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# On New Substances of Urea Derivatives Obtained by the Quantum-mechanical Method ab Initio, Their Structural-geometric, Charge and Energy Properties

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**Abstract:** The body of humans and animals contains large quantities of urea, which is believed to serve as an excretory agent for removing excess protein in it. With regard to the toxicity of this substance in the body there is no clarity, whether it is a uremic toxin, or whether this substance is not toxic. It is possible that the role of urea in the body is connected with its metabolites. It is known that there are substances that are derivatives of urea, which exhibit high biological activity. Instance, the well-known carbamide derivative, hydroxycarbamide has gained recognition as an important anticancer drug and an effective promising therapeutic agent for sickle cell anemia. The discovery of new substances and the establishment of their properties is an important task of science, both theoretical and practical. Urea can be a source of new substances, urea derivatives with interesting properties. The aim of the work was, on the basis of quantum mechanical studies, to find out the fundamental possibility of the existence of other urea-derived substances and some other substances of a similar nature and to carry out a comparative analysis of their properties in terms of the interaction of their molecules with water molecules and with each other. In this work, the possibility of the existence of many substances that are derivatives of urea was discovered. Regarding the new urea-derived substances discovered by us, they can be divided into two groups of substances, substances containing a carbohydroxyl group in their composition and substances not containing it. Among the discovered new substances containing a karbohydroxyl group, a substance was found that is an isomer of urea. Based on the quantum mechanical approach, a comparative analysis of the structure, charge and energy properties of carbamide, hydroxycarbamide, and a number of new virtually synthesized carbamide derivatives is carried out. The work shows how the molecules of these substances interact with each other and with water molecules. Numerical values of geometric, charge and energy characteristics of new substances are given and the results obtained are discussed.

**Keywords:** Carbamide, Urea, Carbamidol, Ureanol, Hydroxycarbamide, Quantum Mechanics, Molecular Structure

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## 1. Introduction

The world of substances around us, in particular, the organic world, is plural and diverse and, apparently, not all of them are known to science and not only about their nature, but also, in general, about their existence. As we know, the first organic matter from inorganic substances was obtained in 1824. This substance was oxalic acid that presented in some plants. It was obtained by synthesizing from inorganic substances by Wohler, a student of the outstanding chemist Berzelius. Later in 1828, Wohler made an even more important discovery; he first

synthesized urea from inorganic substances, a product of animal origin. Surprisingly, even now the last substance remains an unsolved mystery and attracts the attention of many researchers. In organisms the processes of vital activity are accompanied by the accumulation of waste products, the so-called uremic toxins, they can disrupt the regulation of normal cellular functions, especially when there are many of them. These toxins can be divided into relatively small molecules (<500 Da) and medium ones. Among the small water-soluble molecules, urea has the highest concentration in the blood. Urea is a 60 Da molecule, it's the final product of protein

metabolism. It's well established as a surrogate marker of kidney condition, protein intake function, and dialysis adequacy assessment. There has been much debate in the literature about whether urea is actually a pathogenic product. Early experiments of urea infusions research on animal models were performed by Vauquelin and Segalas (1822), followed by Gigot Suard (1870) and Treitz (1859). They showed that there was no toxicity from the injection of urea. Perhaps it was due to the fact that small doses and animals with normal kidney function were then used. In the late 1800s, Herter's detailed research showed that urea does have an effect in the body that appears to be phased, dose-dependent. Herter noted that arrhythmias and muscle spasms would occur at blood urea levels of 0.3% (8–10× above normal blood content), with coma and subsequent cardiopulmonary arrest occurring at levels of 0.4–0.5% [1]. These were the initial primary data and ideas about the action of urea in the body of animals, obtained by using the infusion of this substance. How are things going with this issue at the present time? Note that even now, there are very different ideas regarding the role of urea in the body. Two of them can be noted, somewhat different in essence, but united by one common idea about the non-toxicity of urea. According to one of them, namely in accordance with the ideas of Stryer [2, 3], the role of urea is in follows. An excess of aminoacids relative to the amount required for the synthesis of proteins and other biomolecules in the body cannot be stored in the body and cannot be released from it, unlike fatty acids and glucose. Therefore, excess aminoacids are used as metabolic fuel. In this case, the  $\alpha$ -aminogroups of excess aminoacids are first consumed for the formation of glutamate, then the ammonium ion  $\text{NH}_4^+$  is released, as a result of oxidative deamination of glutamate. Serine and threonine can also be deaminated directly. These direct deamination reactions with the release of  $\text{NH}_4^+$  are catalyzed by the dehydratases enzymes. Formed during the destruction of aminoacids part of the  $\text{NH}_4^+$  is spent on the biosynthesis of nitrogenous compounds. In most terrestrial vertebrates an excess of ammonium ions is converted into urea and is already excreted from the body in this form. In birds and terrestrial reptiles  $\text{NH}_4^+$  is converted to uric acid that excreted from the body, whereas in many aquatic animals it is excreted as such. In most terrestrial vertebrates excess  $\text{NH}_4^+$  is converted into urea, moreover, in the urea cycle, and it's excreted from the body in this form. The urea cycle is the first open cyclic metabolic pathway. The main pathway for removing  $\text{NH}_4^+$  is the synthesis of urea in the liver. Apparently, complete blocking of any of the stages of the urea cycle in the liver is incompatible with life, because there is no other known pathway of urea synthesis. It is common knowledge that urea is a denaturing agent. The mechanism of its denaturing action although isn't fully understood, but it's obvious, that it breaks non-covalent bonds. Native proteins, whose structure is necessary for their functional activity, are supported by non-covalent bonds, which are deprived of these bonds and fold randomly in the 8 M urea solution, i.e., they denature, forming a random tangle. This is evidenced by various physical parameters, such as viscosity and optical rotation spectra. After removal of urea by

dialysis, their native structure can gradually be restored. Of course, such high concentrations of urea can only be created artificially; however, it can be assumed that even at very low concentrations this can take place, of course, on a smaller scale. According to another view presented by Lehninger A. L. [4], the formation of urea is considered as a way to remove toxic free ammonia from the body. It's proved that the complex spatial separation of the reactions of aminoacid catabolism and urea synthesis between the cytoplasm and mitochondria is necessary, apparently, in order to prevent the accumulation of large amounts of free ammonia in the blood, insofar as ammonia is very toxic to ureothelic vertebrates (its toxic effect is especially strong in the central nervous system). The toxicity of ammonia is due to the fact, that it promotes catalyzed by glutamate dehydrogenase reductive amination of  $\alpha$ -ketoglutaric acid in mitochondria. Thus, according to Leninger, the function of neutral non-toxic urea in highly organized organisms is to remove toxic ammonia from them, since its high toxicity is associated with a negative effect on the nervous tissue, primarily on the brain. Perhaps both of these ideas are the essence of the same thing, differing only in terminological nuances. Howbeit, but in both views: with considered highly toxic substances the ammonium ion and with ammonia, the formation of urea is considered as the formation of a non-toxic substance. Indeed, there were some grounds for thinking so. It's known, that urea is often injected into the human body for analytical and even therapeutic purposes. It's also important, that urea is used in animal husbandry as a protein substitute, added to animal feed. At the same time, there is data of another plan. According to them, urea can't be considered neutral, just excreted from the body with urine water-soluble compound. In particular, it's noted in the literature, that urea affects many vital processes in the body. According to our work [5], it was concluded that urea intake significantly affects the state of the body in patients with diseases of the gastrointestinal tract of different etiologies. This conclusion was made on the basis of oral intake of urea by volunteers and patients with diseases of the gastrointestinal tract in doses used in urease tests to detect possible helicobacter infection of patients and to assess their condition by the nature of changes in the material composition of the exhaled air, determined by the method of diode laser spectroscopy [5, 6]. The well-known fact of the effect on the brain of barbiturates, synthesized from urea and contain obvious features or motives of urea, also testifies to the possible activity of urea in the human body. One recently published review article by Wei Ling Lau and Nosratola D. Vaziri with the unusual title "Urea a true uremic toxin: the empire strikes back" [7] draws particular attention to the role of urea in organisms. This work provides a lot of information about urea regarding its role and significance as the main uremic toxin with the highest concentration in the blood. It notes that uremic toxins, to which urea is also ranked, leads to the accelerated occurrence of cardiovascular diseases in chronic kidney disease through such risk factors as chronic inflammation, oxidative stress, protein loss of energy, impaired mineral metabolism and deficiency of endogenous calcification inhibitors. Urea is a well-established surrogate

marker for kidney health, protein intake and dialysis adequacy. However, there has been a lot of controversy about whether urea is actually a pathogenic product. Early experiments on urea infusions in animal models were performed by various researchers as early as the 19th century. Direct toxicity of urea to the animal organism wasn't observed in these experiments. Thus, studies on acute infusion of urea in animals have shown that the level of urea tolerance is 8-10 times higher than normal. However, it should be noted that these were experiments of the pulse one-time type. Perhaps, if the animals had maintained a higher urea level and for a longer time, the result could have been different. This is indicated by the data of more recent studies performed in vitro and in vivo, they state the opposite and demonstrate both direct and indirect toxicity of urea, in particular, it's associated with the observed phenomenon of premature aging, common in chronic kidney disease. Elevated urea levels in high concentrations are commonly found in patients with uremia, who have disruption of the intestinal epithelial barrier, this leads to translocation of bacterial toxins into the bloodstream and causes systemic inflammation. Urea induces apoptosis in vascular muscle cells, as well as endothelial dysfunction, it directly contributes to cardiovascular disease. Further, urea stimulates oxidative stress and causes adipocyte dysfunction, it leads to insulin resistance. Finally, when urea is elevated, there are widespread indirect effects due to the urea-induced carbamylation reaction, when isocyanic acid (a product of urea catabolism) changes the structure and function of proteins in the body. Carbamylation is observed in renal fibrosis, atherosclerosis and anemia. So, according to the authors of this discussed article, urea is a resurgent dark force in chronic kidney disease. It's interesting that here the authors note a fact that doesn't support their views about urea in the body. This fact concerns the results of studies on the intensive elimination of urea (and other water-soluble small substances with low molecular weight) from the body to assess survival. It turned out that this wasn't beneficial, i.e., the survival rate of patients didn't increase from this. The authors found a possible explanation for this contradiction about the harmfulness of urea in the body. They believe that hemodialysis therapy itself causes side effects, including: activation of the inflammatory pathways through the contact of the extracorporeal circuit with the blood, as well as the indiscriminate removal of beneficial small-molecular nutrients. Therefore, the usage of prolonged and / or frequent hemodialysis can cause undesirable effects masking the beneficial effect of increased removal of urea from the blood of patients. The authors of this article, however, say: "We need to abandon the idea that urea is harmless." From the analysis of this review, it seems that, in fact, there is a lot of unclear and contradictory information in the literature about the role and significance of urea in humans and animals. Another very important aspect related to urea is associated with the substances, urea's derivatives. As noted, a number of important substances are formed from urea, the class of substances under the general name barbiturates is best known. There are also drugs based on urea, which include well-known urea derivatives such as Carbamide peroxide, Carbazochrome,

Carbamazepin and others [8]. Carbamide peroxide has the formula  $(\text{H}_2\text{N}-\text{CO}-\text{NH}_2)\cdot\text{H}_2\text{O}_2$  and represents a complex of urea with hydrogen peroxide. Antiseptic and keratolytic effects are important pharmacological action of it. It moisturizes and softens the skin, increases its elasticity. There are other uses for it. Carbazochrome has the formula  $(\text{H}_2\text{N}-\text{CO}-\text{NH})-(\text{C}_9\text{H}_6\text{N}_2\text{O}_2)$ , it means that a complex cyclic structure is connected to urea instead of a single hydrogen atom in nitrogen. Carbamazepine has the formula  $(\text{H}_2\text{N}-\text{CO}-\text{NH})-\text{C}_{14}\text{H}_9$ , i.e., a large hydrocarbon backbone of a ring structure is connected to the urea molecule instead of a hydrogen atom. Pharmacological effect - anticonvulsant, antiepileptic, antipsychotic, antidepressant, analgesic, etc. Urea-derived substances are widely used in veterinary medicine. In particular in literature potential uses are being discussed of six benzoylphenyl ureas which approved as veterinary medicines: diflubenzuron, lufenuron, triflumuron, fluazuron, teflubenzuron and novaluron [9]. In particular, Benzoylphenyl ureas is known as an antiparasitic agent [10]. Recently, the substance hydroxycarbamide has become more famous, it's also a derivative of urea. The general view and structural-chemical formula of this compound are presented in the form, shown in Figure 1.

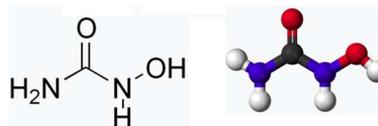


Figure 1. General view and chemical formula of hydroxycarbamide.

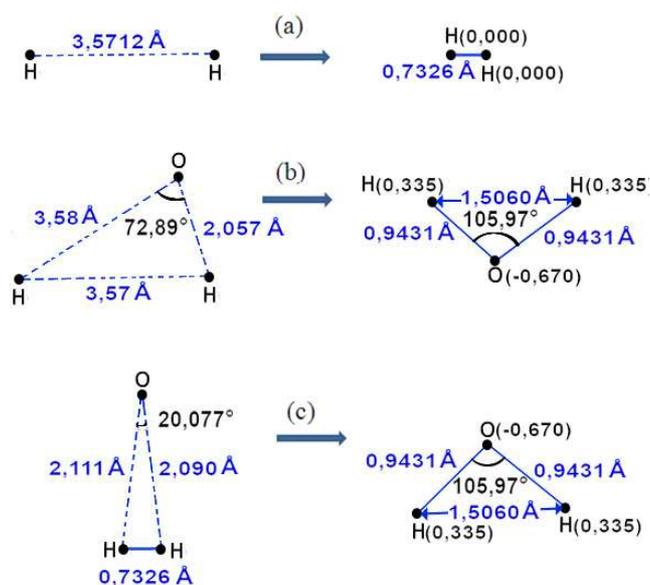
Hydroxycarbamide (hydroxyurea) is a cytostatic drug, an antimetabolite that specifically inhibits DNA synthesis enzymes. Its estimated mechanism of action is in inhibition of nucleotide reductase. It reduces deoxynucleoside triphosphates' content, inhibits DNA synthesis and doesn't affect protein and RNA synthesis. Indications for usage: Chronic (myeloid leukemia, melanoma, ovarian cancer, choriocarcinoma (of the uterus), head and neck tumors, brain tumor, erythremia, cervical cancer). In high doses - in acute leukemia with resistance to standard chemotherapy. It's also used in the mode of pre-induction (premedication before induction) before standard chemotherapy for acute leukemia to quickly reduce the number of circulating white blood cells in the blood and to reduce the risk of developing acute tumor lysis syndrome during standard chemotherapy. In recent years, there have been convincing data on the effectiveness of hydroxycarbamide therapy in sickle cell anemia [11]. There are also published recently review articles on this topic. In a review article by a large group of authors, Inusa B. P. D. et al [12] numerous information about drug trials in patients with sickle cell anemia is provided and the possible mechanisms of the therapeutic effect of hydroxycarbamide on the body of patients with such a hereditary pathology is discussed. It's noted that using this drug has become known as hydroxycarbamide in the UK and as hydroxyurea in the rest of the world. Hydroxycarbamide has several mechanisms of positive effect on hereditary sickle cell pathology The

expression of fetal hemoglobin (Hba) is increased and HbF blocks HbS polymerization due to its action. Hydroxycarbamide reduces the number of platelets and white blood cells, it improves blood flow in patients with this pathology. It improves the hydration and flexibility of red blood cells and reduces abnormal adhesion between blood cells and the blood vessel wall. Hydroxycarbamide increases the formation of nitric oxide, in turn, it stimulates the activity of guanylate cyclase that also increased blood flow. It's also reported that hydroxycarbamide has a positive effect on the spleen and kidneys of patients with this pathology. Together, all of these factors create clinical and laboratory improvement effects. Thus, according to the data of this review that covered a large number of experimental works, it can be assumed, that hydroxycarbamide acquires the features of the first most important therapeutic agent for sickle cell anemia. In relation to carbamide-derived substances, using the examples discussed above, it can be concluded that all of them, including the carbamide itself, affect all the fundamental foundations of the human body in its various aspects. Therefore, research on the identification of new urea-derived substances and their properties continues to be relevant and significant. The results of this work and the new substances discovered in it support this statement. In connection with the above, the purpose of this work was to find out on the basis of quantum mechanical studies the fundamental possibility of the existence of other urea-derived substances and some other substances of a similar nature, and to conduct a comparative analysis of their properties in terms of the interaction of their molecules with water molecules and with each other. In this work, a comparative analysis of the structure, charge and energy properties of carbamide, hydroxycarbamide and a number of new virtually synthesized carbamide derivatives was carried out on the basis of a quantum mechanical approach.

## 2. Methodical Part

The "Polak" algorithm was used for quantum-mechanical calculating and computational procedures, and "Large 6-31G\*\*" was chosen as the basis. This basis was chosen for the reasons that its use gives fairly accurate geometric results not only to some simple substances, for example, to hydrogen molecule and to water molecule, but also to more complex ones [13]. The research was conducted using the software package "HyperChem professional 8". Figure 2 shows the view, structural-geometric and charge characteristics of water and hydrogen molecules obtained after their optimization using the quantum-mechanical ab initio method. By arrangement of atoms the water molecule is a planar shape with a total energy of 47705.54 kcal/mol, with an angle of HOH equal to 105.97 degrees, with lengths of OH forming this angle equal to 0.94307 Å, with charges on oxygen - 0.670 and on both hydrogen atoms + 0.335, expressed in units of e. It is important that regardless of the method of virtual formation, either from three separate atoms (2 hydrogen atoms and one oxygen atom) or from one hydrogen molecule and one oxygen atom, the water molecule is obtained

with identical characteristics shown in this figure. In the latter case, the dynamics of the optimization process tracks the separation of the hydrogen molecule into atoms, which then react with the oxygen atom and form a water molecule as a result. The given data indicate not only their good agreement with the known data, but also, what is important, they will be used in the following further presentation of the obtained results. Numerical values of interatomic distances and angles are given in angstroms and degrees respectively. Total energy molecules is given in kcal / mol. It is important to keep in mind that this dimension is much larger than the dimension KJ / mol. In conclusion, using a specific example, it will be shown to what negative consequences this circumstance can lead. Values of charges distributed across the atoms of the resulting molecules represented in electronic units, are shown in parentheses. Data in other figures will be presented in a similar form. Note that in the dynamics of quantum-mechanical formation of a water molecule from a hydrogen molecule and an oxygen atom, the case (c), there is initially a process of decay of the hydrogen molecule into atoms, their divergence, followed by the gradual formation of a water molecule from a purely atomic system, as in the case of (b). Dotted lines indicate the distances between atoms, and solid lines indicate the lengths chemical of bonds between atoms in molecules obtained after optimization of the initial structures.



**Figure 2.** Results of quantum-mechanical synthesis of hydrogen and water molecules, their geometric and charge properties.

(a) - hydrogen molecule (leftward: two separate hydrogen atoms with their mutual initial location, rightward: the resulting hydrogen molecule after optimization)  $E_{total} = 709,92$  kcal / mol, (b) - water molecule made of two hydrogen atoms and one oxygen atom, on the left - the initial state, on the right - after synthesis (optimization)  $E_{total} = 47705,54$  kcal / mol, (c) - water molecule synthesized from one molecule of hydrogen and one oxygen atom, on the left - the initial state, on the right - after synthesis  $E_{total} = 47705,54$  kcal / mol.

Features of quantum-mechanical research in this work consisted in the fact that at first a rough search for the global extremum (minimum) was realized, when the search gradient was high, for example, it was equal to 1, and then the

resulting structure was optimized more accurately by using a gradient of 0,1, and then even at lower values of the gradient equal to 0,01. The last one was done to obtain greater accuracy of the structural-geometric and charge characteristics of the optimized structures. Characterizing the molecules energetics, molecules' structural-geometric and charge properties, features in the formation of water-substance complexes, and some others were taken into account, while obtaining data on the results of research. The binding energies of water molecules with other molecules were determined according to the following algorithm:  $E_b = E(s \cdot h_2o) - E_s - E_{h_2o}$ . Here:  $E_b$  - the binding energy of a water molecule with substance,  $E(s \cdot h_2o)$  - the energy of a complex,  $E_s$  - the energy of a free molecule and  $E_{h_2o}$  - the energy of a free water molecule. This algorithm was used in the work Marcus Weimann with co-authors [14].

The following considerations were taken into account in the research. Molecules of complex substances made up of a large number of interacting atoms can be in several equilibrium states with corresponding to them energy minima. There is one state among them that has the largest negative energy of the equilibrium state, corresponding to the minimum energy. This largest negative energy minimum is called the global minimum, and it determines the most possible state of the system. All other minima with lower values of negative energy are defined as local levels with corresponding to them states. In accordance with the

Boltzmann principle, there is a certain probability of the molecules existence in these different energy states, however, it's often incomparably less than at the global minimum. In this work, from logical considerations, a new approach is proposed and used to describe the processes of charge transfer between atoms, which determine the steady-state distribution of charges over the atoms of molecular systems. This approach can be interesting in terms of obtaining new data and ideas about the nature of various chemical processes estimated by quantum mechanical methods. This approach can also be useful for checking compliance with charge balances in quantum mechanical studies.

### 3. Results

#### 3.1. Structural-geometric, Charge and Energy Characteristics of Urea According to Quantum-mechanical Research

##### 3.1.1. Structure of a Urea Molecule in a Free State

Figure 3 shows data on the quantum mechanical synthesis of a urea molecule from some arbitrary initial state with an arrangement of atoms corresponding to the chemical formula of this compound. As a result of quantum-mechanical optimization of the initial model structure, a urea molecule was obtained with two types of configurations shown in the indicated figure 3. (a) and 3 (b).

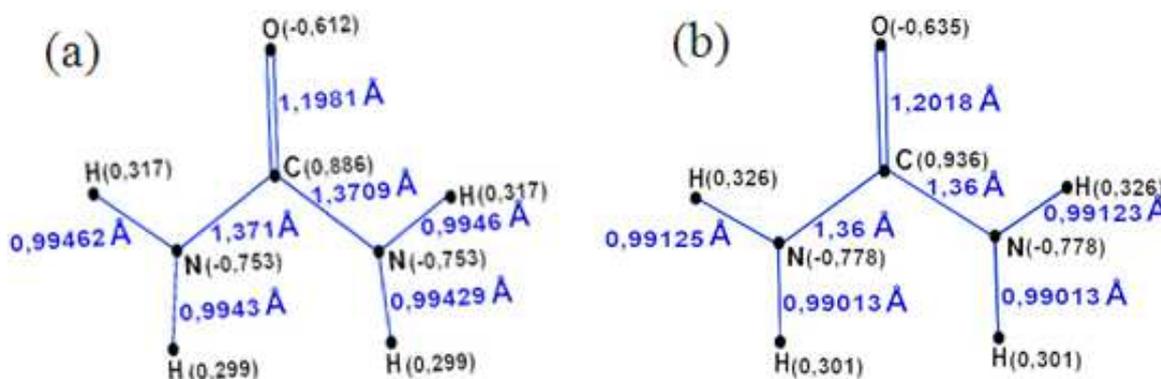


Figure 3. Quantum-mechanical formation of the structures of the urea molecule, their geometric, charge and energy characteristics.

- urea molecule (spatial) with a global minimum of energy obtained after optimization of the initial model structure, (b) - urea molecule (planar) with the nearest local minimum of energy obtained after optimization of the model structure.

The total energy of the obtained urea molecule with a global minimum energy turned out to be 140562,41 kcal / mol. The four O, C, N and N atoms of this optimized urea molecule lie in the same plane, and the hydrogen atoms protrude from it symmetrically to each other at both ends of the molecule. The resulting urea molecule is symmetrical about the OC line. The most significant geometric parameters of this molecule are shown in the figure, of which the bond lengths:  $OC = 1.1981 \text{ \AA}$ ,  $CN = 1.3709 \text{ \AA}$  (on both sides of OC) and, accordingly, the angles between them on both sides of the molecule:  $\angle NCN = 114,17^\circ$ ,  $\angle OCN = 122,91^\circ$ ,  $\angle HNH = 115,26^\circ$ . The distribution of charges over the atoms of the urea molecule is also shown in Figure 3 (data on charges are

given in brackets and are expressed in units - e). With regard to the distribution of charges, the picture of their distribution logically means the following. It is obvious that each nitrogen atom takes a negative charge from two hydrogen atoms at once, from one 0.299e and from the other 0.317e, or 0.616e in total. Since the charge of each nitrogen atom in the molecule is -0.753e, then, consequently, the remaining - 0.137e each of the nitrogen atoms additionally takes away from the carbon atom. In total, nitrogen atoms will be taken from the carbon atom -0.274e. Since the charge on a carbon atom is defined as plus 0.885, it means that in addition to a charge of 0.274e, 0.611e is also subtracted from this carbon atom, the value determined by the following difference

$0.885e - 0.274e = 0.611e$ . It is clear that this  $0.611e$  could only be drawn from the carbon atom by the oxygen atom. Therefore, the charge of the oxygen atom must have a value of minus  $0.611e$ . In fact, this is indeed the case, the charge on the oxygen atom is  $0.611e$  (see Figure 3 (a)).

In addition to the aforementioned, one more circumstance seems to be important, which is revealed during the virtual quantum-mechanical synthesis of the urea molecule. Its essence is that under certain initial conditions, the quantum-mechanical process of optimizing the structure of urea creates another equilibrium structure (see Figure 3 (b)). The total energy of this structure is  $140561,24$  kcal / mol. This structure of urea is a completely planar structure, that is, all its atoms, including hydrogen atoms, all lie in the same plane. It is clear that this structure corresponds to a local energy minimum closest to the global one. In addition to the numerical data that determine this planar structure, we

additionally note the following:  $\angle \text{NCN} = 115,146^\circ$ ,  $\angle \text{OCN}$  (left)  $= 122,427^\circ$ ,  $\angle \text{OCN}$  (right)  $= 122,427^\circ$ ,  $\text{OC} = 1,2018 \text{ \AA}$ ,  $\text{CN} = 1,3599 \text{ \AA}$ ,  $\angle \text{HNH}$  (left)  $= 119,269^\circ$ ,  $\angle \text{HNH}$  (right)  $= 119,276^\circ$ . It can be seen that all geometrical and charge characteristics of this structure of urea differ markedly from those of its own spatial structure corresponding to the global energy minimum (see Figure 3 (a and b)). The difference between these energy states turned out to be negligible, so one can assume about the simultaneous coexistence of two varieties of forms of the urea molecule, planar and spatial. There is no information in the literature on this score. Moreover, it is believed that the urea molecule structurally has only one planar shape [12].

### 3.1.2. Water-carbamide Complexes and Their Properties

Figure 4 shows data on the interaction of a urea molecule with water molecules.

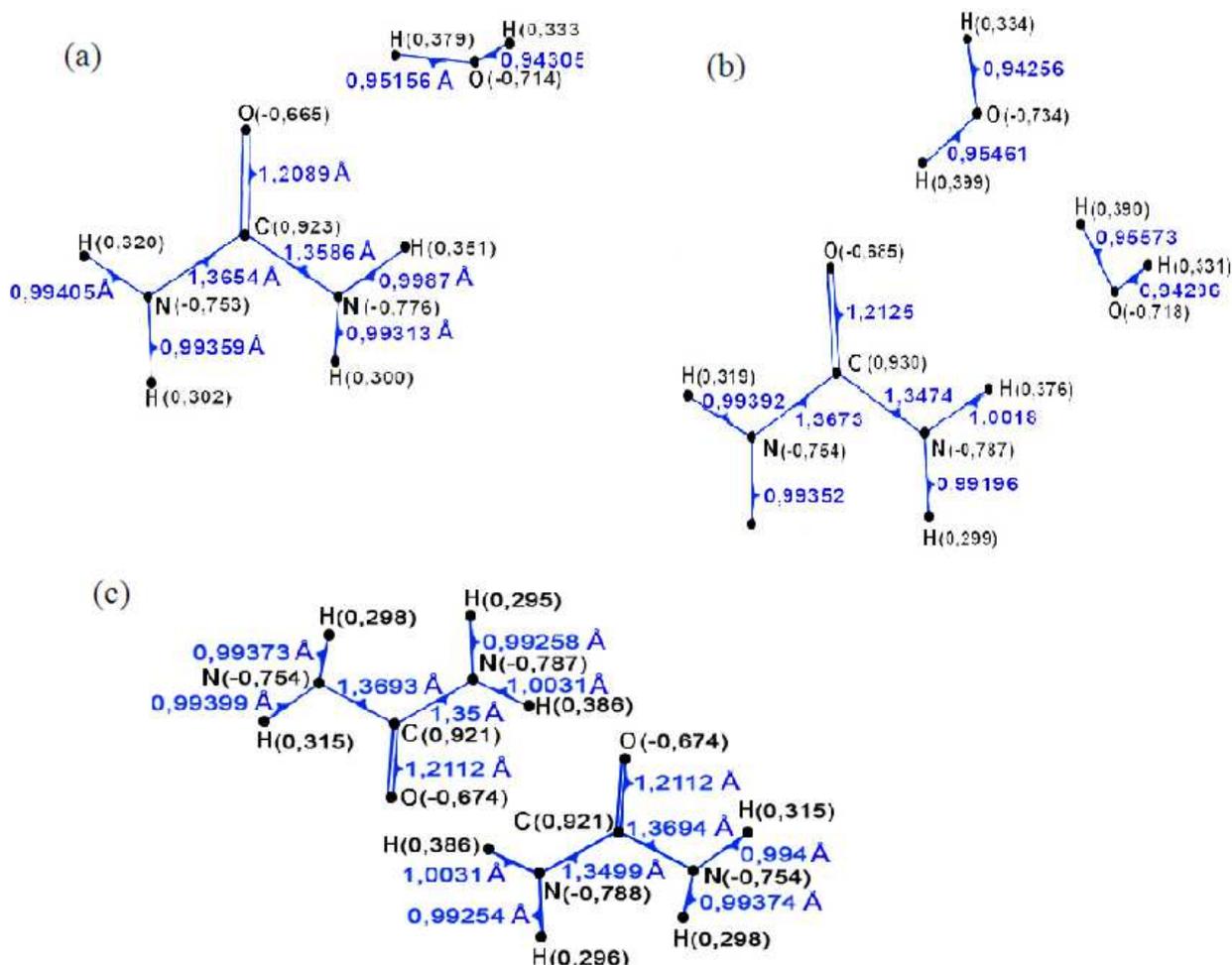


Figure 4. Complexes of a urea molecule with water molecules, one (a) and two (b) and with another carbamid molecule (c).

In addition to the structural, geometric and charge characteristics indicated in this figure, we note several more important ones. For its single-water complex, the total energy is  $188277.75$  kcal / mol. The distance between the oxygen of urea and the hydrogen atom of water is  $2.0047 \text{ \AA}$ , and between the oxygen and water and the nearest hydrogen atom of urea is  $2.148 \text{ \AA}$ . Angles in urea:  $\text{OCN}$  (left)  $121.69^\circ$ ,  $\text{OCN}$

(right)  $123.02^\circ$ ,  $\text{NCN}$   $115.29^\circ$ ,  $\text{HNH}$  (left)  $116.01^\circ$ ,  $\text{HNH}$  (right)  $116.79^\circ$ . The  $\text{HOH}$  angle of the water is  $105.91$  degrees. A water molecule is bound to a urea molecule by two weak (non-chemical) bonds, and its strength is numerically determined by the binding energy ( $E_b$ ) equal to  $E_b = 188277.75 - 140562.41 - 47705.54 = 9.8$  kcal / mol. This is a relatively large value of the bond energy, which indicates its

strength. Figure 4 (b) shows a complex of a urea molecule with two water molecules and shows its numerical characteristics. In addition to the data shown in the figure, we note the following. The distance between the oxygen of urea and the hydrogen atom of the upper water molecule is 1.8879 Å, and the distance between the oxygen of this water and the nearest hydrogen atom of the other (lower) water molecule is 1.9164 Å. The oxygen of this lower water molecule is located at a distance of 2.0147 Å from the nearest urea hydrogen atom (see Figure 4 (b)). Thus, it turns out that both water molecules are linked by two bonds and form a closed ring with urea. The NCN angle in urea is 115.594°, and the OCN angles to the left and right are respectively 120.80 and 123.60 degrees. The energy of the binary complex of urea with water molecules is 235993.23 kcal / mol. In complexes of urea with two molecules of water (c), the binding energy of its second molecule with a one-water complex is determined as follows.  $E_b = 235993.23 - 188277.75 - 47705.54 = 10.4848$  kcal / mol. The total binding energy of a urea molecule with two water molecules is determined as:  $E_b = 235993.23 - 140562.41 - (2 \times 47705.54) = 19.74$  kcal / mol.

### 3.1.3. Urea-urea Complexes and Their Characteristic Properties

Figure 4 (c) shows data on the interaction of urea molecules with each other. The energy of the dimer complex is 281137.51 kcal / mol at gr. 009. In addition to the numerical data characterizing the dimeric urea complex shown in Figure 4 (c) we present several more characteristic parameters. The binding energy of urea molecules in their dimeric complex is 281137.51 kcal / mol - 140562.41 - 140562.41  $\cong$  13 kcal / mol. This is a rather high value of the binding energy between both urea molecules, indicating the stability of the dimeric forms of this substance. It can be noted that the bonds established between two urea molecules go in two directions. One is along the oxygen line of one molecule to H of the other, and the length of this bond is 2.1493 Å. Another bond goes along the line of the hydrogen atom of the first molecule to the nitrogen atom of the second and the length of this bond is 2.3698 Å (see Figure 4 (c)). In this case, the distance between the two nearest hydrogen atoms belonging to different urea molecules is 2.4079 Å.

## 3.2. Structural-geometric, Charge and Energy Characteristics of Hydroxycarbamide According to Quantum Mechanical Research

### 3.2.1. Structure and Other Characteristics of Hydroxycarbamide in Its Free State

In the introduction, the properties of hydroxycarbamide were noted that make this compound important and interesting in terms of its medical applications. In this regard, the question arises, and what is the true structure of this compound and what are its features. After quantum mechanical optimization of the carbamide molecule, initially having the form of the structure as it is represented (see Figure 1), its true optimized structure was obtained, shown in

Figure 5. The total energy of this structure is 187493.11 kcal / mol. Its NCN angle is 112.28 degrees, which is two degrees less than the same angle of urea having a spatial configuration. The OCN is 124.00 degrees on the left and 123.68 degrees on the right. It can be seen that the geometric parameters of the left side of hydroxycarbamide (relative to the OC bond) differ from those of urea, however, insignificantly (see Figure 5).

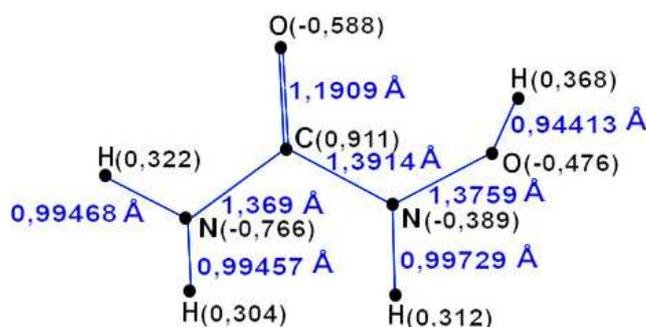


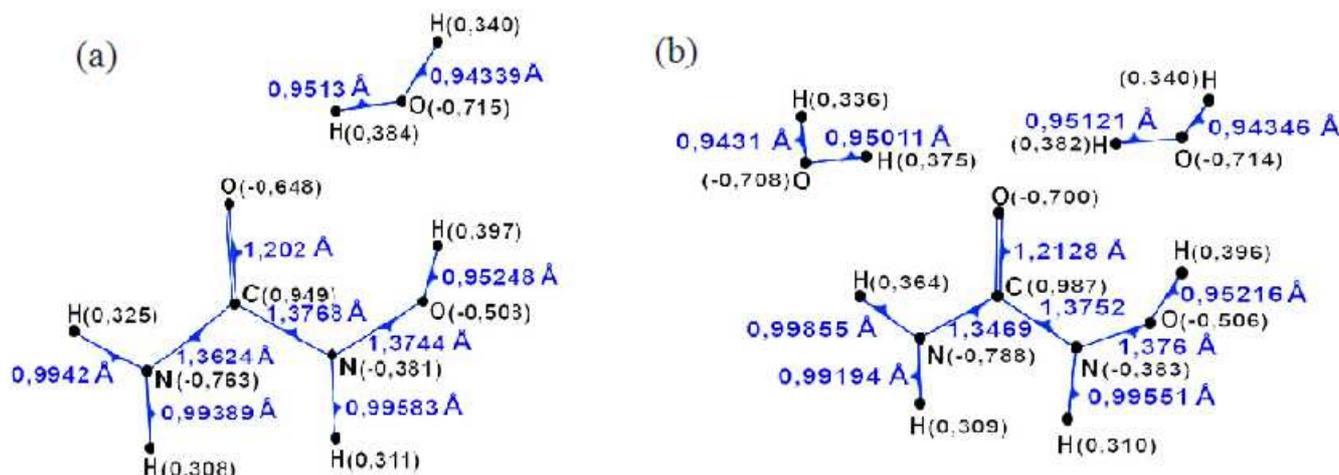
Figure 5. The structure of hydroxycarbamide obtained after its quantum mechanical optimization.

The same situation occurs with the length OC and the charges on the C and O atoms. On the right side of the hydroxycarbamide molecule, the angle HON is 105.627 degrees, that is, it corresponds in magnitude to the angle in the water molecule (see Figure 2 (b)), and the angle CNO = 114.11 degrees. From the figure and the given angular data, it follows that the N, C, O (hydroxyl group bonded to C), O (hydroxyl group bonded to N) and N atoms of the hydroxycarbamide molecule lie in the same plane. With regard to the distribution of charges, the picture of their distribution logically means the following. It is obvious that each nitrogen atom takes a negative charge from two hydrogen atoms at once, from one 0.304e and from the other 0.322e, or 0.626e in total. Since the charge of nitrogen atom in the molecule (left, see figure 5) is -0.766e, then, consequently, the remaining -0.14e of the nitrogen atoms additionally takes away from the carbon atom. On the right in the figure, the oxygen of the hydroxyl group has subtracted 0.368e from its hydrogen atom, and its charge is minus 0.476e. Therefore, he additionally subtracted 0.476 - 0.368 = 0.108 e from the nitrogen atom (on the right in the figure). In turn, the same nitrogen took away 0.312e from its hydrogen and as a result its charge should have been 0.312 - 0.108 = 0.204e with a minus sign, but it is equal to - 0.389e. This means that the missing part of his harmony was taken by him from carbon, namely 0.389 - 0.204 = 0.185e. From the carbon atom in total, the left and right nitrogen atoms subtracted a charge equal to 0.185 + 0.14 = 0.325e. Oxygen bonded to carbon additionally removed a charge equal to 0.588e from it. So, in total, a charge equal to 0.325 + 0.588 = 0.913e has been taken away from carbon. Therefore, the charge of the carbon atom must have a value of minus 0.913e. In fact, this is indeed the case, the charge on the carbon atom is -0.913e (see Figure 5. Total энергия этого вещества  $E_{total} = -187493,11$  kcal / mol.

### 3.2.2. Aqueous Hydroxycarbamide Complexes and Their Properties

It was noted above that hydroxycarbamide turned out to be a very interesting substance in terms of its use, and first of all, medical. At the same time, quantum mechanical studies of this substance are clearly insufficient. As shown above, hydroxycarbamide is a simple derivative of

carbamide and remarkably repeats its structural shape. As has already been shown here, urea binds alternately one and two water molecules with the same binding energy. Perhaps hydroxycarbamide also has this property. Figure 6 shows a view of a hydroxycarbamide complex with water molecules, respectively, with one water molecule (a) and with two (b).



**Figure 6.** Complexes of hydroxycarbamide with water molecules, with one (a) and with two (b). The structure of the dimeric complex formed by the interaction of two molecules of hydroxycarbamide with each other.

The geometric and charge characteristics of the resulting complex are shown in the corresponding figure. In addition, we note a few more. The energy of the complex of hydroxycarbamide with one water molecule has a value of -235209.80 kcal / mol. The binding energy of a water molecule with hydroxycarbamide in this complex is determined by the following expression  $E = 235209.80 - 187493.11 - 47705.54 = 11.15$  kcal / mol. This is noticeably more energy than urea. As has already been shown here, urea binds alternately two water molecules in a practically non-cooperative way. It can be seen that hydroxycarbamide binds two water molecules without showing a positive cooperative character. On the contrary, it exhibits a markedly pronounced negative cooperative effect. Indeed, the energy of the complex of hydroxycarbamide with two water molecules has a value of -282924.32 kcal / mol, hence the binding energy with an atom water molecule is determined as follows.  $E_b = 282924.32 - 235209.80 - 47705.54 = 8.88$  kcal / mol. Obviously, the absence of the phenomenon of cooperativity in urea and the presence of a negative cooperative effect in hydroxycarbamide is explained by the fact that positive cooperativity is manifested only when a chain of two interconnected water molecules binds its beginning and end to the atoms (O and H) directly of the alcoholic hydroxyl group itself. Here, the word alcohol means that the hydroxyl group is directly linked to the carboxyl.

### 3.2.3. Features of the Interaction of Hydroxycarbamide Molecules with Each Other

Hydroxycarbamide molecules interact with each other and form dimeric complexes. The energy of such a complex has a value equal to -375002,96 kcal / mol. Hence, the binding

energy between molecules is easily determined, namely:  $E_b = -16,76$  kcal / mol. This is a great energy of bind. Note that the molecular structures in dimeric hydroxycarbamide complexes are significantly modified. Hydroxycarbamide dimeric complexes can be formed due to the binding of these molecules and at other sites than shown in Figure 6, however, with a lower binding energy, that is, less firmly.

### 3.3. New carbamide Derived from Urea Substances Discovered Based on the Results of Quantum Mechanical Research

#### 3.3.1. Quantum-mechanical Synthesis of New Carbamide Derivatives with a Carbohydroxyl Group, Their Structural, Geometric, Charge and Energy Properties

Based on the urea molecule, we have created a new molecule in the work, like an alcohol molecule, that is, containing a carbohydroxyl group. Such a molecule was created by adding two hydrogen atoms to the urea molecule, spatial type. In this case, one hydrogen atom binds to a carbon atom, and the other binds directly to oxygen itself, which required replacing one double bond with two single ones. It is known that there is a special classification for monohydric alcohols into primary, secondary and tertiary alcohols. It is based on the number of radicals bonded to the carbon atom to which the hydroxyl group is directly bonded, that is, how many hydrogen atoms out of three possible bonded to the carbon atom are replaced by hydrocarbon radicals. If there is one, then it is a primary alcohol, such as ethanol. If there are two, then it is according to the given classification. Secondary alcohol, for example, isopropyl alcohol. And further, for example, tert-butyl alcohol is

considered as a tertiary alcohol. For this classification, methanol can be considered zero alcohol. It seems to be an interesting and important question regarding the requirement of the hydrocarbon nature of radicals. The structure of the spatial type of urea considered here can be easily transformed

into a kind of secondary alcohol by introducing two hydrogen atoms into its molecule, linking one of them with oxygen, and the other with carbon (see Figure 7). The substance, theoretically created in this way, was used to study its properties in a quantum-mechanical way.

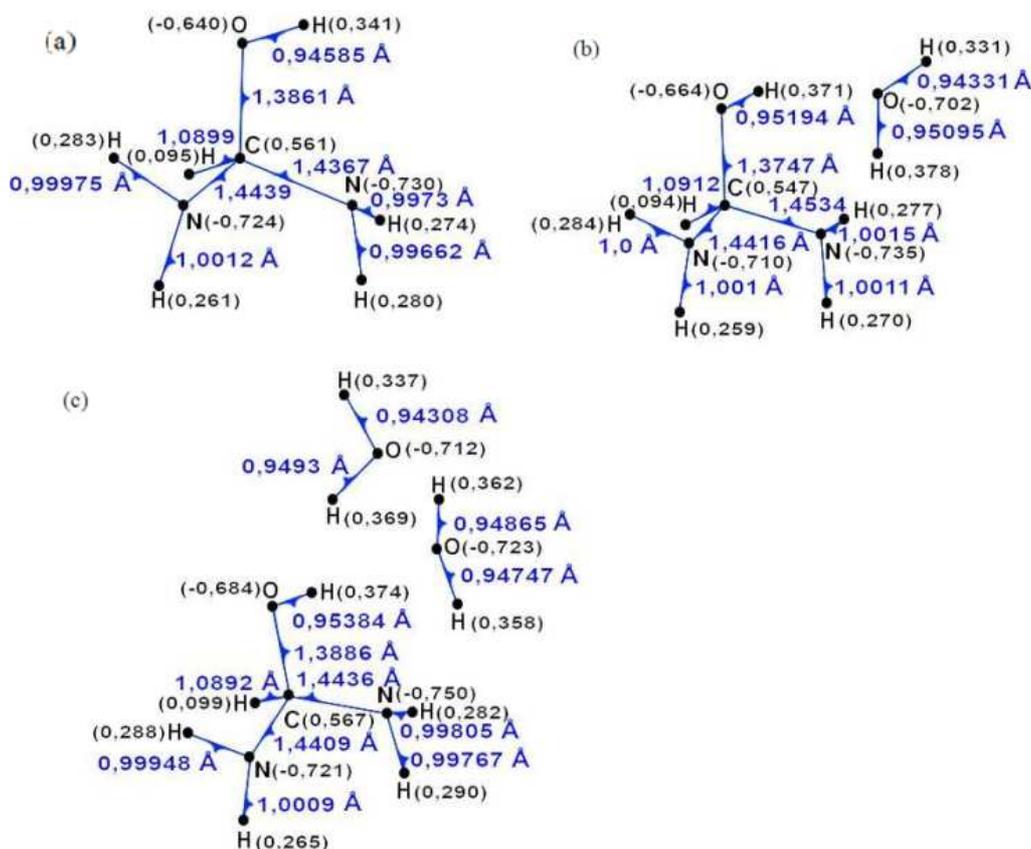


Figure 7. Quantum-mechanical formation of carbamidol1 substance and its properties and its interaction with water molecules.

(a) is the structure of a molecule of a free substance, (b) is the structure of a complex of carbamidol1 with one water molecule, and (c) is a complex of carbamidol1 with two water molecules.

On the image 7 (a) the structures of this initial substance and the substance obtained from it after optimization are presented. The energy of the obtained product turned out to be equal to  $E = -141267.04$  kcal / mol with the value of the search gradient equal to 0.01. The resulting structure has a spatial configuration. The angle (HOC) in its carbohydroxyl group with apex on oxygen has a value of  $107,103^\circ$ . Note that the value of this angle significantly exceeds the value of the angle at the top on oxygen near water (see Figure 2 (b) and (c)). The most significant characteristics regarding the lengths of bonds between atoms and charges on them are shown in Figure 7. Thus, the creation of a carbohydroxyl group in a spatial-type urea molecule after its optimization, a stable structure was obtained, indicating the formation of a new substance. The most important of the data is the value of the angle HOC equal to  $107,103^\circ$  which is significantly greater than the angle HOH of the water. This obtained substance was conventionally named carbamidol1 and ureanol1. With regard to the distribution of charges, the picture of their distribution logically means the following. It

is obvious that nitrogen atom (left) takes a negative charge from two hydrogen atoms at once, from one 0.261e and from the other 0.283e, or 0.544e in total. Since the charge this of nitrogen atom in the molecule is  $-0.724e$ , then, consequently, the remaining  $-0.180e$  of the nitrogen atom additionally takes away from the carbon atom. Similarly, the right-handed nitrogen atom subtracted a total of 0.554e from its protons. Its charge is 0.730e, which means that this nitrogen has taken away the missing share of the backward from carbon, namely 0.176 e. In total, both nitrogen atoms were subtracted from carbon 0.356e. Carbon itself subtracted 0.095e from its hydrogen volume and, therefore, its charge should be equal to  $+0.261e$ , but it is equal to  $+0.561e$ . It follows from this that a part of the charge was taken from it by an oxygen atom and this part is equal to  $0.561-0.261 = 0.3e$ . In addition, oxygen has subtracted 0.341e from its hydrogen atom (hydroxyl group) and, as a result, its charge should have a value equal to 0.641, e. In fact, it is so (see figure 7).

On the image 7 the data characterizing this substance in terms of its interaction with one water molecule are

presented. The one-water complex of that substance has a spatial structure, the energy of which is  $E = -188982,63$  kcal/mol. The binding energy of a water molecule in this complex will be defined as  $E_b = 188982,63 - 141267,04 - 47705,54 = 10,05$  kcal/mol. The same figure (c) shows the results on the binding of the monohydrate complex to the second water molecule with the formation of the complex of carbamidol 1 with two water molecules. The binding energy of the second water molecule with the mono-water complex of the given substance takes on a value equal to  $E_b = 236694,76 - 188982,63 - 47705,54 = 7$  kcal / mol. In this case, the binding energy of two water molecules with carbamidol1 itself has a value equal to  $-236694,76$  kcal / mol. The binding energy of a two water molecule in this complex will be defined as  $E_b = 236694,76 - 141267,04 - (2 \times 47705,54) = 17$  kcal / mol. It follows from these data that there is an additivity property when carbamidol1 binds two water molecules.

When using the planar structure of urea to create the same new substance from it according to the same scheme, which was obtained from urea of the spatial type, the result after its optimization turned out to be unexpected. On the image 8 this result is presented. It can be seen from the figure that, as a result of quantum mechanical optimization of the original structure, the carbohydroxyl (COH) group acquired its characteristics close to those of methanol and ethanol. The general features of the resulting structure are similar in appearance to the structure of urea (see Figure 3). At the same time, it is clearly seen that two hydrogen atoms, initially bound: one with a carbon atom, and the other with a nitrogen atom, have been isolated from the structure and moved to large distances. Separated from the rest of the structure, these two atoms turned out to be connected to each other, forming a hydrogen molecule (see Figure 2). The energy of the resulting structure is  $141253,17$  kcal / mol ( $Gr = 0.009$ ). However, there are also significant differences between this structure and urea. So the NCN angle of the obtained structure of the ureanol molecule, equal to  $122.501$  degrees, differs upward from the same angle for urea, equal to  $112.282$  degrees, by almost 10 degrees. The CN line of ureanol is very noticeably tilted to the left, that is, away from the double bond. This is obvious, since the OCN angle of ureanol is on the left ( $109.928^\circ$ ), and on the right ( $127.551^\circ$ ). Urea, on the other hand, is a symmetrical molecule. The lengths of CN bonds on the left and right of ureanol are not equal to each other ( $1.3607 \text{ \AA}$  on the left, and  $1.2564 \text{ \AA}$  on the right), as is the case in urea. Since the distant hydrogen atoms have become weakly bound to the rest, the decision suggests itself to remove these atoms altogether from the structure and instead establish a double bond between the carbon atom and the corresponding nitrogen atom. After this adjustment, the new structure is worth evaluating through quantum mechanical optimization. As a result of such operations, a new structure was obtained, which has the form shown in the figure 8 with the specified values of the most significant geometrical parameters, energetics and

charges on atoms (see Figure 8). Thus, we obtained a new substance, and which we called carbamidol 2 or ureanol 2 after the name of simple alcohols, methanol and ethanol, as well as others. This name justifiably reflects the presence of the -ol suffix in it and the fact that the characteristic group of this compound is a hydroxyl group directly bonded to a carbon atom, that is, forming an lcarbohydroxyl group - COH. The energy of ureanol 2 was found to be  $140542.35$  kcal / mol. In the case of the new substance carbamidol 2, the movement of charges along its molecule, which caused a steady distribution of charges on its atoms, can be judged on the basis of the following reasoning. It is obvious that nitrogen atom (left, see Figure 8 (c)) takes a negative charge from two hydrogen atoms at once, from one  $0.310e$  and from the other  $0.318e$ , or  $0.628e$  in total. Since the charge this of nitrogen atom in the molecule is  $-0.683$ , then, consequently, the remaining  $-0.055e$  of the nitrogen atom additionally takes away from the carbon atom. Similarly, the right-handed nitrogen atom subtracted  $0.238e$  from its hydrogen atom. Its charge is  $0.721e$ , which means that this nitrogen took away the missing fraction of the charge from carbon, namely  $0.483e$ . In total, both nitrogen atoms subtracted charge from carbon  $0.538e$ . But the charge of carbon is not that, but equal to  $+0.800e$ , therefore, the missing part of the charge from it was taken by the oxygen atom and this part is equal to  $0.800 - 0.538 = 0.262e$ . In addition, oxygen subtracted  $0.354e$  from its hydrogen atom (hydroxyl group), and as a result, its charge should have a value equal to  $0.616e$  and so it really is (see Figure 8 (c)). It should be especially emphasized that carbamidol2 ( $H_2NCOHNH$ ) is an isomer of another very well-known compound, namely, carbamide itself. That is, urea and ureanol 2, having the same formula of the chemical composition  $N_2H_4CO$ , the same molecular weight are different substances, possibly alcohol and urea. These are not the only cases of isomerism for alcohols. It is known, for example, that ethyl alcohol and dimethyl ether, both having the same formula of the chemical composition  $C_2H_6O$ , are isomers, but their atoms in space are located differently and the chemical bonds in them differ significantly. It is easy to verify from the angular data that ureanol 2 has the same planar figure as the original urea (see Figure 3 and Figure 8). The criterion for belonging to the alcohol of ureanol 2 can be the property found in methanol, ethanol, as well as in some other simple alcohols, to cooperatively bind two water molecules through their hydroxyl groups that are part of their alcohol carbohydroxyl groups (-COH). Carbamidol2 molecules with their carbohydroxyl groups can bind water molecules. When one water molecule binds, a complex is formed with a total energy of  $188256.49$  kcal / mol. In this case, a water molecule with its oxygen forms a bond with a hydrogen atom of the carbohydroxyl group of carbamidol2 with a distance of  $1.9265$  angstroms between them. The binding energy of this water molecule with carbamidol2 will be determined:  $E_b = 188256 - 140542.35 - 47705.54 = 8.6$  kcal / mol.



### 3.3.2. Quantum-mechanical Synthesis of New Carbamid-derived Substances, in Which Various Substitutes are Used Instead of the Carbohydroxyl Group

In the previous section, we considered new substances synthesized by a quantum mechanical method containing a carbohydroxyl group. This section considers new substances with various substitutes for the carbohydroxyl group, the quantum mechanical synthesis of which has been successfully performed. These substances can be conditionally defined as carbamidones. The simplest derivative of urea is obtained if oxygen bound to carbon is replaced by two hydrogen atoms in it.

Thus, instead of a hydroxyl group, a hydrogen atom was directly attached to the carbon of this molecule. This structure has been subjected to quantum mechanical optimization. Based on the results of its optimization, a conclusion was made about its stable configuration, that is, about the possibility of the existence of this substance. Such a substance lacking a carbohydroxyl group will have the chemical formula  $N_2CH_6$  and may be called carbamidon1. Figure 11 (a) shows the type and numerical characteristics of this first in simplicity urea-derivative substance that does not contain a carbohydroxyl group in its pure form. The total energy of this new substance is 94285.91 kcal / mol. Its type and parameters characterizing this structure are shown in this figure.

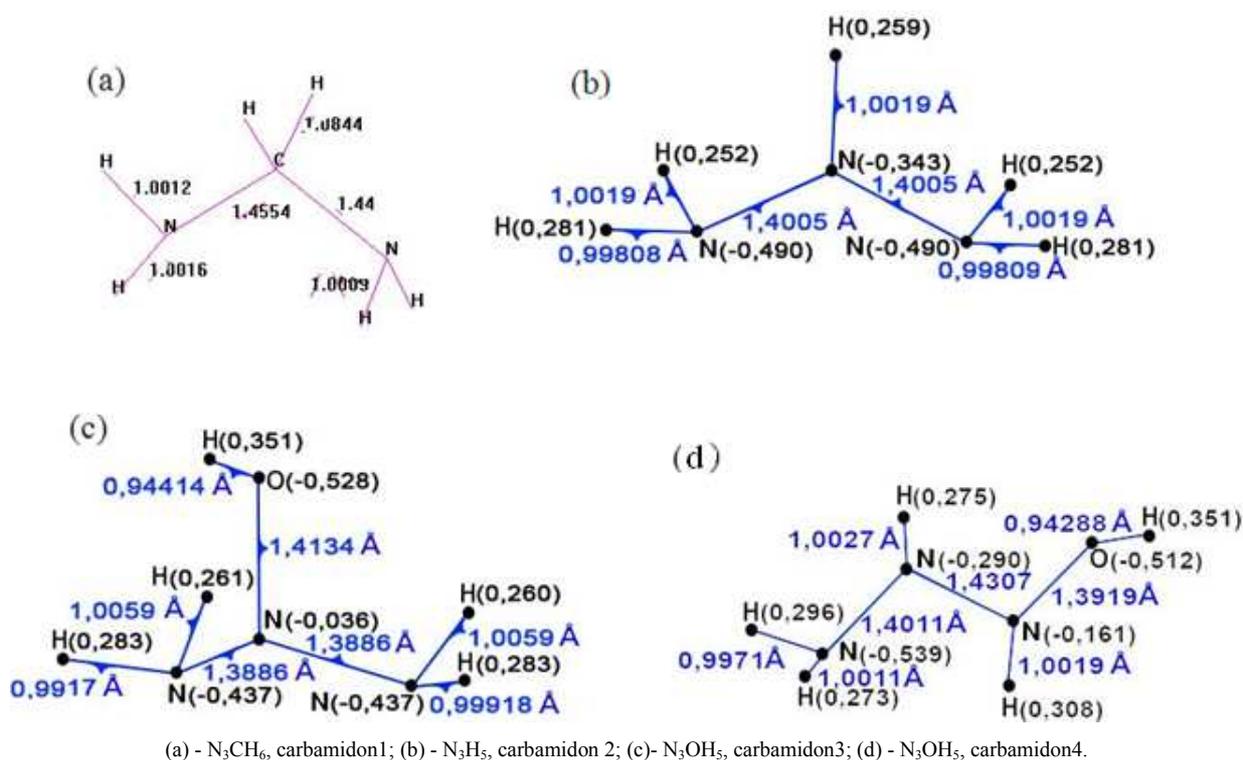


Figure 11. Simple substances synthesized by a quantum mechanical method, with various substitutes for carbohydroxyl groups.

The second substance synthesized by the quantum mechanical method, which does not have a carbohydroxyl group, is shown in Figure 11 (b). Instead of carbon, a nitrogen atom was used in the molecule of this substance, to which a hydrogen atom was directly attached. This replacement creates a system of three nitrogen atoms, in which the middle atom directly bonds one hydrogen atom. This substance is the simplest one, with the chemical formula  $N_3H_5$ , that is, it is nitrogen hydrogen, and the parameters characterizing it are presented in Figure 11 (b). Its total energy is 104276.74 kcal / mol. In conclusion, this substance will be discussed in more detail.

The next substance we have discovered, which is offered to our attention, has the chemical formula  $N_3OH_3$  and contains a hydroxyl group in its composition. This substance, synthesized by a quantum mechanical method, which does not have a carbohydroxyl group, is shown in Figure 11 (c).

Instead of carbon in the molecule of this substance, as in

the previous two, a nitrogen atom was used, to which a hydroxyl group was directly attached, that is, the carbohydroxyl group was replaced by an azohydroxyl group. This replacement creates a system of three nitrogen atoms carrying a hydroxyl group. Figure 10 (c) provides data on this issue. It is seen that such a system is stable with a strictly defined spatial arrangement of its atoms (see Figure 10 (c)). This new substance has an energy of  $E = -151229.92$  kcal / mol. What kind of substance is this, which can conditionally be called azohydroxyl in addition to the name carbamidone3, and what are its properties, primarily in terms of possible application, this is the subject of his special research. It should be especially noted that the angle HON in it, equal to 105.133 degrees, corresponds to the angle HOH of water.

Figure 11 (d) presents data on another substance derived from urea. This substance with the chemical formula  $N_3OH_5$  contains a hydroxyl group associated with extreme nitrogen /. Its energy is 151187,53 kcal / mol.

## 4. Conclusion

In the introduction, from a retrospective analysis of literature data on the role of carbamide or urea in the body, it was concluded that this issue is not understood and clarified at the present time. Perhaps this is due to the fact that there is a lot of incomprehensible, unknown and contradictory about urea itself, as a substance of organic nature. This is evidenced by the data obtained in this work of ours, in which a new unknown fact was discovered about the existence of urea in the form of two different forms, spatial and planar. A number of new urea derivatives are obtained from these two forms of urea with their various chemical modifications and subsequent quantum-mechanical optimization. The way they are forming shows how and how they acquire their specific properties, arising from of properties the urea itself, through its various modifications. This applies both to the well-known and already widely used urea-derived substances, discussed in the introduction, and to new substances discovered by us, and the possibility of the existence of which in nature is substantiated here. From the discussion of the issue of carbamide derivatives, which have already found wide medical and biological applications, it was concluded above that the search for new other substances of this nature is urgent. In relation to known urea-derived substances, their characteristic parameters are given in the work, in particular for hydroxycarbamide (see Section 3.2). Regarding the new urea-derived substances discovered by us, they can be divided into two groups of substances, substances containing a carbohydroxyl group in their composition and substances not containing it (see Sections 3.3.1 and 3.3.2). Among the discovered new substances containing a carbohydroxyl group, a substance was found that is an isomer of urea. Thus, in this work, an unknown phenomenon of isomerism for urea was discovered.. To make sure whether we have really discovered new and unknown substances to science and the world, we carried out a search for information on this matter. When searching for such information, two links were issued from which it followed that among the newly discovered substances from the group that do not contain a carbohydroxyl group, one substance with the chemical formula  $N_3H_5$  is already known to science and it exists under the name "Triazan". Triazane is the third simplest acyclic azane after ammonia and hydrazine. It can be synthesized from hydrazine, but it is unstable and cannot be isolated in the form of a free base, only in the form of salts such as triazane sulfate. Triazan was first synthesized as a ligand for a complex silver ion: tris ( $\mu$ -triazan- $\kappa$ N, N) disilver (2+). It was also synthesized in electron-irradiated ammonia ices and found as a stable gas-phase product after sublimation. That is, in essence, we have discovered a substance that exists in nature and has already been discovered, although still little studied. That is, in this case it turns out that we have discovered what is already open and known. Nevertheless, the fact of discovery is present here. The discovery in this case is that we discovered the existence of the affinity of this compound of triazane to urea, which is its derivative. This is also an important value in itself. It indicates the pathway for

the synthesis of this substance, which may be important for the future. How do you know? On the other hand, the situation with triazan is of great importance as proof of the legitimacy and reliability of all the results of this work in terms of discoveries of other new substances. With regard to the search for data on their mention, it turned out to be negative, no links to this account were found. In the case of carbamidol2, the situation is somewhat different. Search engines give out a lot of links, but they all refer only to the urea itself and nowhere is it mentioned about its isomer, carbamidol2. On this basis, it can be assumed that science does not know about the phenomenon of isomerism for urea, and even more so about the substance of its isomer. Therefore, there is every reason to believe about the discovery of two groups of new substances in terms of their possible existence in nature or their creation by a synthetic method.

With regard to the substances considered here and the properties of these substances, discovered by a quantum-mechanical method that substantiated their possible existence, the weighty word here belongs to chemists engaged in the synthesis of new substances in practical terms.

The work focuses on the energy characteristics of the processes of quantum-mechanical creation of new substances, their interaction with water molecules and other types of their interactions. Energy characteristics are given in calorimetric units (kcal / mol) as larger scale than joule units (kJ / mol).

In conclusion of this work, I would like to draw your attention to the fact that the works with low total energy values found in the literature may be due to confusion with its dimensions, kcal / mol and kJ / mol.

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