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A STUDY ON THE INTERACTION OF N–ACETYLNEURAMINIC ACID WITH MONOSACCHARIDES ADSORBED ON ULTRAFINE SILICA SURFACE

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Nowadays, it is relevant to study the processes that occur at the boundary of biomolecule (cell)-nanoparticle phase distribution. There is a growing interest in studying the interaction of ultrafine silica (UFS) with saccharides, in particular glucose and fructose, as well as with N-acetylneuraminic acid (NANA) (which is a part of the body’s cell membrane), for further creation of nanocomposites with biomolecules to use in biological systems. Using the density functional theory method (DFT) within the polarization continuum model (PCM), the interaction peculiarities of monosaccharides with silica surface were examined and the influence of the NANA molecule on this process was determined. The results of the analysis of quantum chemical calculations indicate that glucose and fructose can be used as modifiers for NANA adsorption. The molecules of these carbohydrates are related to silica surface and form a complex with N-acetylneuraminic acid. It is found that hydrogen bonds between hydroxyl groups of carbohydrates and silanol groups of the UFS surface play a major part in the formation of intermolecular complexes. The calculations show that the adsorption of monosaccharides on silica surface is possible considering their location, and it also depends on how to carry out the adsorption. That is, whether the adsorption of saccharides and then of NANA, or the adsorption from monosaccharides-NANA solution on silica surface is sequential.

Keywords: glucose, fructose, silica surface, adsorption, density functional theory method, cluster approach

INTRODUCTION

Nanocomposites based on biomolecules and ultrafine silica are quite promising for use in many fields of biotechnology. There are many methods of obtaining such materials, in particular, it is adsorption from liquid or gas phases.

Saccharides are found in the human body, they are involved in metabolic process, so it is reasonable to use such substances while working with biomolecules.

In this paper, we consider such monosaccharides as fructose, glucose and N-acetylneuraminic acid (NANA), which is a part of glycoproteins and glycolipids, and is also a carbohydrate.

The main purpose of the study is the quantum-mechanical calculations of the “models” with obtained experimental data taken into account, which would show that adsorption is possible for both saccharides and NANA.

As it is known from the literary sources [1], monosaccharides: glucose, fructose and NANA are not adsorbed on the hydroxylated surface of UFS from the aqueous phase.

However, adsorption of saccharides, in particular glucose and lactose from the gas phase is possible by impregnation [2, 3]. From these data it can be concluded that the modification takes place in a cluster way. This is due to the fact that during adsorption there is a slight change in the activity of the adsorption centers of the surface, and position of the saccharide molecules in the adsorption complex does not affect this process. Thus, a part of their hydroxylated groups will be oriented outward molecules. It is capable to interact with both the surface and the adsorbed modifier molecule. There are also literature data that glucose, fructose can be sorbed on the surface of UFS together with molecules of bovine serum albumin [4].

Our preliminary calculations by semi-empirical methods indicate [5–7] a possibility to form the adsorption complexes of some monosaccharides, in particular glucose and fructose on silica surface. Therefore, an important task was to find modifiers that can change the surface of silica for the adsorption of saccharides and to study their capability to modify the surface of silica. Such modifiers are selected saccharides that are biocompatible with NANA. It should be noted that such composites should not have a damaging effect when interacting with biological objects.
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Comparing the above literature data with the results of quantum chemical calculations it is possible to evaluate the peculiarities of the interaction of monosaccharides with silica surface and to determine the influence of the NANA molecule on this process.

OBJECTS AND METHODS OF RESEARCH

Using the density functional theory method (DFT) with B3LYP functional [8, 9] with Grimme variance correction D3 [10, 11] and the basic set 6-31G (d, p) using the GAMESS (US) program [12] within the polarization continuum model PCM [13, 14], the energy values of intermolecular interaction and adsorption were calculated. Equilibrium spatial structures of molecules of initial compounds and formed intermolecular complexes were found by minimizing the norm of the total energy gradient [15]. The stationarity of the points corresponding to the minima of optimized structures is proved by the absence of negative eigenvalues of Hesse matrices (matrices of force constants), according to Marrell – Leidler theorem [16].

In this work, models of glucose and fructose monosaccharides in the most thermodynamically stable cyclic forms were used [17], in particular, glucose in the form of β-D-glucopyranose (Fig. 1 a), fructose in the form of α-D-fructopyranose (Fig. 1 b).

N-acetyleneuraminic acid is sialic acid, which is a part of glycoproteins and glycolipids (Fig. 2 a). A cluster consisting of eighteen silicon-oxygen tetrahedra (Fig. 2 b), gross composition Si_{18}O_{48}H_{24} and is commensurate with the NANA molecule and the studied monosaccharides was chosen as the model of silica surface.

![Equilibrium spatial structure of monosaccharides: a – glucose, b – fructose](image1.png)

![Models: a – N-acetyleneuraminic acid, b – silica cluster](image2.png)
The energy of intermolecular interaction between two identical molecules (glucose, fructose and NANA) in the formation of dimers was calculated by the following formula (1):

\[ \Delta E_{\text{dim.}} = E(\text{compl}) - 2E(\text{mol}) \]  

\( E(\text{compl}) \) – is the total energy of the intermolecular complex, \( E(\text{mol}) \) – total energy of the number plate molecule.

The calculations of the physical adsorption energy (\( \Delta E_{\text{ph.ads}} \)) of one test molecule on the surface of silica were performed according to formula (2):

\[ \Delta E_{\text{ph.ads.}} = E(\text{ph. ads. compl}) - (E(\text{surf}) + E(\text{mol})) \]  

\( E(\text{ph. ads. compl}) \) – total energy of the adsorption complex, \( E(\text{surf}) \) and \( E(\text{mol}) \) – the total energy of the silica cluster and the test molecule, respectively.

The energy of formation of NANA intermolecular complexes with monosaccharides was calculated by formula (3), similar to the above mentioned:

\[ \Delta E_{\text{int. react}} = E(\text{intermolec. compl.}) - (E(\text{NANA}) + E(\text{monosacch})), \]  

\( E(\text{intermolec. compl.}) \) – is the total energy of the intermolecular complex, \( E(\text{NANA}) \) and \( E(\text{monosacch}) \) – are the total energies of the NANA molecule and of the investigated monosaccharide, respectively.

To study the mutual influence on the adsorption of monosaccharides and N-acetylneuraminic acid on silica surface, it is necessary to consider several cases of interactions of the three-component system: silica – NANA – monosaccharide; silica – NANA – monosaccharide, according to the schemes shown in Fig. 3.

According to “Scheme 1”, the energy effect of the interaction of the monosaccharide molecule with the pre-formed silica-NANA complex was calculated according to formula (4):

\[ \Delta E_{\text{scheme1}} = E(\text{SiO}_2-\text{NANA–monosacch}) - (E(\text{SiO}_2-\text{NANA}) + E(\text{monosacch})), \]  

\( E(\text{SiO}_2-\text{NANA–monosacch}) \) – total energy of the three-component intermolecular complex, \( E(\text{SiO}_2-\text{NANA}) \) – total energy of the intermolecular complex of the silica cluster with NANA.

According to “Scheme 2”, the energy effect of the interaction of the NANA molecule with the silica-monosaccharide complex was calculated according to formula (5):

\[ \Delta E_{\text{scheme2}} = E(\text{SiO}_2-\text{monosacch–NANA}) - (E(\text{SiO}_2) + E(\text{NANA–monosacch})), \]  

\( E(\text{SiO}_2-\text{monosacch–NANA}) \) – total energy of the intermolecular complex of silica surface with monosaccharides.

According to “Scheme 3” (Fig. 3), the energy effect of the interaction of the silica cluster with the NANA-monosaccharide complex was calculated, in which the silica binds to the complex through the NANA molecule according to formula (6):

\[ \Delta E_{\text{scheme3}} = E(\text{SiO}_2-\text{NANA–monosacch}) - (E(\text{SiO}_2) + E(\text{NANA–monosacch})), \]  

\( E(\text{SiO}_2) \) – total energy of the intermolecular cluster of silica, \( E(\text{NANA–monosacch}) \) – total energy of the intermolecular complex NANA with monosaccharide.

According to “Scheme 4” (Fig. 3), the energy effect of the interaction of the silica cluster with NANA-monosaccharide complex where silica surface binds to the complex

\[ \Delta E_{\text{scheme4}} = E(\text{SiO}_2-\text{monosacch–NANA}) - (E(\text{SiO}_2) + E(\text{NANA–monosacch})), \]  

\( E(\text{SiO}_2-\text{monosacch–NANA}) \) – is the total energy of the intermolecular complex of silica surface with monosaccharides.
through a monosaccharide molecule was calculated according to formula (7):
\[ \Delta E_{\text{scheme}} = E(\text{SiO}_2-\text{monosacch}-\text{NANA}) - \left( E(\text{SiO}_2) + E(\text{NANA-\text{monosacch}}) \right), \]  
(7)

\[ E(\text{SiO}_2) \] – total energy of the molecular cluster of silica.

RESULTS AND DISCUSSIONS

Before investigating the peculiarities of the interaction of monosaccharides with silica surface and with NANA, it is necessary to analyze the geometric and energy characteristics of dimeric intermolecular complexes of these substances. These complexes can be formed both in aqueous solution and by interaction with silica surface. The Fig. 4 a, b shows that these complexes arise due to the formation of intermolecular bonds between the hydroxyl groups of monosaccharides. And in the case of NANA, carboxyl (–COOH) and imide (–NH–) groups are involved in the formation of hydrogen bonds. The analysis of the calculation results of intermolecular interaction energy between two identical molecules by formula (1) shows that the greatest value of \( \Delta E_{\text{int. react.}} \) is specific for dimer of two NANA molecules and it equals to –188.2 kJ/mol. Since, for this dimer, as we can see in Fig. 4, the largest number of hydrogen bonds is characteristic too. The intermolecular interaction energy is significantly lower for the fructose dimer (–91.7 kJ/mol), but for glucose dimer it is –66.3 kJ/mol).

Fig. 4. Intermolecular complexes of monosaccharides: a - glucose dimer, b - fructose dimer, c - N-acetylneuraminic acid dimer

Adsorption complexes of monomers of glucose, fructose and NANA with silica surface (Fig. 5) are formed due to intermolecular bonds between the polar functional groups of monosaccharides and NANA with silanol groups of silica surface. It should be noted that the number of hydrogen bonds in the case of interaction of glucose and fructose with a cluster of silica (Fig. 5 a, b) is much greater than that in the formation of dimers (Fig. 4 a, b). Analysis of the adsorption energy values for these three adsorption complexes, which were calculated according to formula (2), shows that the greatest energy effect of the formation of the adsorption complex with silica was for fructose, which is –174.8 kJ/mol (Table 1). A slightly smaller similar value was found for the complex with glucose (–161.0 kJ/mol) and almost the same value of \( \Delta E_{\text{ph.ads}} \) is inherent in the adsorption complex with NANA (–163.2 kJ/mol), which is 25 kJ/mol lower than the value \( \Delta E_{\text{dim}} \) for NANA dimer (–188.2 kJ/mol). This is due to the fact that for the complex of silica cluster with NANA (Fig. 5 c), the number of intermolecular hydrogen bonds is slightly smaller compared to the NANA dimer (Fig. 4 c), because in this adsorption complex there is no interaction of silanol groups of silica with the imide group of the NANA molecule.
To determine how NANA affects the adsorption of monosaccharides and vice versa - monosaccharides affect the adsorption of NANA on silica surface, it is first of all necessary to determine the geometric and energy characteristics of the interaction of these monosaccharides with the NANA molecule. For this purpose, intermolecular NANA complexes with glucose and fructose were localized (Fig. 6). The interaction between molecules occurs through the formation of intermolecular hydrogen bonds as well as in the above mentioned cases.

![Fig. 5. Adsorption complexes of silica with monosaccharides: glucose (a), fructose (b), N–acetylneuraminic acid (c)](image)

![Fig. 6. Intermolecular complexes of N–acetylneuraminic acid and monosaccharides: a – glucose, b – fructose](image)

The calculation analysis of $\Delta E_{\text{int, react}}$, defined by formula (3) shows that NANA-fructose complex has the highest value $-145$ kJ/mol, and for the complex with glucose, this value is $12$ kJ/mol less ($-132.9$ kJ/mol). See Table 1. This is due to the fact that in the complex of NANA with fructose, is shown on the Fig. 6, there are more hydrogen bonds compared to the NANA-glucose intermolecular complex.

It should be noted (see Table 1) that for fructose the interaction energy for all considered cases of dimer formation, complexes with that for silica cluster and NANA is higher in comparison with glucose. In addition, the interaction energy, regardless the nature of the monosaccharide for adsorption complexes and NANA, is higher than for the corresponding dimers (Fig. 4).
When considering the mutual influence on the adsorption of monosaccharides and N-acetylnenuraminic acid on silica surface, the structures of intermolecular complexes of three-component systems were found: silica–monosaccharide-NANA (Fig. 7) and silica – NANA – monosaccharide (Fig. 8).

Figures 6 and 7 show that these complexes are formed due to hydrogen bonding between molecules and a silica cluster.

Table 1. Energy of intermolecular interaction of monosaccharides (in kJ/mol)

| Types of intermolecular complexes                               | Glucose | Fructose |
|-----------------------------------------------------------------|---------|----------|
| Dimers                                                          | –66.3   | –91.7    |
| Adsorption complexes with SiO₂                                   | –161.0  | –174.8   |
| Intermolecular complexes with NANA                              | –132.9  | –145.0   |

According to Scheme 1, the monosaccharide molecule interacts with the NANA molecule, which is pre-adsorbed on silica. Analysis of the calculation results based on formula (4) shows that the highest adsorption energy is specific for glucose and it is –196 kJ/mol (Table 2), which is 35 kJ/mol greater than the same value in the case of direct interaction of the glucose molecule with silica, which is –161 kJ/mol (Table 1). It should also be noted that the energy of the intermolecular interaction between NANA and glucose without the involvement of silica is also lower by 63 kJ/mol.

When fructose interacts with NANA preadsorbed on silica, the adsorption energy is slightly lower (16.5 kJ/mol) compared to the similar value for glucose and is equal to –179.5 kJ/mol. However, its absolute value is still greater than the energy effects of the intermolecular interaction of fructose separately with silica (–174.8 kJ/mol) and a single NANA molecule (–145.0 kJ/mol), see Table 1.

Scheme 2 provides for the study of the interaction energy between a NANA molecule that interacts with a monosaccharide molecule already adsorbed on silica. After calculating by the formula (5), we can see (Table 2) that the highest value of $\Delta E_{\text{scheme2}}$ was also found for the complex with glucose, which is –160.9 kJ/mol, compared to the complex of fructose which is –104.0 kJ/mol. However, when glucose interacts with an isolated NANA molecule, only 132.9 kJ/mol is released, and in the case of fructose interaction, the presence of silica...
decreases the energy of intermolecular interaction by 41 kJ/mol (–145 kJ/mol, Table 1).

Schemes 3 and 4 provide for the evaluation of intermolecular complexes adsorption energy of the corresponding monosaccharide and NANA with silica surface. The difference between these schemes is as follows: Scheme 3 shows that intermolecular complex interacts with silica from NANA side, and in the Scheme 4 it interacts from monosaccharide side (Fig. 3). The analysis of the calculations results made by the formula (6) shows that $\Delta E_{\text{scheme3}}$ for the complex with glucose has a maximum value (Table 2) which is –226.3 kJ/mol. This is much more than that for the interaction of pure NANA with silica, which is equal to –163.2 kJ/mol). For a similar complex with fructose, there is also a high value of the interaction energy, equal to –197.7 kJ/mol.

Fig. 8. Three-component adsorption complexes: a - cluster of silica – N–acetylneuraminic acid – glucose; b - silica cluster – N–acetylneuraminic acid – fructose

| Monosaccharide | Interactions scheme |
|---------------|---------------------|
|               | Scheme 1 | Scheme 2 | Scheme 3 | Scheme 4 |
| Glucose       | –196.0   | –160.9   | –226.3   | –188.9   |
| Fructose      | –179.5   | –104.0   | –197.7   | –133.9   |

The results of calculations made by formula (7) show (Table 2) that the interaction of silica and intermolecular glucose complex with NANA –188.9 kJ/mol is more favorable than that of the fructose complex with NANA –133.9 kJ/mol provided that monosaccharide molecule will interact. As compared to the similar value of silica interaction with pure monosaccharides (Table 1) where the interaction with the molecule of fructose (–174.8 kJ/mol) is more advantageous than with glucose (–161 kJ/mol).

CONCLUSIONS

Thus, the analysis of calculation results of complexation energies shows that the interaction of silica with fructose is 13 kJ/mol more favorable than with glucose, and the interaction energy of the glucose molecule with the pre-adsorbed molecule of N–acetylneuraminic acid on silica surface is 16.5 kJ/mol lower than the analogue in case with fructose.

It illustrates that there is a mutual influence of substances in the mixture of NANA –
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monosaccharides on the interaction with silica in comparison with the interaction of substances with silica alone.

The calculations show that the adsorption of monosaccharides on silica surface is possible if we take into account their location, and also depends on how to carry out the adsorption. That is, whether the adsorption of saccharides and then NANA, or the adsorption from monosaccharides – NANA solution on the surface of silica is sequential.

Дослідження взаємодії N–ацетилнейрамінової кислоти з моносахаридами,
адсорбованими на поверхні високодисперсного кремнезему

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На сьогоднішній день актуальними є дослідження процесів, що відбуваються на межі поділу фаз біомолекула (клітинна) - наночастина. Цікавим є вивчення взаємодії високодисперсного кремнезему з сахаридами, зокрема глукозою і фруктозою, а також з N-ацетилнейраміновою кислотою (NANA) (яка є в складі клітинної мембрані організму), для подальшого створення нанокомпозитів із біомолекулами для застосування їх в біологічних системах. Методом теорії функціоналу густини (DFT) в межах моделі поляризаційного континууму РСМ були досліджені особливості взаємодії моносахаридів з поверхнею кремнезему та з’єднаний вплив на цей процес молекули NANA.

Результати аналізу квантовохімічних розрахунків свідчать, що глукоза і фруктоза можуть використовуватися як модифікатори для адсорбції NANA. Молекули цих вуглеводів споріднені до поверхні кремнезему та створюють комплекс з N-ацетилнейраміновою кислотою. Встановлено, що водневі зв’язки між гідроксильними групами вуглеводів і силанольними групами поверхні ВДК відіграють основну роль в утворенні міжмолекулярних комплексів.

Проведені розрахунки показують, що адсорбція моносахаридів на поверхні кремнезему можлива, якщо враховують їх розташування, а також залежить від того, яким чином проводиться адсорбція. Тобто, чи послідовна адсорбція сахаридів, а потім NANA, чи адсорбція із розчину моносахаридів-NANA на поверхні кремнезему.

Ключові слова: глукоза, фруктоза, поверхня кремнезему, адсорбція, метод теорії функціоналу густини, кластерне наближення

Изучение взаимодействия N–ацетилнейраминовой кислоты с моносахаридами,
adсорбированными на поверхности высокодисперсного кремнезема

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Сегодня одним из актуальных направлений исследований является исследование процессов, которые происходят на границе раздела фаз: биомолекула (клеточная)-наночастица. Стоит обратить внимание на изучение взаимодействия высокодисперсного кремнезема с сахаридами, например, с глукозой и фруктозой, а также с N-ацетилнейраминовой кислотой (NANA) (которая имеется в составе клеточной мембраны организма), для дальнейшего получения нанокомпозитов с биомолекулами для использования их в биотехнологиях. Методом теории функционала плотности (DFT) в рамках модели поляризационного континуума РСМ было исследовано особенности взаимодействия моносахаридов с поверхностью кремнезема, также изучили влияние на этот процесс молекулы NANA. Результаты анализа квантовохимических расчетов показывают, что глукозу и фруктозу можно использовать в качестве...
модификаторов для адсорбции NANA. Молекулы этих углеводов родственны поверхности кремнезема и могут создавать комплексы с N-ацилглюкозаминовой кислотой. Было показано, что водородные связи между гидроксильными группами углеводов и силанольными группами ВДК играют главную роль при образовании межмолекулярных комплексов. Расчеты, которые были проведены, показывают, что адсорбция моносахаридов на поверхности кремнезема возможна, но стоит учитывать их размещение, а также зависит от метода проведения адсорбции. Возможна последовательная адсорбция сахаридов, а потом NANA, или адсорбция из раствора моносахаридов и NANA на поверхности кремнезема.

Ключевые слова: глюкоза, фруктоза, поверхность кремнезема, адсорбция, метод теории функционала плотности, кластерное приближение

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