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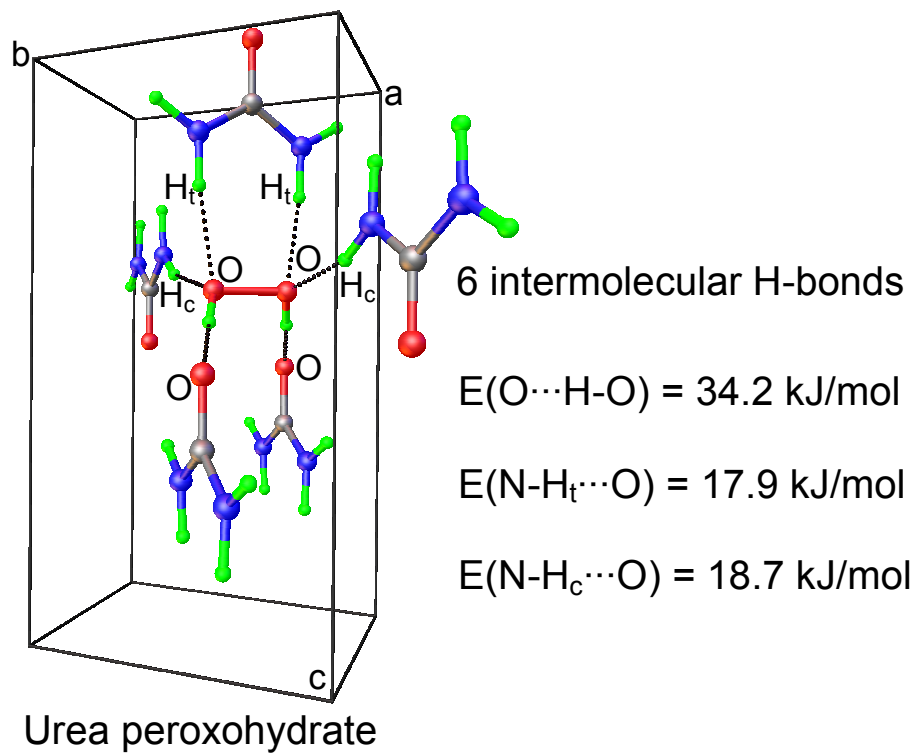


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The Applicability of the Dimeric Heterosynthon Concept to Molecules with Equivalent Binding Sites. A DFT Study of Crystalline Urea-H₂O₂.

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ABSTRACT

The limited applicability of the dimeric heterosynthon concept for a two-component urea-H₂O₂ crystal is reported. It is due to the absence of the relatively short O-H...O bonds, i.e. primary interactions, in the urea-H₂O₂ 1:1 complex. The target O-H...O bonds do exist in *trimeric heterosynthons*, i.e. the urea-2(H₂O₂) and 2(urea)-H₂O₂ complexes. Mutual orientation of the H₂O₂ molecules in the gas-phase complexes differs from the one in the crystalline structure due to existence of additional N-H...O bonds which are absent in the crystal. Implicitly accounting for polar environment does not change the molecule conformations in the considered complexes. It is found that the DFT computations with/without accounting for polar solvent are not sufficient for the deduction of such a heterosynthon. The results of the database analysis should be used for unambiguous identification of the molecules' conformations in the target trimeric heterosynthon. An approach for deducing the trimeric heterosynthon structure for molecules with equivalent binding sites is developed. It includes three steps. (i) Identification of structural motifs formed by the considered molecules in the two-component crystals using database analysis. (ii) Establishing a hierarchy of the intermolecular interactions in the crystals by solid-state DFT followed by Bader analysis of the periodic electronic density. (iii) Evaluation of the structure and relative stability of the trimeric heterosynthons by DFT methods with/without accounting for environmental effects.

Keywords: H-bond pattern in two-component crystals, electron-density features at the bond critical point, primary and secondary interactions, molecular recognition, trimeric heterosynthon

Introduction.

In the context of crystal engineering, and of the formation of pharmaceutical salts and cocrystals in particular, the following question is meaningful. Given the molecular structure of a heterodimer, what is the structure of the two-component crystal, with a 1:1 ratio of its components? A crucial assumption is that the heterodimer is a reasonable approximation to the two-component crystal.¹ The active pharmaceutical ingredients are usually characterized by a single binding site (e.g. an acid or amide group).² Heterodimers, formed by these ingredients and a second component that is a solid under ambient conditions do present a reasonable approximation to so-called *cocrystals*.³ A second-component molecule is often characterized by multiple binding sites.² However, these sites are usually not equivalent. Thus the concept of the primary heterosynthon⁴ comes into play. In contrast to cocrystals, formation of hydrates or peroxohydrates is difficult to predict.⁵ This feature may be due to the presence of the *equivalent* binding sites in water or H₂O₂.

Since H-bonds are the strongest and most specific (directional) interactions, they typically play a dominant role in the crystallization (nucleation and growth) and stability of pharmaceutical solids.^{6,7} H-bonds of different strength usually exist in these crystals.⁸⁻¹⁰ In solution, molecules recognize each other first through primary interactions,⁴ i.e. the strongest H-bonds. The main outcome of this process is the formation of robust heterosynthons. They form two-component crystals using secondary interactions, i.e. moderate or relatively weak H-bonds. The applicability of this scheme to molecules with equivalent binding sites is not straightforward. For example, the structure of the most stable gas-phase urea-H₂O₂ 1:1 complex has no relation to the crystalline state.¹¹ This is due to the absence of relatively short O-H...O bonds,¹² i.e. primary interactions, in the urea-H₂O₂ heterodimer. The target O-H...O bonds do exist in *trimeric heterosynthons*, i.e. the urea-2(H₂O₂) and 2(urea)-H₂O₂ complexes. An approach for deducing the trimeric heterosynthon structure for molecules with equivalent binding sites is developed in the present study. It includes three steps. (i) Identification of structural motifs formed by H₂O₂ and urea in two-component crystals using a database analysis. (ii) Establishing a hierarchy of the intermolecular interactions in the considered crystals by density functional theory with periodic boundary conditions (solid-state DFT) followed by Bader analysis of the crystalline electronic density. (iii) Evaluation of the structure and relative stability of the trimeric heterosynthons in solvents by the DFT method coupled with the polarizable continuum model (PCM) of solvation.

The paper is organized as follows: In Sec. 2 we introduce the methodology of the DFT computations taking into account the environmental effects. Results of the database analysis and numerical computations are given in Sec. 3 and discussed in Sec. 4. The paper is summarized in Sec. 5.

2. Methodology

Different DFT-based approaches with an implicit/explicit account of polar environment are suggested in the literature.¹³⁻¹⁶ According to Refs. 17-28 DFT computations coupled with the PCM model of solvation describe the structure, relative stability and vibrational properties of the H-bonded species in solvents fairly well. The PBE, B3LYP and M06-2X functionals are used in such studies. The B3LYP and PBE are usually employed in theoretical studies of H-bonded systems in the crystalline state.²⁹⁻³⁵ These functionals with a suitable basis set for noncovalent interactions are capable of giving an excellent description of H-bonded systems (see for example Ref. 36). The hydrogen bonds play a predominant structure forming role in the urea-H₂O₂ systems and for this reason it is not necessary to use density functionals that account for dispersion. In the present study the PBE functionals are employed with the all-electron Gaussian-type localized orbital 6-31+G** basis set.³⁷

2.1. The DFT/PCM computations.

The structures and the vibrational spectra of H-bonded complexes in the gas phase and in a polar environment have been computed in the PBE/6-31+G** approximations using Gaussian09.³⁸ The effect of the environment has been taken into account in terms of the CPCM approach (acetonitrile)³⁹ with the radii=UAKS option.

2.2. The solid-state DFT computations.

CRYSTAL09⁴⁰ is used in the present study. The space groups and unit cell parameters of the considered two-component crystal obtained in the neutron diffraction study are fixed, and structural relaxations are limited to the positional parameters of atoms. This approximation yields a reasonable description of different properties of two-component crystals.⁴¹⁻⁴⁵ The atomic positions determined by experiment are used as the starting point in the solid-state DFT computations. Details of the solid-state DFT calculations are given in the supplementary materials.

The optimized geometrical parameters of the crystalline urea-H₂O₂ are used in the PBE/6-31+G** computations of the periodic electronic wave-functions by CRYSTAL98.⁴⁶ The quantum theory of atoms in molecules and crystals (Bader) analysis^{47, 48} of the periodic electron density obtained from the crystalline wave-function is performed with TOPOND.⁴⁹ The calculation methodology is presented elsewhere.^{50, 51} The energy of the particular noncovalent (intermolecular) interaction, E_{int} , is evaluated according to⁵² as

$$E_{int}[\text{kJ/mol}] = 1124 \cdot G_b [\text{atomic units}], \quad (1)$$

where G_b is the positively-defined local electronic kinetic energy density. Equation (1) yields reasonable E_{int} values for molecular crystals with H-bonds, C-H...O and π -stacking contacts etc.⁵³⁻⁵⁵

The enthalpy ($-\Delta H_{\text{HB}}$) of the intermolecular H-bond in liquids, solids and solutions can be estimated via the application of empirical relationship (2)⁵⁶.

$$-\Delta H = 0.134 [R(\text{H}\dots\text{O})]^{-3.05} \quad (2)$$

where the $R(\text{H}\dots\text{O})$ is the H...O distance (nm) and $-\Delta H$ is in kJ/mol. Eq. (2) gives reasonable $-\Delta H$ values for intermolecular H-bonds of moderate strength in polycrystalline amino acids and peptides.⁵⁷

A specific feature of Eqs. (1) and (2) is the possibility to use the G_b and $R(\text{H}\dots\text{O})$ values obtained from experiment (high resolution X-ray, neutron diffraction) or the solid-state DFT computations followed by the Bader analysis of the periodic electronic density.

3. Results.

3.1. Structural motifs in the two-component crystals formed by urea and H_2O_2 .

According to the Cambridge Structural Database (version 5.36, February 2015)⁵⁸ the torsion angle of the H_2O_2 molecule in crystalline adducts varies from 83° ⁵⁹ to 180° .⁶⁰ In most cases the hydrogen peroxide molecule has a skewed geometry (C_2 -symmetry), with torsion angle H-O-O-H ranging within 90 - 120° , not far from the H_2O_2 conformation in the crystalline H_2O_2 (90°)⁶¹ and gas phase (120°).⁶² One H_2O_2 molecule can form up to six H-bonds: 4 hydrogen bonds as acceptor and 2 as donor of protons. To the best of our knowledge the maximum number of hydrogen bonds of hydrogen peroxide molecule is accomplished only in the crystal structure of the urea- H_2O_2 adduct.¹² The H_2O_2 molecule in other crystals participates in one, two or three hydrogen bonds⁶³⁻⁶⁵ as acceptor or doesn't form this kind of H-bonds at all.^{59, 66} On the other hand, due to acidic properties hydrogen peroxide always forms two relatively short and almost linear O-H...X H-bonds (where X = O and N) as a proton donor regardless the nature of the other molecules in the crystalline adduct;^{59,67} these H-bonds play a predominant role in two-component crystal formation.

Thus, the typical features of the H_2O_2 molecule in the crystal structure of crystalline adducts are the following: i) the H_2O_2 molecule has either a planar or skewed conformation with an H-O-O-H torsion angle value above 80° (180° or around 100° , respectively); ii) each H_2O_2 molecule always forms two relatively short and almost linear O-H...X bonds (where X = O and N) as H-donor and therefore these H-bonds can be assigned as primary interactions;⁴ (iii) the H_2O_2 molecules do not interact with each other via H-bonds. For instance, the serine- H_2O_2 adduct reveals the most common case of H_2O_2 structure in two-component crystals, where H_2O_2 conformation is skewed (the H-O-O-H dihedral angle is 109°), and each H_2O_2 molecule forms 2 H-bonds as acceptor and two H-bonds as

donor of protons. The latter are relatively short (the O...O distance < 2.70 Å) and practically linear O-H...O bonds.^{59,64}

The planar conformation with C_{2v} symmetry is typical for urea molecules in two-component crystals similar to that in crystalline urea (Fig. 3a in Ref. 68), for instance in urea-oxalic acid,⁶⁹ urea-barbituric acid,⁷⁰ 4-nitrophenol-urea,⁷¹ urea-acetic acid,⁷² urea-N,N-dimethylformamide,⁷³ urea-imidazolidone,⁷⁴ urea-bis(4-aminobenzoic acid),⁷⁵ urea-salicylic acid,⁷⁶ and urea-succinic acid⁷⁷ solvates. According to the Ref. 78 a search of the Cambridge Database for urea solvates gave 31 structures where the urea oxygen accepts three or more hydrogen bonds from an NH or OH donor and 62 where it accepts one or two H-bonds.

3.2. The pattern of H-bonded interactions in the crystalline urea-H₂O₂.

The crystalline urea-H₂O₂ (solvate) has the orthorhombic space group $Pnca$ with $Z = 4$ and $Z' = 1$.¹² The hydrogen peroxide molecule has a skewed conformation in the crystal structure of urea peroxosolvate with the H-O-O-H dihedral angle equal to 99° .^{12,79} Each H₂O₂ molecule in the solvate interacts with 5 adjacent urea molecules by two O-H...O and four O...H-N bonds (Fig. 1). The O-H...O bonds are relatively short (the O...O distance is 2.616 Å) and practically linear (the O-H...O angle equal to 175 deg.). Each urea molecule has 5 neighboring H₂O₂ molecules linked through 6 hydrogen bonds (Fig. 2).

Geometrical parameters of the H-bonded fragments in the solvate computed using solid-state DFT methods are in reasonable agreement with the available experimental data (Table S1). The H-bond energies in the crystalline urea-H₂O₂, evaluated using Eq. (1), are given in Table 1. The O-H...O bonds are relatively strong (~ 47 kJ/mol).⁸⁰ This value is comparable with the H-bond energy of ~ 43 kJ/mol⁶⁷ between the OH group of H₂O₂ and the CO₂- group of serine in the serine-H₂O₂ crystal. The N-H...O bonds are of moderate strength (~ 19 kJ/mol). The latter energy agrees with the experimental value (21.9 kJ/mol) obtained from the sublimation energy of crystalline urea.⁸¹ We note that the electron-density features at the H...X bond critical point (Table 1) are comparable to both the experimental and theoretical electron density parameters in crystalline urea⁸². The H-bond enthalpies in the solvate, evaluated using Eq. (2), are given in Table 1. In accord with Ref. 45, Eq. (2) gives enthalpy values which are usually lower those obtained by Eq. (1). It should be noted, that the O-H...O bond energy, evaluated using the Lippincott and Schroeder model,⁸³ equals to ~ 30 kJ/mol.

The cumulative characteristic of noncovalent interactions in solids is the sublimation enthalpy ΔH_{sub} . Its absolute value extrapolated to 0 K corresponds to the crystal lattice energy, E_{latt} . The experimental ΔH_{sub} value of crystalline urea is ~ -96 kJ/mol.⁸⁴ The ΔH_{sub} value of crystalline H₂O₂

was estimated from the heats of fusion and vaporization⁸⁵ and equals to ~ -65 kJ/mol. The calculation methodology of E_{latt} in the two-component crystals is presented elsewhere⁸ and shortly described in the supporting information. The calculated E_{latt} value equals to 171 kJ/mol. It is larger than the sum of the absolute sublimation energies of the crystalline urea and H_2O_2 (~ 161 kJ/mol) in accord with the simple thermodynamic arguments of Kuleshova et al.⁸⁶ In our recent studies^{8,87} the E_{latt} value of the two-component crystals (cocrystals and solvates) was always essentially lower than the sum of the absolute sublimation enthalpies of their pure components. The relative number of H-bonds and their strength were found to be larger in the crystalline urea H_2O_2 than in its pure components. Therefore, the E_{latt} value of the crystalline urea H_2O_2 is expected to be larger the sum of the E_{latt} values of crystalline urea and H_2O_2 .

3.3. The structure and relative stability of the trimeric heterosynthons

A theoretical study of the urea- H_2O_2 1:1 complexes¹¹ was used as a starting point. The gas-phase global-minimum structure (Fig. 3I) has no relation to the crystalline state. According to the DFT-PCM computations (Table S2), heterodimer (II) corresponds to the local-minimum structure in acetonitrile. The global minimum structure in this solvent (Fig. 3II) has no clear-cut correlation to the crystalline state. This is due to the absence of the two relatively short O-H...O bonds, i.e. primary interactions, in heterodimers (I) and (II) (Fig. 3). To overcome this deficiency, two model complexes, urea-2(H_2O_2) and 2(urea)- H_2O_2 , were extracted from the crystalline urea- H_2O_2 (Figs. 4III and 5III). A specific feature of these “crystalline” structures is the existence of the two relatively short O-H...O bonds and the absence of interactions between adjacent urea or H_2O_2 molecules.

The gas-phase global-minimum structure of urea-2(H_2O_2) has relatively short (~ 2.60 Å) practically linear O-H...O bonds (Fig. 4I). The H-O-O-H torsion angle value is around 99° . Mutual orientation of the H_2O_2 molecules differs from the one in the “crystalline” structure (Fig. 4III) due to the existence of additional N-H...O bonds which are absent in the crystal. A lot of different local-minimum structures resulting from the geometry optimizations with different starting structures are localized (Table S3 and Fig. S2). The account of the polar aprotic solvent changes the relative stability of the structures, see Table S3. The global-minimum structure in acetonitrile is characterized by only one O-H...O bond (Fig. 4II). However, the H_2O_2 molecules in this structure interact with each other. Such an interaction is absent in the crystalline state (Figs. 1 and 2).

The gas-phase global-minimum structure of 2(urea)- H_2O_2 (Fig. 5I) has relatively short (~ 2.70 Å) practically linear O-H...O bonds. The H-O-O-H torsion angle value is around 107° . Mutual orientation of the urea molecules differs from the one in the “crystalline” structure due to existence of the additional N-H...O bonds which are absent in the crystal. A lot of different local-minimum

structures resulting from the geometry optimizations with different starting structures are localized (Table S4 and Fig. S3). Structures (a) - (e) are characterized by relatively short O-H...O bonds and the H-O-O-H torsion angle value varying from 176 to 91°. Structures (f) - (i) have only one O-H...O bond and are characterized by the interaction of the urea molecules with each other. The account of the polar aprotic solvent changes relative stability of the structures, see Table S4. The global-minimum structure in acetonitrile has relatively short (~ 2.60 Å) practically linear O-H...O bonds (Fig. 4II). Mutual orientation of the urea molecules differs from the one in the “crystalline” structure due to existence of additional N-H...O bonds.

We conclude that in the case of molecules with equivalent binding sites the concept of a *trimeric heterosynthon* has to be explored.⁸⁸ DFT computations with/without accounting for the environmental effects are not sufficient for the deduction of such a heterosynthon. The results of the database analysis should be used for unambiguous identification of the molecules conformations in the target trimeric heterosynthon.

4. Discussion

Crystalline urea-H₂O₂ is a tractable model of the H-bonded network formed by molecules with multiple binding sites in the condensed phase. It is a widely used commercial source of active oxygen which is produced on an industrial scale of several hundred tons by simple recrystallization of urea from aqueous hydrogen peroxide solution.⁸⁹ On the other hand, urea and H₂O₂ molecules play an important role in metabolism.⁹⁰⁻⁹² Therefore, investigation of their interaction with each other and with other molecules, including studies of H-bonding, is relevant.⁹³ For example, the urea molecule contains a carbonyl group and amino groups available for H-bond formation with biomolecules and acts as an effective denaturant of proteins and nucleic acids.^{94, 95} Many attempts to understand the urea-induced protein and nucleic acid denaturation mechanism were done by different methods.⁹⁶⁻¹⁰¹ Recent research was directed to urea's ability to form two-component crystals with organic substances for crystal engineering purposes.⁷⁸

The approach developed in the present study is similar to the one suggested very recently in Ref. 4. A new feature of our approach is the use of DFT methods with/without accounting for the environmental effects for evaluation of the structure of the dimeric/trimeric heterosynthon. The database search is a key point of both approaches. According to our computations, the DFT methods cannot predict the structure of the most stable trimeric heterosynthon without some hints from the database analysis.

The structure of crystalline urea-H₂O₂ is determined solely by the intermolecular H-bonds. The same is true for some water ices.^{102, 103} Relatively weak intermolecular interactions exist in different molecular crystals, in particular, van-der-Waals crystals.¹⁰⁴⁻¹⁰⁶ An adequate description of these interactions¹⁰⁷ requires the use of different empirical corrections.¹⁰⁸ Sophisticated schemes are suggested in the literature^{109, 110} and should be used in the theoretical treatment of the above-mentioned crystals.

5. Conclusions.

The structural motifs formed by H₂O₂ and urea in two-component crystals are determined using a database analysis. The typical features of the H₂O₂ molecule in the crystal structure of the crystalline adducts are the following: i) the H₂O₂ molecule has either planar or skewed conformation with H-O-O-H torsion angle value above 80° (180 or around 100°, respectively); ii) each H₂O₂ molecule always forms two relatively short and almost linear O-H...X bonds (where X = O and N) as H-donor and from one to four H-bonds as acceptor; (iii) the H₂O₂ molecules do not interact with each other via H-bonds.

The pattern of H-bonded interactions in the crystalline urea-H₂O₂ has been identified and quantified using the electron density features derived from solid-state DFT calculations. Each H₂O₂ forms six H-bonds with 5 adjacent urea molecules: 4 O...H-N bonds as acceptor and 2 O-H...O bonds as donor of protons. The N-H...O bonds are of moderate strength (~ 19 kJ/mol). The O-H...O bonds are relatively strong (~ 47 kJ/mol) and can be treated as the primary interactions. The theoretical lattice energy (~ 171 kJ/mol) is larger than the sum of the absolute sublimation energies of the crystalline urea and H₂O₂ (~ 161 kJ/mol). The difference is caused by the existence of relatively short/strong O-H...O bonds in the crystalline urea-H₂O₂ which are absent in its pure components.

The concept of the dimeric heterosynthon has limited applicability for prediction of the structure of crystalline urea-H₂O₂. This is due to the absence of short O-H...O bonds, i.e. primary interactions, in the urea-H₂O₂ 1:1 complex. The concept of a *trimeric heterosynthon* has to be explored in the case of molecules with equivalent binding sites. It should be stressed that the DFT computations with/without accounting for the environmental effects are not sufficient for the deduction of such a heterosynthon. The results of the database analysis should be used for unambiguous identification of the molecules' conformations in the target trimeric heterosynthon.

Acknowledgements

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Supporting Information Available: Details of the solid-state DFT calculations; parameters of the X-H...O fragments, where X = O and N, in the crystalline urea-H₂O₂ computed by solid-state DFT; relative stability of the urea-H₂O₂ 1:1 complexes in gas phase and acetonitrile evaluated by PBE/6-31+G** (Table S2 and Figure S1); relative stability of the 2(urea)-H₂O₂ and urea-2(H₂O₂) complexes in gas phase and acetonitrile evaluated by PBE/6-31+G** (Tables S3, S4 and Figures S2, S3).

Table 1. Computed values of the $R(H...X)$ distances, where $X = O$ and N , the electron-density features at the $H...X$ bond critical point in electron density (ρ_b , G_b) and the H-bond energy E_{HB} ^{a)} in the crystalline urea- H_2O_2 . The H-bond enthalpy $-\Delta H_{HB}$ ^{b)} is given in the last column.

H-bonded fragment ^{c)}	$R(H...X)$ Å	ρ_b , a.u.	G_b , a.u.	E_{HB} , kJ/mol	$-\Delta H$, kJ/mol
O...H-O	1.589 (1.625) ^{d)}	0.061	0.0420	47.2	34.2
N-Ht...O	1.962 (2.011)	0.026	0.0176	19.8	17.9
N-Hc...O	1.988 (1.982)	0.023	0.0165	18.6	18.7

^{a)} see Eq. (1);

^{b)} see Eq. (2), the neutron-diffraction distances were used in $-\Delta H_{HB}$ evaluation;

^{c)} see Fig. 1;

^{d)} experimental values¹² are given in parentheses.

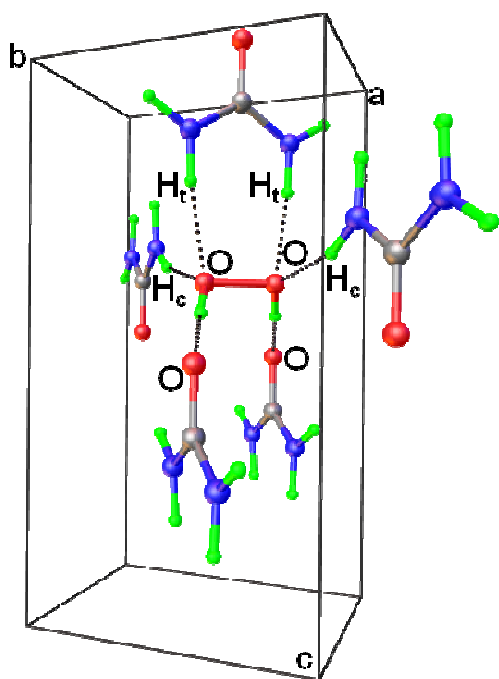


Fig. 1. The fragment of the crystalline urea-H₂O₂ (the solvate). The H-bonds are given by the broken lines. The red, blue and green circles represent the oxygen, nitrogen and hydrogen atoms, respectively.

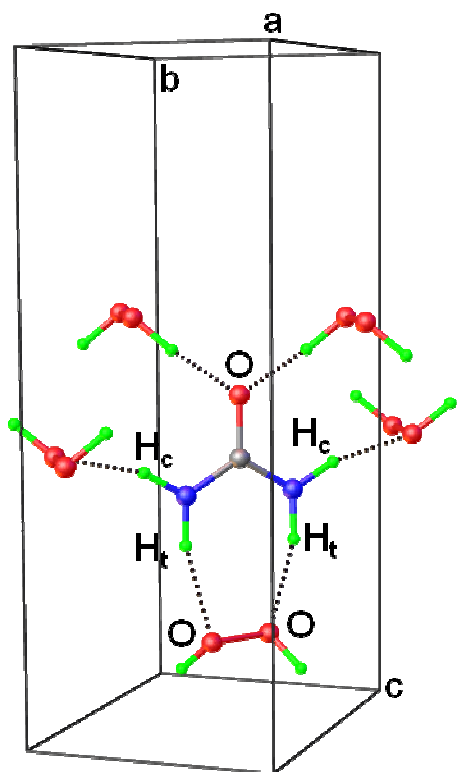


Fig. 2. The fragment of the solvate. The H-bonds are given by the broken lines.

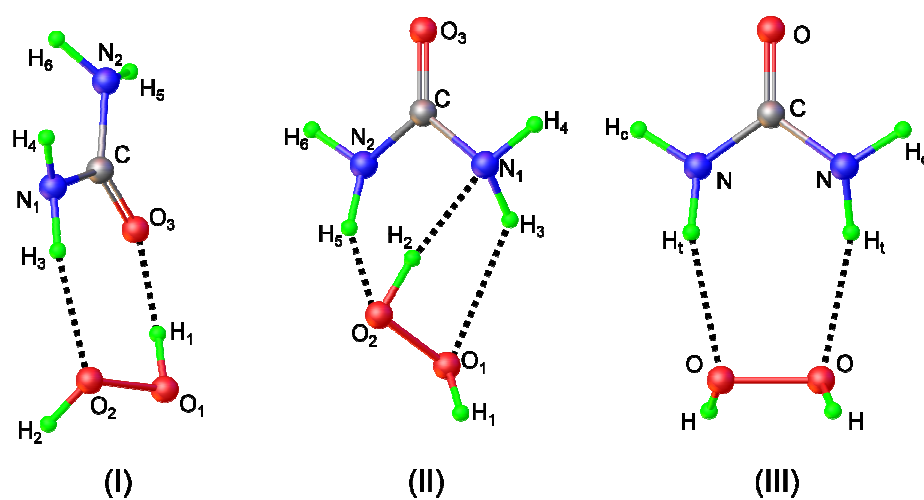


Fig. 3. The structures of the urea- H_2O_2 dimer corresponding to the global-minimum structures in the gas-phase (I) and acetonitrile (II). Heterodimer (III) denotes the urea- H_2O_2 dimer in crystalline state. H-bonds are denoted by dotted lines.

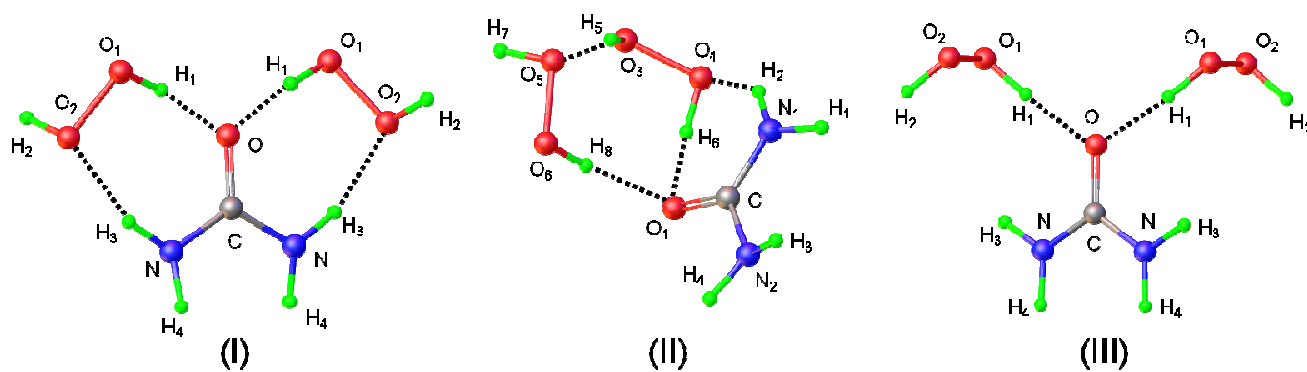


Fig. 4. The structure of the urea-2(H₂O₂) complex. (I) The global-minimum gas-phase structure; (II) the global-minimum structure in acetonitrile; (III) the structure extracted from the crystalline urea-H₂O₂. H-bonds are denoted by dotted lines.

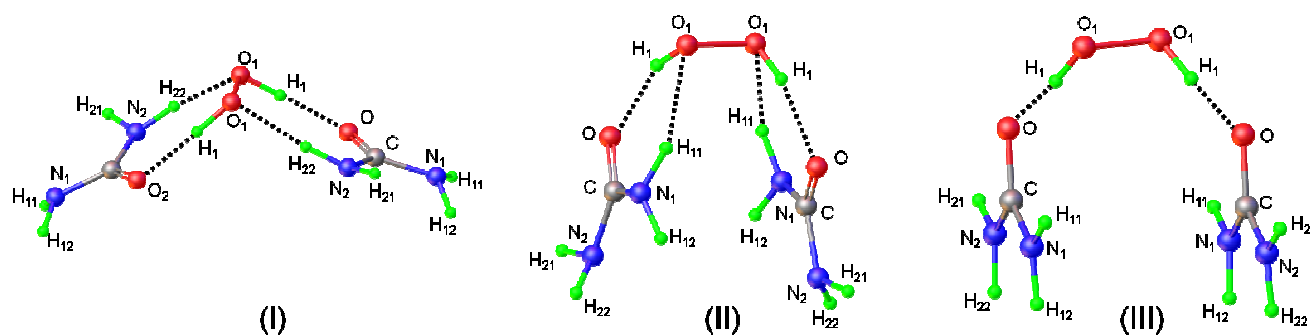


Fig. 5. The structure of the 2(urea)-H₂O₂ complex. (I) The global-minimum gas-phase structure; (II) the global-minimum structure in acetonitrile; (III) the structure extracted from the crystalline urea-H₂O₂. H-bonds are denoted by dotted lines.

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