

Chemical equilibria of complexes in urine. A contribution to the physicochemistry of infectious urinary stone formation



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ABSTRACT

The formation of infectious urinary stones is a complex physicochemical process that occurs in urine. Infectious urinary stones are formed only when the urinary tract is infected by microorganisms producing urease. The presence of urease-positive bacteria in urine causes the elevation of the concentration of ammonia and carbon dioxide. As a consequence, the presence of bacteria in the solution of urine causes the changes in concentration of various ions and influences on the chemical equilibria of various complexes in urine. In this paper, the analysis of chemical complexes created in the solution of artificial urine of basic composition and with additional quantity of ammonia and carbon dioxide is presented. These two cases correspond to the situation without and with infection within the urinary tract, respectively. In other words, in this paper we try to answer to the question how the presence of urease-positive bacteria in urine influences on the chemical equilibria of various complexes in urine.

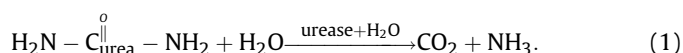
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1. Introduction

Infectious urinary stones are a serious clinical problem that affects up to 20% of the worldwide population [1,2]. This kind of stones is formed only in the case of infection of urinary tract by microorganisms producing urease [3,4]. They are mainly the microorganisms from species of *Proteus*, which are isolated in the case of 70% of infectious stones [5,6]. Most frequently used procedure for infectious urinary stones is extracorporeal shock wave lithotripsy (ESWL), usually associated with long-term antibiotic therapy. Both these procedures do not bring fully positive curing result. This happens because microorganisms can survive in the interior of urinary stone [7] and the applied ESWL can release microorganisms into the urinary tract. Such microorganisms may serve as centres for heterogeneous nucleation. Besides, even dead bacteria can be active centres of recrystallization [7]. Consequently, the recurrence after treatment occurs in 50% cases [2,8]. Apart from ESWL, a long-term antibiotic treatment is advised in the case of infectious urinary stones [9]. However, bacteria are difficult of access for antibiotics in the interior of stone. In addition, long-term antibiotic therapy may

be associated with development of many adverse effects such as emergence of bacterial resistance.

As stated above, the mechanism of the formation of infectious urinary stones is related with urease which has a main participation in the process of crystallization of infectious urinary stones. Urease is a characteristic bacterial enzyme which decomposes urea ($\text{CO}(\text{NH}_2)_2$), normally present in urine of healthy person, into carbon dioxide, CO_2 , and ammonia, NH_3 [4,10–13]:



Ammonia, NH_3 , in water environment creates ammonium ion, NH_4^+ , and an increase in pH of urine takes place according to the reaction [14]:



In the alkaline environment carbon dioxide reacts with water creating the carbonic acid, H_2CO_3 [14]:



Then, the carbonic acid, H_2CO_3 , dissociates according to the

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reactions [14]:



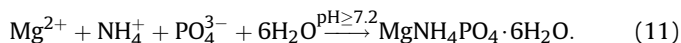
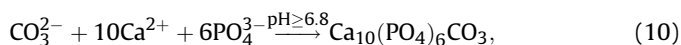
Then, dissociated CO_3^{2-} and HCO_3^- ions undergo the hydrolysis reactions according to the following equations:



In the solution of urine there are also reactions which lead to the formation of phosphate ions [14]:



Such cascade of reactions leads to the supersaturation of solution of urine with the Mg^{2+} , NH_4^+ , PO_4^{3-} , Ca^{2+} , CO_3^{2-} ions. These ions are indispensable to the precipitation of carbonate apatite $\text{Ca}_{10}(\text{PO}_4)_6\text{CO}_3$ (CA), and magnesium ammonium phosphate hexahydrate (MAPH), $\text{MgNH}_4\text{PO}_4 \cdot 6\text{H}_2\text{O}$, known as struvite, according to the reactions [4,10–13]:



CA precipitates first, for $\text{pH} \geq 6.8$. Struvite crystallizes for pH higher than 7.2. CA and struvite crystals are the main components of infectious urinary stones [15,16]. Appearing struvite crystals and CA deposit mix with bacteria and the precipitation process of these two solid phases may be enhanced. The precipitation process may also take place on the bacterial surface. Bacteria surrounded by struvite crystals and CA deposits create the centres of survival inside the infectious urinary stone. Bacteria inside the stone [7] are with difficulty accessible for antibiotics applied to treat the urinary tract infection. Simultaneously, urease-positive bacteria assure the continuity of chemical reactions allowing to keep high pH of urine. Such pH of urine warrants the insolubility of struvite crystals and CA. For the above reasons, infectious urinary stones are still serious medical problem.

The review of literature demonstrates that it is lack of detail analysis of chemical complexes which are able to be formed in the solution of urine. Additionally, there is no analysis of the effect of the presence of microorganisms on the chemical equilibria of various complexes in urine. Therefore, the aim of this paper is the theoretical analysis of chemical complexes created in the solution of urine of basic composition and with the elevated concentration of ammonia, NH_3 , and carbon dioxide, CO_2 . The case of elevated concentration of the NH_3 and the CO_2 corresponds to the presence of microorganisms in urine. In other words, the aim of the presented theoretical analysis is to investigate the influence of microorganisms on the formation of various complexes and their chemical equilibria in urine.

2. Computational procedure

The composition of artificial urine taken into account to analyse the chemical complexes and their chemical equilibria is the

following (with concentrations in g/l in brackets) [17,18]: $\text{CaCl}_2 \cdot 2\text{H}_2\text{O}$ (0.651), $\text{MgCl}_2 \cdot 6\text{H}_2\text{O}$ (0.651), NaCl (4.6), Na_2SO_4 (2.3), KH_2PO_4 (2.8), KCl (1.6), NH_4Cl (1.0), $\text{Na}_3\text{C}_6\text{H}_5\text{O}_7$ (0.65), $\text{Na}_2\text{C}_2\text{O}_4$ (0.023), $\text{CO}(\text{NH}_2)_2$ (urea) (25.0), $\text{C}_4\text{H}_9\text{N}_3\text{O}_2$ (creatinine) (1.1). This is the composition of artificial urine widely accepted in literature [18,19] and the content of the mineral components in such artificial urine corresponds to mean concentration found in 24-h period in natural urine of healthy person. The initial concentrations of individual ions which follow from this composition of urine are presented in Table 1. In particular, from Table 1 it follows that the concentration of the NH_4^+ ions is equal to 18.7 mM. This amount of these ions follows from the fact that in urine the component NH_4Cl exists. Additionally, the concentration of the CO_3^{2-} ion is equal to 0 mM because, in the case of absence of bacteria, the decomposition of urea does not take place.

When urease-positive bacteria are present in the solution of artificial urine, they decompose urea into the CO_2 and the NH_3 as described by Eq. (1). In this paper it is assumed that bacteria decompose all accessible urea (25 g/l). It is also assumed that all released CO_2 and NH_3 (in the gaseous phase) dissolves in the solution of artificial urine. Carbon dioxide, CO_2 , and ammonia, NH_3 , dissolving in urine take different ionic and molecular forms, in particular the CO_3^{2-} and NH_4^+ form, respectively (Eqs. (2) and (5)). From this it follows that in the case of presence of urease-positive bacteria in the solution of artificial urine, the elevated concentrations of the CO_3^{2-} and the NH_4^+ ions occur in urine. The elevated concentrations of the NH_4^+ and CO_3^{2-} ions are equal to 800 mM and 400 mM, respectively (Table 1).

Analysis of speciation of complexes in urine was carried out by using computer program HySS (Hyperquad Simulation and Speciation) [20]. HySS is a program that can be used to perform two distinct functions: titration simulation and calculation of concentrations of species. Details concerning the algorithm used in the program and its other features are given in Ref. [20]. In our case the program HySS is used for speciation analysis of complexes in artificial urine for basic and elevated concentrations of the NH_4^+ and the CO_3^{2-} ions. By entering into the program the initial concentrations of all the components of urine and the values of stability constants of the complexes which might create in it, we are able to compute the molar or percentage concentrations of those complexes depending on pH . By changing the initial concentrations of the components of urine such as the CO_3^{2-} and NH_4^+ ions we again compute the concentrations of different complexes created in the urine. This particular procedure makes it possible to compare chemical equilibria between different complexes in the urine of basic composition with the chemical equilibria of those complexes being created for elevated concentrations of the NH_4^+ and CO_3^{2-} ions.

The stability constants used in HySS program were mainly calculated with the aim of computer code EQUIL [21] (the program EQUIL is widely used in studies of the physicochemical processes which underlie the various stone salt crystallization) and some others were taken from literature [22–24]. The details are given in the Section 3 and the caption of Table 2 which gives the values of these stability constants. It should be emphasised that we have not found in literature the stability constant for the $\text{Ca}_{10}(\text{PO}_4)_6\text{CO}_3$ complex. However, the stability constant for the $\text{Ca}_5(\text{PO}_4)_3\text{OH}$ complex is equal to 38.97 [22]. It is assumed that the stability constant for $\text{Ca}_5(\text{PO}_4)_3\text{CO}_3$ is the same as for the $\text{Ca}_5(\text{PO}_4)_3\text{OH}$ complex. As we consider in the present study the $\text{Ca}_{10}(\text{PO}_4)_6\text{CO}_3$ complex we assumed for this complex the stability constant equal to $2 \cdot 38.97$. The stability constant for the $\text{Ca}_{10}(\text{PO}_4)_6\text{CO}_3$ complex is assumed in the same way in Ref. [25]. Having entered in the HySS computer program the data from Tables 1 and 2, specific molar and percentage concentrations of various complexes and their

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