	120.45	121.4	117.5
Θ[N(1)—C(9)—C(10)]	118.59	118.95	118.38	118.9	124.5
Θ [C(9)—C(10)—N(2)]	112.39	110.00	110.01	110.0	111.0
Θ [C(10)—N(2)—C(11)]	114.86	117.31	117.43	116.7	116.2
Φ[C(1)—C(15)—O(4)—N(3)	147.05	174.38	173.25	171.9	
Φ[C(1)—C(15)—O(5)—N(3)	−163.17	−176.12	−174.93	−171.9	
Φ[N(1)—C(1)—C(15)—O(4)]	−22.32	−30.65	−33.12	−25.8	−25.6
Φ[C(1)—N(1)—C(9)—O(1)	−2.84	−0.39	−0.26	−5.2	2.5
Φ[C(1)—N(1)—C(9)—C(10)	176.49	177.63	178.39	173.8	−179.8
Φ[N(1)—C(9)—C(10)—N(2)]	126.83	131.92	132.38	128.9	153.7
Φ[N(1)—C(9)—C(10)—C(16)]	−111.24	−109.75	−109.44	−112.5	−88.3
Φ[C(9)—C(10)—N(2)—C(11)	−55.71	−63.11	−54.19	−63.3	−67.8
Φ[C(10)—N(2)—C(11)—C(12)	173.01	171.20	173.71	169.5	−173.6
Φ[N(2)—C(11)—C(12)—C(13)]	−63.21	−58.76	−55.34	−58.9	−96.9
Φ[C(11)—C(12)—C(13)—C(14)]	−59.99	−62.12	−59.38	−62.0	−177.8
Φ[C(10)—N(2)—C(11)—C(17)]	−67.30	−67.36	−63.17	−69.4	−52.1
Φ[N(2)—C(11)—C(17)—O(2)]	−31.38	−20.32	−14.75	−26.2	
Φ[N(2)—C(11)—C(17)—O(3)]	148.21	160.88	165.79	155.4	
Φ[C(11)—C(17)—O(3)—C(18)]	177.20	176.56	178.02	177.5	
Φ[C(17)—O(3)—C(18)—C(19)]	167.64	−178.93	−178.69	179.5	

conformation. For propanoyl substituent the syn-clinal conformation is characteristic (dihedral angle Φ [C(11)—C(12)—C(13)—C(14)], Table 3). The geometrical parameters of perindopril in the gas phase and solid state differ only slightly. However, the mutual structural arrangement of the perindopril and erbumine parts of the complex are in diverse environments different (dihedral angles Φ[C(1)—C(15)—O(4)—N(3) and Φ[C(1)—C(15)—O(5)—N(3), Table 3). For this difference the crystal packing forces are obviously responsible.

Based on the preliminary X-ray investigations of the monoclinic form of the perindopril erbumine, where a different alkyl chain conformation could be identified, we also computed the equilibrium structure of this form (Table 3).

For monoclinic structure the optimized structure at both HF and DFT levels of theory corresponds to the salt formed by two symmetrical ionic hydrogen bonds of the $NH_3^+\cdots^-OOC$ type (Table 3). This proton transfer hydrogen bond is also found in water solution. The largest structural differences between these two polymorphic forms were observed for the stereochemical orientation of the flexible hydrophobic side chains (Fig. 5). As it is manifested by dihedral angles [N(2)—C(11)—C(12)—C(13)], [C(11)—C(12)—C(13)—C(14)], [N(2)—C(11)—C(17)—O(2)], [N(2)—C(11)—C(17)—O(3)] and [C(11)—C(17)—O(3)—C(18)] the propanoyl substituent and the ethyl ester group are oriented in the different conformational space of complexes (Table 3).

The environmental effects were investigated using the SCRF formalism of Wong et al. [31,32] in combination with the HF/6-31G(d) method. Water (ε = 78.5) has a remarkable effect on the geometry and stability of the individual complexes studied, especially ionic complexes. The calculations indicate that the most stable structure is in solvated state the complex involving charged (ionic) hydrogen bond. Two hydrogen atoms of the protonated amine group of the erbumine are symmetrically coordinated to two oxygen atoms of the carboxylate moiety of perindopril with the O···H bond lengths of about 1.77 Å. The calculated hydrogen bond geometries of the ionic complex in H_2O are quite different (Table 3). Largest changes upon solvent are observed in the stereochemical arrangement of the ionized complex of the perindopril erbumine (dihedral angles [C(1)—C(15)—O(4)—N(3) and [C(1)—C(15)—O(5)—N(3), respectively). Comparison the structures and relative energies of triclinic and monoclinic perindopril erbumine show that the triclinic polymorph is substantially more stable. The triclinic form is by about 82 kJ/mol and 48 kJ/mol for HF and DFT calculation, respectively, more stable. The same order of stability is also present in water solution. Triclinic perindopril erbumine is also in water more stable by about 26 kJ/mol (HF/SCRF) and 42 kJ/mol (DFT/SCRF), respectively. Thus in both the gas phase and water solution the perindopril erbumine will exist in prevailing triclinic form.

Table 3 also contains structural data for perindoprilat, an active metabolite of perindopril, bound to its enzyme target (PDB code 2X94). An analysis of these X-ray data shows that perindoprilat in this complex exists in biologically active conformation which slightly differs from those observed for perindopril in its complex with erbumine (Table 3). Larger difference was observed for the hydrophobic parts of perindopril (the propanoyl substituent and cyclohexane ring, respectively) (Fig. 6). The cyclohexane ring is in bound perindoprilat in boat conformation and the propanoyl group in more extended form owing to the better alignments of this moiety at the receptor.

4. Conclusions

This study reports both the X-ray structural analysis of a perindopril erbumine and the computationally predicted properties of molecules. The structure crystallizes in the triclinic system, in the space group *P*1. The asymmetric unit of the title compound, $C_{34}H_{30}N_2O_4$, contains two molecules and two water molecules. The crystal packing is stabilized by intermolecular N—H···O and C—H···O hydrogen-bond interactions. Calculations carried out at the HF and DFT levels of theory showed that in the isolated state triclinic form of perindopril erbumine exists as a neutral complex. The optimized structure of monoclinic form at both HF and DFT levels of theory corresponds to the salt formed by two symmetrical ionic hydrogen bonds of the $NH_3^+\cdots$—OOC type. This proton

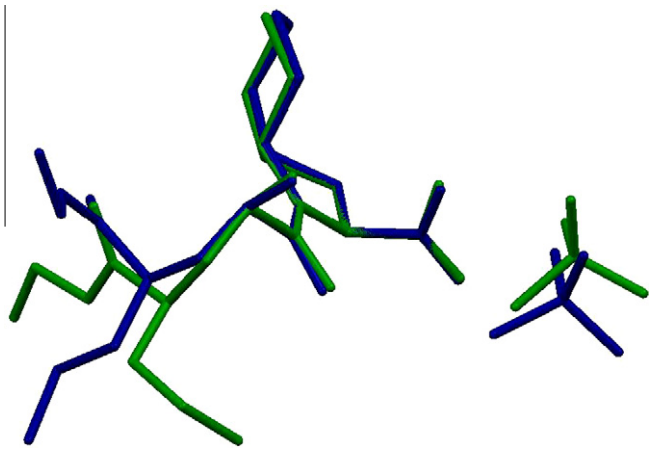

Fig. 5. Molecular superimposition of the Becke3LYP optimized molecular structure of triclinic (green) and monoclinic (blue) forms of perindopril erbumine. For simplicity the hydrogen atoms are omitted. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

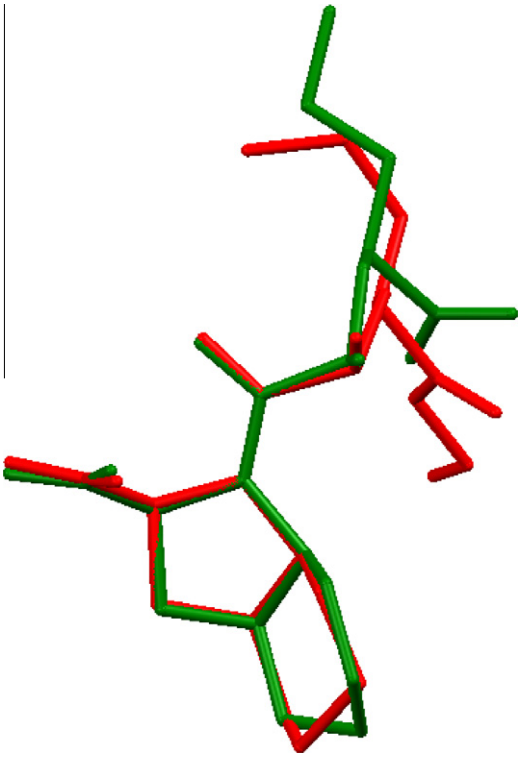

Fig. 6. Molecular superimposition of the X-ray structure of erindoprilat, PDB code 2X94 (green) and DFT optimized perindopril part of its erbumine salt (red). For simplicity the hydrogen atoms are omitted. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

transfer hydrogen bond is also found in water solution. In both the gas phase and water solution the perindopril erbumine will exist in prevailing triclinic form.

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