

**COMPUTATIONAL INVESTIGATIONS OF BIO-
COMPATIBLE METAL ORGANIC FRAMEWORKS (BIO-
MOFs) FOR ADSORPTION-BASED UREMIC TOXIN
SEPARATION**

A Thesis

by

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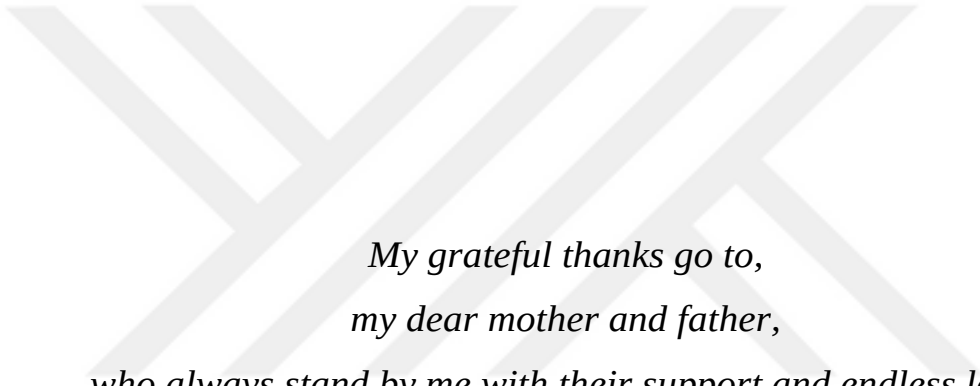
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*My grateful thanks go to,
my dear mother and father,
who always stand by me with their support and endless love.*

ABSTRACT

Polymeric membranes in dialysis machines are currently used to separate uremic toxins from blood of chronic kidney patients. However, polymeric membranes can filter only small water-soluble uremic toxins such as urea and creatinine and generally show poor separation performance (<40 mg/g) for uremic toxins. As an alternative to membranes, adsorption-based separation methods can be used to remove uremic toxins from blood. In this thesis, we identify adsorption-based uremic toxin separation performances of 315 bio-compatible metal organic frameworks (bio-MOFs) by performing atomically-detailed simulations. We first identified hydrophobic bio-MOFs and then computed their urea, creatinine, and water uptakes by performing grand canonical Monte Carlo (GCMC) simulations at 310 K and 1 bar. Results showed that several bio-MOFs outperform traditional adsorbents such as zeolites, activated carbons, zeolite-polymer composite nanofibers and polymers in terms of creatinine and urea uptakes. Adsorption selectivities for urea/water, creatinine/water and creatinine/urea separations were calculated at both infinite dilution and 1 bar, 310 K. Adsorption selectivities of most bio-MOFs for urea/water separation calculated at 1 bar were found to be much higher than those computed at infinite dilution. However, adsorption selectivities for creatinine/water separation calculated at 1 bar were much lower than those computed at infinite dilution for most bio-MOFs due to the difference in interaction strength of creatinine and urea molecules within the frameworks. We also performed computationally demanding GCMC simulations for binary and ternary mixtures of uremic toxins and results showed that creatinine uptakes of bio-MOFs do not change significantly in the presence of water since creatinine is strongly adsorbed within the pores of bio-MOFs. However, water adsorption in bio-MOFs slightly increased at mixture condition due to the hydrogen bonds occurred between uremic toxins and water molecules. Overall, adenine-based bio-MOFs including bio-MOF-11 (YUVSUE) and bio-MOF-12 (BEYSEF) and a dicyanamide based MOF, KEXDIB were found to be promising candidates for both urea/water and creatinine water separations. Our results will be highly useful for development of high-performance bio-MOF adsorbents for uremic toxin separation.

ÖZETÇE

Polimer membranlar kronik böbrek hastalarının kanından üremik toksinleri ayırmak için diyaliz makinelerinde şu anda kullanılmaktadır. Fakat polimerik membranlar üre ve kreatinin gibi sadece suda çözünür küçük üremik toksinleri filtreleyebilir ve genellikle üremik toksinleri ayırmada düşük performans (<40 mg/g) göstermektedirler. Membranlara alternatif olarak, üremik toksinleri kandan uzaklaştırmak için adsorpsiyona dayalı ayırma yöntemleri de kullanılabilir. Bu tezde, atomik düzeyde detaylı simülasyonlar gerçekleştirilerek 315 biyolojik-uyumlu metal organik yapının (biyo-MOFların) adsorpsiyona dayalı üremik toksin ayırma performansları belirlenmiştir. Öncelikle hidrofobik biyo-MOFlar tayin edilmiş ve daha sonra 310 K ve 1 bar'da Grand Canonical Monte Carlo (GCMC) simülasyonları kullanılarak bu hidrofobik biyo-MOFlar içerisinde tutunan üre, kreatinin ve su miktarları hesaplanmıştır. Sonuçlar birkaç biyo-MOF'un kreatinin ve üre alımı açısından zeolitler, aktif karbonlar ve polimerler gibi geleneksel adsorbanlardan daha iyi performans sağladığını göstermiştir. Üre/su, kreatinin/su ve kreatinin/üre ayrımları için adsorpsiyon seçicilikleri hem sonsuz seyreltmede hem de 1 bar, 310 K'de hesaplanmıştır. Çoğu biyo-MOF için üre/su ayrımı için 1 bar'da hesaplanan adsorpsiyon seçiciliği, sonsuz seyreltmede hesaplanan seçicilik değerlerinden çok daha yüksek bulunmuştur. Fakat biyo-MOFların gözenekleri içindeki kreatinin ve üre moleküllerinin etkileşim gücündeki farklılık nedeniyle 1 bar'da kreatinin/su ayrımı için hesaplanan adsorpsiyon seçiciliği sonsuz seyreltmede hesaplanan seçicilik değerlerinden çok daha düşük bulunmuştur. Ayrıca, hesaplama gücü gerektiren GCMC simülasyonları üremik toksinlerin ikili ve üçlü karışımları için gerçekleştirilmiştir ve sonuçlar biyo-MOFların kreatinin alımlarının su ortamında önemli ölçüde değişmediğini göstermiştir çünkü kreatinin, biyo-MOFların gözenekleri içinde güçlü bir şekilde tutulmuştur. Bununla birlikte, biyo-MOFlarda adsorplanan su miktarı, üremik toksinlerin ve su moleküllerinin arasında meydana gelen hidrojen bağları nedeniyle karışım durumunda biraz artmıştır. Genel olarak, adenin bazlı biyo-MOFların (biyo-MOF-11 (YUVSUE) ve biyo-MOF-12 (BEYSEF) gibi) ve disyanamit bazlı bir MOF olan KEXDIB'in hem üre/su hem de kreatinin/su ayrımları için umut verici adaylar olduğu bulunmuştur. Sonuçlarımız, üremik toksin ayrımı için yüksek performanslı biyo-MOF adsorbanların geliştirilmesi için oldukça faydalı olacaktır.

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NOMENCLATURE

AC	:Activated carbons
Bio-MOFs	:Bio-compatible MOFs
CC	:Critical constant
CFC MC	:Continuous Fractional Component Monte Carlo
CKD	:Chronic kidney disease
$C_{\max}$	:Maximum concentration
C_N	:Blood concentration of healthy people
C_U	:Blood concentration of people with kidney failure
CNT	:Carbon nanotube
CREDIT	:Turkish Chronic Kidney Disease Prevalence Study
CSD	:Cambridge Structure Database
$\text{Cu}_3(\text{BTC})_2$	:Dry copper based MOF
Da	:Dalton
DFT	:Density functional theory
ESP	:Electrostatic potential
ESRD	:End Stage Renal Failure
GCMC	:Grand Canonical Monte Carlo
GFR	:Glomerular Filtration Rate
GO	:Graphene oxide
H-MIP	:Hybrid organic-inorganic imprinted polymer
H_2O	:Water
k_B	:Boltzmann constant
K_{Henry}	:Henry's constant
LJ	:Lennard-Jones

LCD	:The largest cavity diameter
LD ₅₀	:Oral lethal dose
MC	:Monte Carlo
MCBs	:Mesoporous carbon beads
MIL	:Materials of Institut Lavoisier
MOF	:Metal Organic Framework
MFI	:Microporous zeolite silicalite
MMM	:Mixed matrix membrane
MXene	:Two-dimensional transition metal carbide
N	:Amount of maximum adsorption
N _A	:Number of atom
NKF-KDOQI	:National Kidney Foundation - Kidney Disease Outcomes Quality Initiative
NU	:Northwestern University
N ₂	:Nitrogen
OPLS	:Optimized Potentials for Liquid Simulations
PAm	:Polyamide
PAN	:Polyacrylonitrile
P _c	:Critical pressure
PES	:Polyether sulfan
PLD	:Pore limiting diameter
PSf	:Polysulfone
PV	:Pore volume
q	:Particle atomic charge
Q _{eq}	:Charge equilibration method

Q_{st}	:Isosteric heat of adsorption
r	:Separation distance
r_i	:Position of the i^{th} particle
RDF	:Radial Distribution Function
RRT	:Renal Replacement Therapy
S	:Selectivity
SA	:Surface area
SBA-15	:Mesoporous silica
T_b	:Normal boiling point
T_c	:Critical temperature
TSN	:Turkish Society of Nephrology
U	:Potential energy
UFF	:Universal Force Field
ZIF	:Zeolitic imidazolate framework
ρ	:Density
ϕ	:Porosity
ω	:Acentric factor
σ	:Molecular length
ϵ_0	:Electric constant
ϵ	:Well depth

CHAPTER I

INTRODUCTION

A healthy people's kidney filters and eliminates metabolic wastes in blood. As kidney loses its function, concentration of metabolic wastes containing uremic toxins increases with time and death may occur within a week [1]. Therefore, it is important to eliminate uremic toxins from blood to reduce risk of death. Definitive treatment for patients with chronic kidney failure who have lost all their kidney functions is kidney transplantation. However, patients may have physiological and psychological problems based on the acute and chronic rejection of organs, compliance with drug regimens during the organ transplantation process [2]. In addition, kidney transplantation requires a huge cost for patients [3]. Therefore, as an alternative to kidney transplantation, hemodialysis method is commonly used for patients with renal dysfunction [4]. Hemodialysis mainly consists of two steps: purification of blood from uremic toxins in dialysis machine and giving the purified blood back to patient. Current dialysis machines use a semi-permeable membrane and dialysate, a solution containing pure water, electrolytes, and salts, to separate uremic toxins from blood. Urea and creatinine are small and water-soluble uremic toxins and mostly accumulate in patients with kidney failure [5]. Today, polymeric membranes are still used in dialysis machines to remove these small-sized uremic toxins. However, dialysis membranes are not useful for removing some uremic toxins such as p-cresol and indoxyl sulfate due to their strong protein binding [6, 7]. In addition, dialysis treatment is applied for three times a week due to low efficiency and low separation capacity of hemodialysis membranes, and patients spend 2 to 4 hours for each time in dialysis centers. This procedure also has some side effects such as headache, nausea, leg cramps and weakness in patients [8]. For these reasons, developing new and efficient methods as an alternative to hemodialysis is highly required to purify uremic toxins from blood.

Uremic toxins are generally divided into three classes; (i) small and water-soluble molecules ($MW < 500$ Da), (ii) medium-sized molecules ($MW > 500$ Da) and (iii) protein-bound small uremic toxins ($MW < 500$ Da) which are very difficult to remove with membranes [9, 10]. 90 uremic toxins have been identified in the literature so far [11]. Concentrations of uremic toxins in blood range from nanograms per liter to grams per liter. Concentration of medium-sized molecules is usually low. Among them, small and

water-soluble molecules with the highest concentration are urea and creatinine. Although hemodialysis membranes can remove most of these small molecules from blood, their separation performance is low for medium-sized and protein bound uremic toxins that accumulate in the blood [11]. Uremic toxin separation performances of membranes were studied by using different polymer materials such as polyacrylonitrile (PAN), polyamide (PAm) and polysulfone (PSf) membranes in the literature so far [12-14]. However, these membranes have poor uremic toxin removal capacities resulting in long treatment hours. In addition, since patients undergoing hemodialysis treatment experience anaemia, inflammation and oxidative stress, dialysis membranes coated with bioactive materials are required today to reduce these side effects [15].

Adsorption-based uremic toxin separation can be used for blood purification as an alternative to membrane-based separation. Adsorption is the result of physical attractive forces between the surface of porous solids and the adsorbate (uremic toxin) molecules. If an adsorbent has a high internal surface area, it creates a high uptake capacity required for successful separation or purification [16]. It should be noted that besides high uremic toxin removal capacity of an adsorbent, its biocompatibility is also important for an effective separation considering the side effects on living tissues. Some large-pored adsorbents such as activated carbons (AC), [17] zeolites, [12] two-dimensional transition metal carbide (MXene), [18] graphene oxide (GO), [19] polymers, [12, 14, 20] carbon nanotube (CNT) [21] and mesoporous silica (SBA-15) [22] were previously studied for adsorption of uremic toxins. However, uremic toxin adsorption capacity of these adsorbents is low, [18, 19, 23] except for SBA-15. In addition, their biocompatibility is still an important issue. Therefore, developing efficient and bio-compatible adsorbents is very important for hemodialysis applications.

In this thesis, as a first time in the literature, we examined the potential of bio-compatible metal organic frameworks (bio-MOFs) for adsorption-based uremic toxin separations using atomically-detailed simulation techniques. MOFs are recently recognized as promising materials for various different applications including but not limited to gas adsorption, [24] gas and liquid separations [25] and catalysis [26] due to their tuneable physical and chemical properties, high porosities (0.3-0.9), high thermal stabilities and large surface areas (1000-10,000 m²/g) [27, 28]. Due to these superior properties, they can exhibit high performance for uremic toxin separation. We specifically focused on bio-MOFs since materials used in human body can have some side effects on

blood and living tissues such as coagulation of uremic toxins [29, 30]. Structural features of 315 bio-MOFs, that we previously identified [31], including density (ρ), the largest cavity diameter (LCD), pore limiting diameter (PLD), porosity (ϕ), pore volume (PV), and surface area (SA) were first calculated. After this analysis, Henry constants of water for 315 bio-MOFs were computed at infinite dilution, and hydrophobic 122 bio-MOFs were identified to eliminate the effect of water during separation of uremic toxins from an aqueous medium. We also computed Henry constants of urea and creatinine to calculate ideal selectivities of bio-MOFs towards uremic toxins at infinite dilution. We then computed single-component adsorption of urea, water and creatinine in bio-MOFs using grand canonical Monte Carlo (GCMC) simulations at 310 K and 1 bar. We considered continuous fractional component Monte Carlo (CFC MC) moves to compute urea and creatinine adsorption in hydrophobic bio-MOFs. Since uremic toxins form a dense system due to their large structural size, CFC MC was used to solve low insertion and deletion efficiencies in these dense systems[32]. The top-performing 10 bio-MOFs with the highest selectivity towards urea and creatinine were identified at infinite dilution and 1 bar, 310 K. Simulating uremic toxins in an aqueous medium is important for identifying promising bio-MOFs because uremic toxins are transported in body through the blood. For this reason, binary mixture simulations were carried out to examine the interaction of uremic toxins with water. Ternary mixture simulations (urea/creatinine/water) were also performed for promising 6 bio-MOFs for urea/water and creatinine/water separations. Blood of patients with kidney failure may have different uremic toxin concentrations. Therefore, different bulk compositions of uremic toxins for their binary and ternary mixtures were studied in molecular simulations. All mixture simulations were conducted at vapour pressure of water and 310 K. We calculated several adsorbent performance metrics such as uremic toxin uptake capacity and adsorption selectivity at both single-component and mixture conditions. Finally, to mimic a regular dialysis machine, five different types of uremic toxins (urea, creatinine, uric acid, p-cresol and indoxyl sulfate) with water were modelled in senary mixture simulations. The hydrogen bonds between atoms were investigated in detail with Radial Distribution Function (RDF) analysis during GCMC simulations. Isosteric heats for uremic toxin adsorption in bio-MOFs were also computed during molecular simulations.

This thesis focuses entirely on adsorption-based uremic toxin separation in bio-MOFs using a computational screening approach. Chapter II gives information about the

chronic kidney disease and its treatment methods. As an alternative to current treatment methods, adsorption-based separation method was introduced considering both experimental and computational studies. In Chapter III, the computational methodology used in this study was discussed in detail. In Chapter IV, urea and creatinine uptakes of 60 bio-MOFs were evaluated at infinite dilution, single-component (1 bar), and multi-component conditions. Promising bio-MOF adsorbents for uremic toxin separation were then identified. In Chapter V, p-cresol and uric acid uptakes of 60 bio-MOFs were investigated at infinite dilution, single-component and binary mixture conditions and the competitive adsorption was discussed. We believe that the methods used in this thesis can guide both experimental and computational studies for the development of artificial membranes and/or adsorbents used for uremic toxin separations.

CHAPTER II

LITERATURE REVIEW

Chronic kidney disease (CKD) is seen as a serious public health problem in all over the world. However, the awareness rate of this disease does not exceed 10% in the world.[33] Based on the Turkish Chronic Kidney Disease Prevalence study, conducted by Turkish Society of Nephrology (TSN), the awareness of CKD in Turkey is below 2% [34]. CKD progresses to the End Stage Renal Failure (ESRD) due to low awareness in patients. CKD consists of 5 stages shown in **Table 1** according to the National Kidney Foundation - Kidney Disease Outcomes Quality Initiative (NKF-KDOQI).[35] Glomerular Filtration Rate (GFR) is used to form an international criterion in the treatment of patients. GFR indicates the amount of blood filtered from the glomeruli in one minute. When the kidney functions are damaged, the filtration rate in the glomeruli decreases and waste products begin to accumulate in blood [36]. Normal GFR in young adults is from ~120 to 130 mL/min/1.73 m², [35] whereas GFR is ~107 mL/min/1.73 m² in healthy adults between 20–40 years of age and reduces at a rate of ~0.7mL/min/1.73 m² per year [37]. A healthy human's kidney contains approximately 1–1.5 million nephrons, called the functional unit of kidney. The number of nephrons in the human body decreases and this causes a decrease in GFR [38]. The kidney poses a low risk for CKD up to stage 2, but an irreversible loss of nephrons begins in the kidney of a patient who reaches to stage 2 to 4. Having lost most of its nephrons, the kidney reaches to the ESRD [37].

Table 1. Stages of chronic kidney disease [37].

Stages	Definition	GFR (ml/min/1.73 m ²)	Risk
1	Kidney damage with normal or high GFR	≥90	Low risk
2	Kidney damage with mildly decreased GFR	60-89	Low risk
3	Moderate kidney failure	30-59	Moderately increased risk
4	Severe kidney failure	15-29	High risk
5	End-stage renal disease	≤15	Very high risk

ESRD patients need dialysis or kidney transplant treatments called Renal Replacement Therapy (RRT) to survive. Incidence and prevalence of ESRD per million population of Europe countries including our country are shown in **Figure 1**. The incidence and prevalence values represent the number of newly acquired and pre-existing patients in population at risk, respectively. In 2016, Greece has the highest incidence in

Europe with 251 per million population (pmp) while Ukraine has the lowest incidence of 32 pmp. Turkey is in the middle of this list with 140 pmp (**Figure 1(a)**). The incidence value is determined by the number of patients who need RRT treatment, and it is seen that not all patients can recover after treatment and the number of patients increases the prevalence value. On the other hand, Portugal (1906 pmp) shows the highest prevalence in Europe, surpassing Greece (1284 pmp). This may indicate that Greece is more successful than Portugal in the treatment of RRT. In addition, while Ukraine (188 pmp) has the lowest prevalence value, Turkey is in the middle with 933 pmp again (**Figure 1(b)**) [39]. Rates of rise in ESRD are affected by many factors. Differences in incidence and prevalence rates in high-income countries are mainly due to ethnic, racial, and genetic differences. In low-income countries, however, the ESRD rate is severely affected by the low access to dialysis treatments [40].

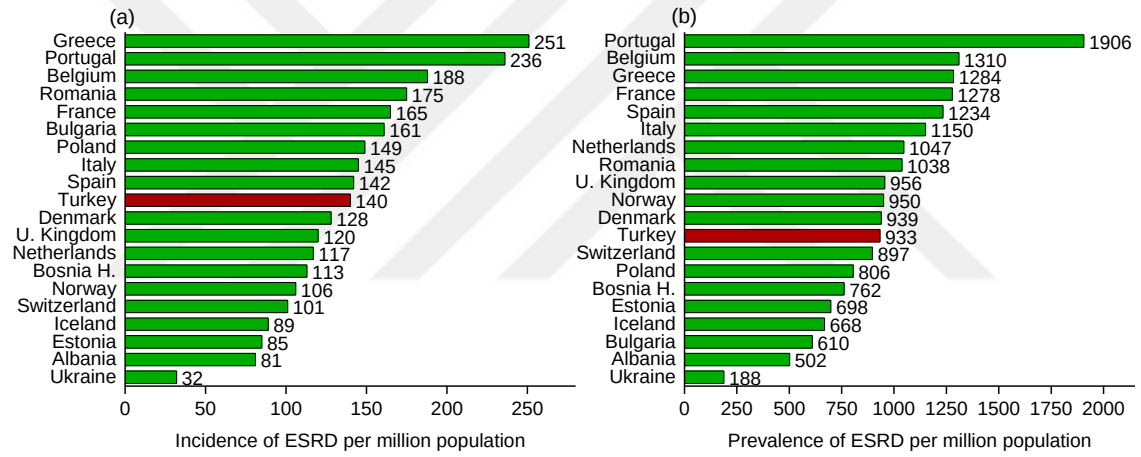


Figure 1. Incidence and prevalence of ESRD in various countries according to the US Renal Data System 2016 report (Figure is modified from ref. [39, 41]).

According to the data of TSN Kidney Registration System, prevalence of ESRD is increasing in our country. Distribution of ESRD patients in Turkey by years is shown in **Figure 2**. Although incidence value shows a horizontal distribution in Turkey, the number of patients with ESRD, which was 491 per million population in 2005, has increased nearly twice in 14 years and reached 1008 in 2019 [41].

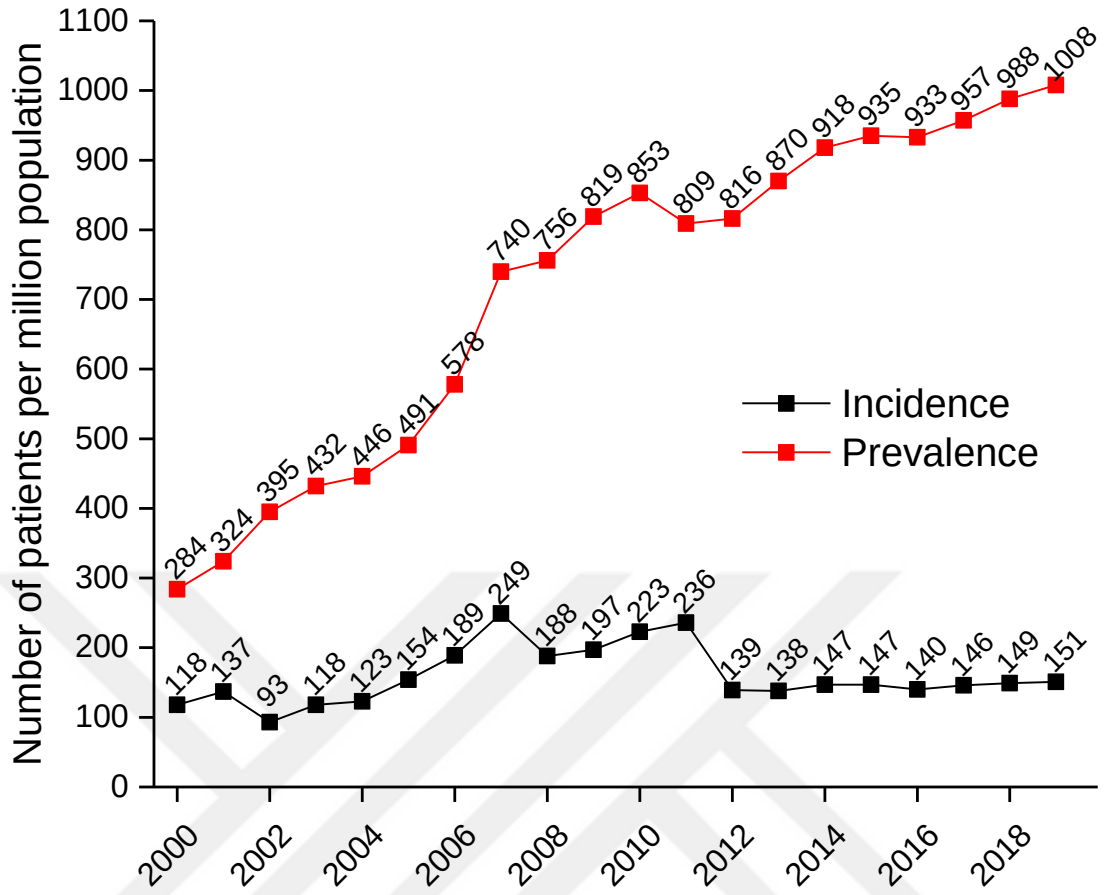


Figure 2. Comparison of incidence and prevalence of ESRD in Turkey (Figure is modified from ref. [41]).

The most appropriate treatment for ESRD patients is kidney transplantation, which restores all kidney functions. However, due to the limitations of transplantation possibilities, most of the patients have dialysis treatment. Only 22% of more than 2.6 million patients in the world have undergone kidney transplantation [40]. Hemodialysis is still the most widely used method for blood purification in all over the world.

2.1 Hemodialysis

Hemodialysis is the key treatment for people with ESRD whose kidney functions are damaged [6]. Dialysis is defined as the diffusion of molecules in solution flowing across a semipermeable membrane. Hemodialysis aims to restore the intracellular and extracellular fluid environment like the normal kidney. It uses a dialysate flowing across the membrane to provide this environment. Dialysate is defined as a pure water mixture containing salts and electrolytes such as sodium and bicarbonate. While soluble uremic toxins such as urea are transported from blood to the dialysate, salts and electrolytes are

transported into the blood (**Figure 3**). Thus, it can remove uremic toxins accumulated in the blood by diffusion process. In addition to diffusion, an ultrafiltration process maintained by a hydrostatic or osmotic pressure gradient is also applied in hemodialysis due to excessive fluid accumulation in the body of ESRD patients [6]. In this process, called peritoneal dialysis, sugar is added to the dialysate. Sugar molecules cannot pass through the membrane and provide excess water in blood to pass into the dialysate [42].

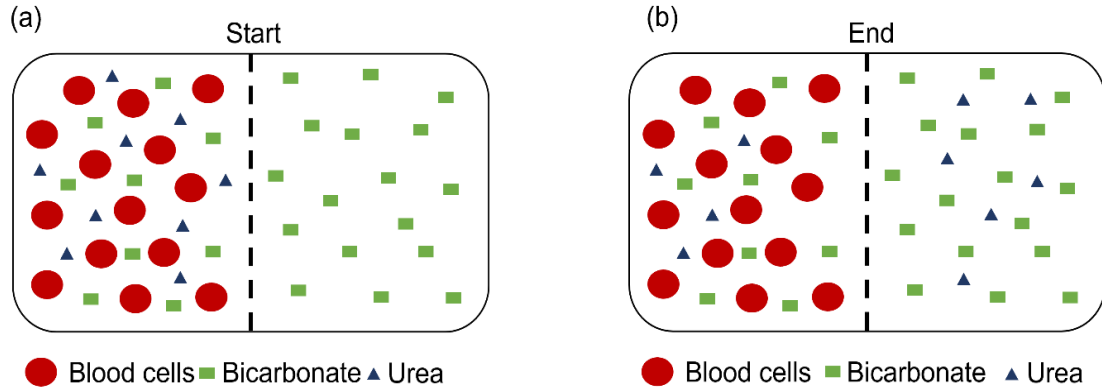


Figure 3. Representation of the pattern of solute removal with hemodialysis considering (a) initial and (b) final processes (Figure is modified from ref. [6]).

Today, hemodialysis method is used at a rate of 76% for ESRD, although the patients are treated under very difficult conditions [41]. In addition to the size and weight of the equipment used in hemodialysis, treatment time is important for the removal of solutes and excess fluid. Treatment times are long in hemodialysis since short treatment times does not provide an effective removal [6]. Generally, patients receive treatment by 2-3 times a week and between 2 and 4 hours for each session. Despite long treatment periods, mortality rates are still very high (~17% to 20% per year) [43] because conventional hemodialysis systems cannot efficiently remove uremic toxins. For example, Lesaffer et al.[7] investigated uremic toxin removal performances of different hemodialysis membranes and found removals as 75% for urea, 66% for creatinine, 29% for p-cresol and 35% for indoxyl sulfate. Therefore, enhancing the uremic toxin removal capacities of membranes used in dialysis is still an important issue.

Urea and creatinine are free and water-soluble solutes, and they have low molecular weights. Due to their water solubility, urea and creatinine can be separated by hemodialysis membranes. However, protein-bound uremic toxins such as p-cresol and indoxyl sulfate cannot be effectively separated by membranes due to their high albumin-binding property. For example, Tijink et al.[44] investigated the application of a hollow

fiber mixed matrix membrane (MMM) containing polyethersulfon (PES) for removal of uremic toxins. They showed that ~ 27 mg/g creatinine can diffuse through MMM whereas p-cresol sulfate and indoxyl sulfate can only diffuse through MMM with a very low concentrations of 2.8 and 4.2 mg/g, respectively. Patients with CKD can survive with hemodialysis, but some side effects may be seen due to ineffective separation of uremic toxins. The main side effects of hemodialysis treatment are fatigue, lack of energy, dry mouth and skin, anaemia, low blood pressure, nausea, leg cramps, sleeping sickness and headache [45]. Therefore, it is very important to develop a more economical, fast, and effective separation method for the treatment of kidney failure.

2.2 Adsorption-Based Uremic Toxin Separation

As an alternative to hemodialysis, adsorption-based separation can be used for blood purification. Adsorption is based on van der Waals and coulombic interactions between adsorbents and adsorbates. Large surface area and high porosity are generally required for an efficient adsorption-based separation and the identity of an adsorbent material determines the efficiency of separation [31, 46]. To date, several porous adsorbent materials such as activated carbons (AC), [23, 47, 48] zeolites, [49-51] two-dimensional transition-metal carbide (MXene), [18, 52] graphene oxide (GO), [19] polymers, [20, 53-55] carbon nanotube (CNT) [21] and mesoporous silica (SBA-15) [22, 56] have been used for adsorption of uremic toxins. For example, Kameda et al.[23] examined adsorption of urea, creatinine, and uric acid in a spherical activated carbon at three different temperatures and reported the highest equilibrium adsorption of urea, creatinine, and uric acid at 10 °C as 1.59, 18.4 and 24.3 mg/g. Wernert et al.[12] compared adsorption time and p-cresol uptake in microporous zeolite silicate (MFI) with those used in dialysis membranes. They showed that zeolite silicate provides a quick reach (almost 2 minutes) to the equilibrium concentration than dialysis membranes (3 hours). Zeolite silicate adsorbed almost 106 mg p-cresol/g whereas dialysis membranes only adsorbed ~ 37 mg p-cresol/g of membrane, suggesting that zeolite silicate can outperform dialysis membranes in terms of p-cresol uptake.

In another study, Meng et al.[52] studied urea removal from both aqueous solution and dialysate in MXene and reported the maximum urea adsorption in this adsorbent as 10.4 mg/g and 21.7 mg/g at 298 K and 310 K, respectively. Similarly, Zhao et al.[18] used the same adsorbent, MXene to remove creatinine and uric acid from an aqueous solution and dialysate and found 45.7 and 17 mg/g creatinine and uric acid

uptakes, respectively. Cheng et al.[19] calculated the maximum adsorption capacity of p-cresol, creatinine and urea in three different types of adsorbents (AC, three zeolites ZSM-5 and GO). They showed that GO exhibits the highest p-cresol (~434 mg/g) and creatinine (~114 mg/g) uptakes whereas zeolite (ZSM5-400) provides the highest urea (~42 mg/g) uptake. They also investigated adsorption of p-cresol and creatinine within a composite adsorbent (GO, zeolite-400 and AC) and found similar equilibrium adsorption amounts of ~206 mg/g for p-cresol and ~42 mg/g for creatinine in pristine and composite adsorbents. Chang et al.[53] reported 32 mg adsorbed creatinine/g of a hybrid organic-inorganic imprinted polymer (H-MIP). Ye et al.[21] studied the adsorption properties of creatinine on CNT and reported 25 mg/g creatinine uptake at 310 K. Cheah et al.[22] compared the urea adsorption performance of four different adsorbents. They found that amine-functionalized SBA-15 (542.6 mg/g) has the highest urea uptake compared to commercial dense silica (109.6 mg/g), mesoporous silica SBA-15 (498.6 mg/g), and commercial activated carbon (348.8 mg/g). This was attributed to strong intermolecular interactions between urea molecules and functional amine groups of SBA-15. Nguyen et al.[56] investigated adsorption of urea, creatinine and hippuric acid within amine-functionalized SBA-15 and reported the maximum urea, creatinine and hippuric acid uptakes as 950.4 mg/g, 56.5 mg/g and 111.7 mg/g, respectively. The high adsorbed amount of urea was attributed to strong hydrogen bonds between the amine groups of urea and SBA-15. They also examined co-adsorption of urea and hippuric acid and found the maximum uptake of urea (711.1 mg/g) and hippuric acid (88.8 mg/g). Here, competition between urea and hippuric acid molecules reduced the maximum adsorption amounts of uremic toxins in SBA-15. In another study, creatinine uptakes of poly(ether sulfone)/activated carbon (87 mg/g)[17] composite and polyacrylonitrile zeolite nanofiber (880 mg/g)[50] composite were found to be much higher than those of pristine activated carbon (18.4 mg/g)[23] and pristine zeolite (37.5 mg/g) [5]. All these studies show that adsorbents provide better performance than traditional membranes (<40 mg/g) used for uremic toxin separation in hemodialysis [14, 50, 57]. However, although the uremic toxin separation performance of these materials has been studied for biomedical applications, their biocompatibility is not known. Biocompatibility of a material used in a human body has positive effects on living tissues [30]. Therefore, using biocompatible adsorbents to separate uremic toxin from the blood is significant. Zeolites,[58] MXenes, [59] polymers [60] and mesoporous silicas [61] can be biocompatible materials and be used directly for uremic toxin separation. However, direct contact between particles of

activated carbons, [62] graphene oxides, [63] and carbon nanotubes [64] and tissue cells may cause cellular damage. Separation performance of these adsorbents in a living tissue may only be examined when adsorbents are coated with a biocompatible material [65].

2.3 Metal Organic Frameworks (MOFs)

Metal organic frameworks (MOFs), as a new class of porous materials, have attracted attention and widely studied for gas storage [66], separation [67], and catalysis [26] applications in recent years due to their tuneable structural properties [68]. MOFs are built from metal ions or clusters and organic ligands to create strong coordinate bonds (**Figure 4**) [28]. Metal sites during MOF synthesis can be selected as almost any cation, including alkaline earth, transition metals, and lanthanides, while organic ligands can consist of phosphonates, carboxylates, pyridyl, polyamines (benzene, imidazole, oxalic acid), and cyano groups [69].

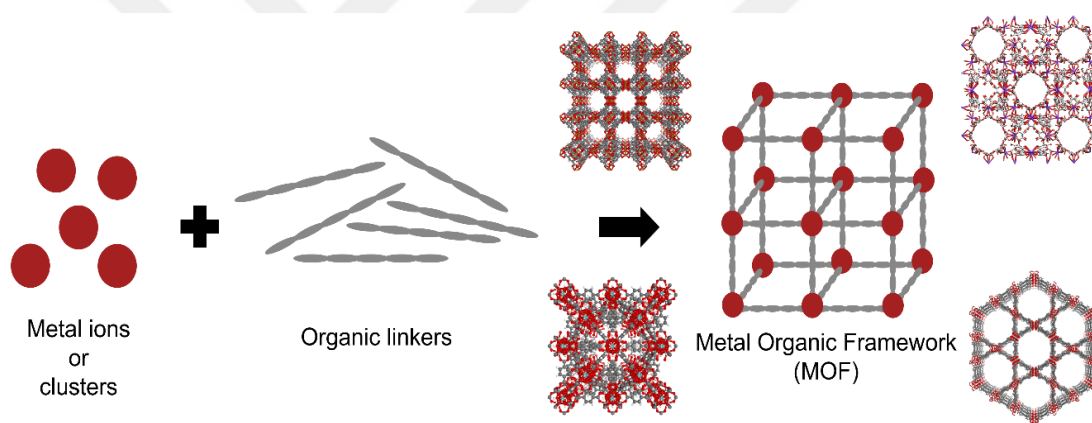


Figure 4. Representation of the structure of metal organic frameworks (MOFs).

Due to their large surface areas and highly porous structures, MOFs have been recently tested for uremic toxin separations. For example, Horcajada et al.[70] reported urea uptakes in MIL-100(Fe) and MIL-53(Fe) as 692 mg/g and 635 mg/g, respectively. Yang et al.[71] examined thermodynamics of creatinine adsorption in MIL-100(Fe) and creatinine adsorption in this MOF was found as 190.2 mg/g. Kato et al.[72] showed that NU(Northwestern University)-1000, a Zr-based MOF, exhibits the highest potassium p-cresol sulphate uptake of 440 mg/g and the highest potassium indoxyl sulfate of 193 mg/g at 303 K. Loera-Serna et al.[73] observed adsorption of urea on a dry copper based MOF ($\text{Cu}_3(\text{BTC})_2$) and reported that $\text{Cu}_3(\text{BTC})_2$ can adsorb 250 mg/g of urea. In another study,[74] a composite adsorbent of cotton fabric and zirconium-based MOF were synthesized and the maximum creatinine adsorption amount of this composite was found

as 212.8 mg/g. In all these experimental studies, single-component uremic toxin adsorption in various adsorbents was investigated. However, separation of uremic toxins from blood occurs collectively in a hemodialysis process. Therefore, it is important to study multi-component adsorption of uremic toxins in adsorbents to understand the effect of collaborative adsorption on separation process. To the best of our knowledge, co-adsorption has rarely studied in the literature. For example, Kameda et al.[75] examined co-adsorption of urea, creatinine, and uric acid in activated carbon and almost similar uptakes of uremic toxins were found in ternary mixture. This was explained by the fact that urea, creatinine, and uric acid do not have a competitive adsorption in the mixture. Although there are few experimental studies on uremic toxin adsorption in the literature, there are just a few computational studies. Considering the enormous number of experimentally synthesized MOFs available in the Cambridge Structure Database (CSD) [76], performing experiments for each single MOF is really challenging considering time, source and cost. Herein, molecular simulations can provide information about adsorption mechanisms of uremic toxin molecules in MOFs. Molecular simulations can be also used for identifying the best materials for uremic toxin separation prior to experimental efforts. For example, Wernert et al.[12] performed GCMC simulations to compute p-cresol adsorption in a microporous adsorbent, zeolite silicate and their predictions (112.8 mg/g) were in a good agreement with their experimental measurements (106.2 mg/g). In another study, Narasimhan et al.[77, 78] performed GCMC simulations for single-component p-cresol adsorption and also investigated p-cresol adsorption within the pores of two different zeolites in the presence of water. They found that in the presence of water, the amount of adsorbed p-cresol decreases from 500 mg/g to 100 mg/g since water molecules filled pores of zeolites and hinder adsorption of p-cresol. In these studies, only zeolite adsorbents were considered, there is no computational study on uremic toxin adsorption in MOFs. Therefore, computational studies on both single-component and multi-component uremic toxin adsorption in MOFs are highly required. In addition, since MOFs will be in direct contact with blood during hemodialysis, predetermination of biocompatible MOFs for uremic toxin separation is important to eliminate MOFs with toxic effects. Details of molecular simulations used in this thesis are mentioned in the following chapter.

CHAPTER III

COMPUTATIONAL METHODOLOGY

Molecular simulations can provide accurate predictions about adsorption mechanism of an adsorbate within a material. This chapter describes our material selection criteria, structural analysis of materials, and the computational methodology used in this thesis to predict the adsorption amounts of uremic toxins in bio-MOFs. Grand Canonical Monte Carlo (GCMC) simulations were used to calculate the adsorbed amounts of uremic toxins within the pores and surfaces of bio-MOFs.

3.1 Selection of Biocompatible MOFs (Bio-MOFs)

The Cambridge Structural Database (CSD)[76] includes all synthesized MOF structures with their crystallographic coordinates and each structure is stored with a unique ‘refcode’ which consists of 6 letters. The 2016 MOF database consists of 69,666 MOFs available in CSD [27]. Gulcay and Erucar[31] showed that this MOF database contains 1525 bio-MOFs, which have endogenous organic linkers such as amino acids, porphyrins, nucleobases, proteins, and cyclodextrins and metal sites. **Figure 5** shows the number of metal sites and linkers which are commonly found in these 1525 bio-MOFs. Since bio-MOFs have a variety of linkers and metals, “others” are also listed in **Table A1**. The formate linker (453) has the highest occurrence among 28 different endogenous linkers identified in the literature [79, 80]. Zn (260) is also a commonly preferred metal during synthesis of bio-MOFs based on the oral lethal dose parameter (LD₅₀) [79]. Among these bio-MOFs, 315 bio-MOFs were selected based on pore size and accessible surface area criteria [31]. These materials are expected to perform well in uremic toxin separation and will be studied in detail for uremic toxin adsorption. For this reason, 315 bio-MOFs were selected as an initial bio-MOF subset in this thesis.

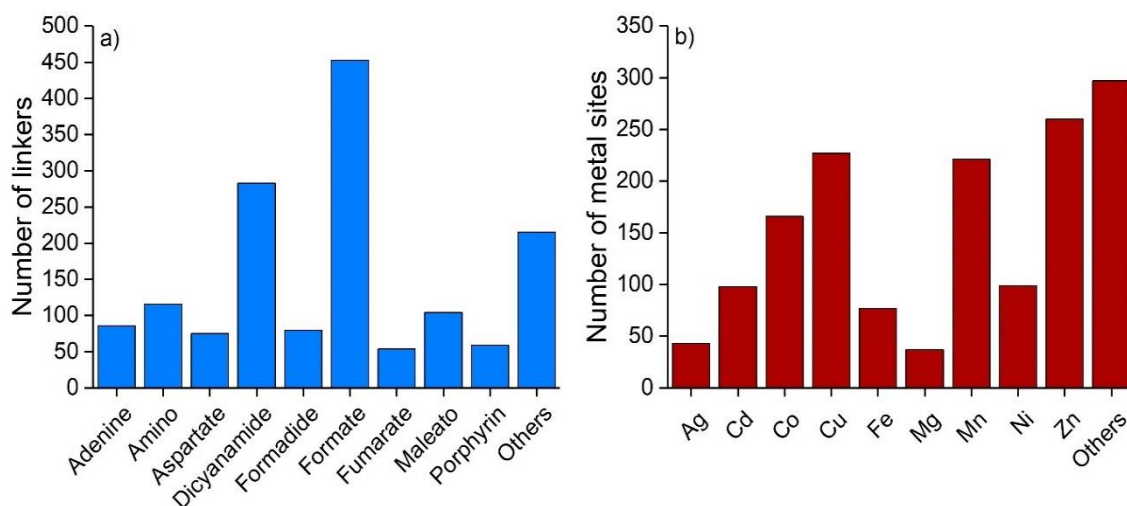


Figure 5. Comparison of metal sites and linkers of 1525 bio-MOFs.

3.2 Structural Characterization

Besides different metal sites and linkers, MOFs also have different structural properties such as the largest cavity diameters (LCDs), pore limiting diameters (PLDs), densities (ρ), porosities (ϕ), pore volumes (PVs), and surface areas (SAs). Structural properties of 315 bio-MOFs were calculated using Zeo++ software (version 0.3) [81]. Pore diameters including PLD, and the LCD give information about the pore geometry of MOFs (**Figure 6**). SA can be defined as the accessible surface area of the framework calculated with a probe. SA calculations were computed using the probe size as a kinetic radius of N_2 (1.86 Å) and step number was set to 2000. PV is defined as the total volume that can be reached by the framework atoms. PV was determined using a zero probe size to specify the maximum free volume and step number was set to 50,000.

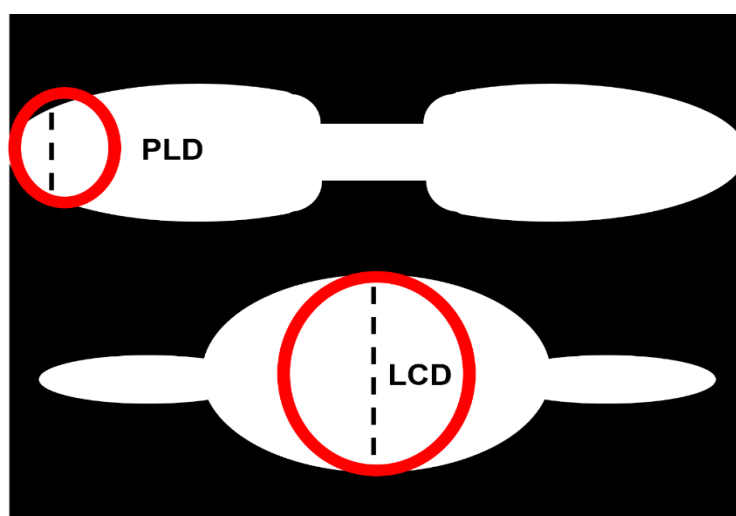


Figure 6. Representations for the LCD and PLD in a pore system.

Figure 7(a) shows the computational methodology followed in this study. Since water (H_2O) can adversely affect the adsorption of urea and creatinine, we firstly identified hydrophobic bio-MOFs by computing Henry's constant of H_2O ($K_{\text{H},\text{wat}}^0$) at infinite dilution and 298 K. Following the literature, [82, 83] we defined an arbitrary limit (dashed line) using the data of a well-known hydrophobic bio-MOF, ZIF-8. The plot in **Figure 7(b)** shows the distribution of 315 bio-MOFs with respect to their PLDs and porosities. Based on the arbitrary limit, 122 bio-MOFs having $K_{\text{H},\text{wat}}^0 < 1.36 \times 10^{-6}$ mol/kg/Pa were determined as hydrophobic bio-MOFs with a large porosity range of 0.30-0.75. PLDs of these bio-MOFs ranged between 4.21 Å and 26.59 Å, while their LCDs were between 3.72 Å and 10.21 Å.

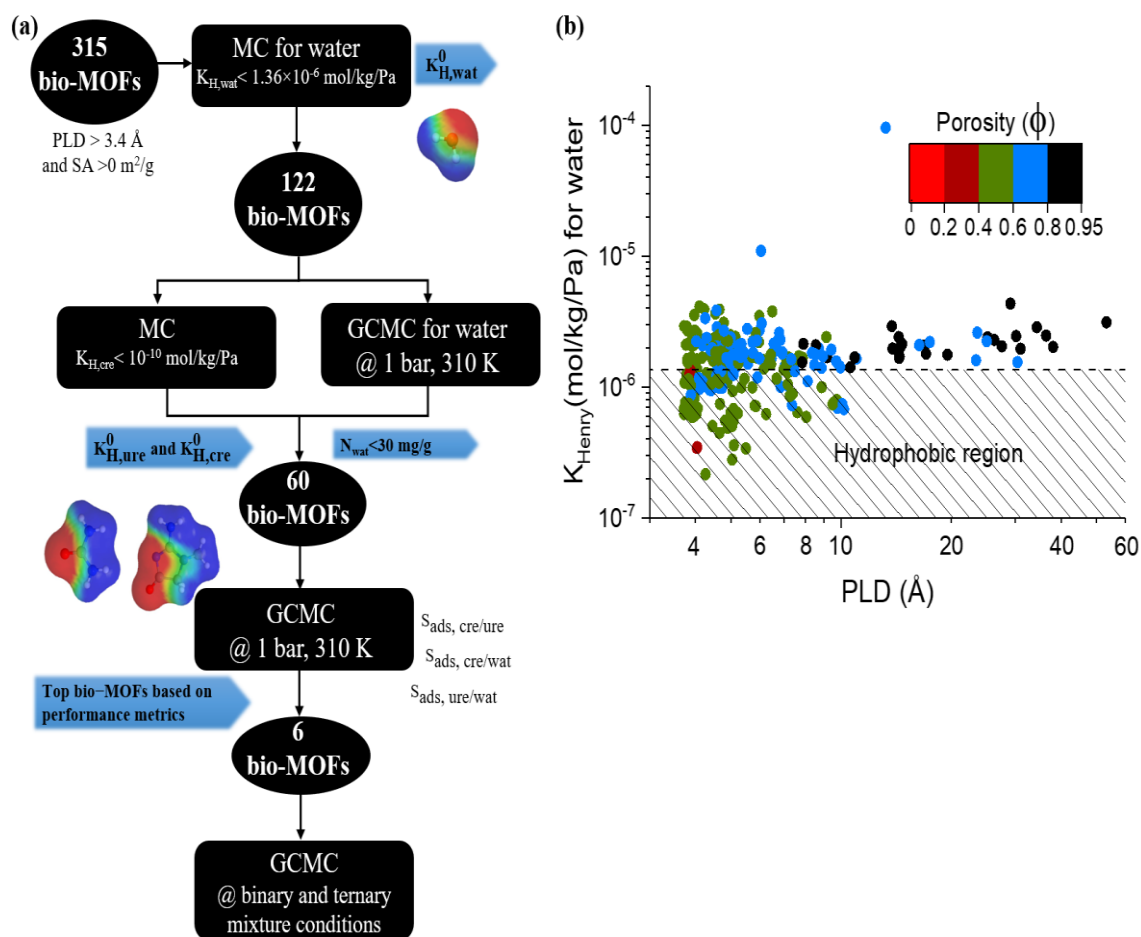


Figure 7. (a) Computational methodology followed in this work and (b) identification of hydrophobic bio-MOFs.

Henry's constant of uremic toxins was also calculated for 122 hydrophobic bio-MOFs. Bio-MOFs having lower Henry's constants than 10^{-10} mol/kg/Pa for urea and creatinine were excluded because of the possibility of poor adsorption of urea and

creatinine. Hydrophobic analysis of bio-MOFs using the Henry's constant of H₂O is important for making a preliminary determination, but water uptake at 1 bar gives a more accurate assessment for hydrophobic bio-MOFs. Therefore, single-component H₂O adsorption in 122 bio-MOFs was computed by utilizing atomically-detailed simulations at 1 bar and 310 K. Bio-MOFs having H₂O adsorption higher than 30 mg/g were eliminated. As a result of this eliminations, 60 bio-MOFs were selected as the optimum members for uremic toxin separation. Subsequently, single-component adsorption simulations of uremic toxins (urea, creatinine, uric acid, and p-cresol) were performed for 60 bio-MOFs. Selectivity of bio-MOFs was calculated at two different conditions: (i) *infinite dilution and 298 K*. Infinite dilution or zero coverage condition is valid at the Henry's law regime. At this condition, interactions between an adsorbate and a material surface are only considered. Thus, adsorption data can be measured down to very low vapor concentrations.[84] The validity of this method has been shown in different studies [66, 85, 86]. Infinite dilution condition was used in this study because it gives information about the uremic toxin adsorption of bio-MOFs at very low pressures. (ii) *1 bar and 310 K* to represent the body conditions. Under these conditions, the top 10 bio-MOFs having the highest selectivity for urea/water and creatinine/water separations were identified and 6 bio-MOFs were identified as common materials for these two separations. GCMC simulations for uremic toxin mixtures were performed for these promising 6 bio-MOFs due to the high computational cost. Simulations for binary mixture of uremic toxins (urea, creatinine, uric acid, and p-cresol) and water were conducted to mimic a realistic mixture in blood. Because urea and creatinine are the most accumulated uremic toxins in blood, simulations were also performed for ternary mixtures of uremic toxins including equal molar and 5/95 bulk composition of urea and creatinine. Henry's constant of indoxyl sulfate and its uptake in promising 6 bio-MOFs were included in our study to examine the adsorption of different types of uremic toxins in bio-MOFs. Finally, simulations of five uremic toxins in a senary mixture with H₂O were performed for promising 6 bio-MOFs to simulate a realistic uremic toxin composition in blood.

3.3 Details of Grand Canonical Monte Carlo (GCMC) Simulations

All GCMC simulations were performed by using RASPA software [87] to calculate adsorption of uremic toxins in a specified temperature and pressure. Volume (V), temperature (T), and chemical potential (μ) are initially defined to determine the number of adsorbed uremic toxin molecules in the system. The number of adsorbate

molecules changes with different molecular movements (rotation, insertion, deletion) in an adsorbent with an imaginary gas reservoir. A chemical equilibrium is established between the studied system and the reservoir, and the adsorbed uremic toxin amounts in the unit cell of the bio-MOFs are obtained from simulations considering the ensemble average of adsorbate molecules. Reservoir pressure and temperature are important parameters to calculate the adsorbate amounts of species. Chemical potential is determined based on the fugacity calculated using the Peng-Robinson equation of state [88]. In simulations, translation, reinsertion, rotation, and insertion movements are defined for guest molecules. These MC moves are processed with a Metropolis scheme and are accepted or rejected according to the probability values calculated based on the Boltzmann-energy. In this thesis, translation, rotation, regrow and swap move of molecule were used for H₂O molecules in GCMC simulations. However, fugacity coefficient, CFSwapLambdaProbability and IdealGasRosenbluthWeight were also added due to structural size of uremic toxin molecules. CFSwapLambdaProbability moves is the move of the continuous fractional component MC (CFC MC). It gradually turns on and off the interactions between the target molecule and the environment by increasing the acceptance rate of the standard insertion-deletion action [89, 90].

Coulomb and Lennard-Jones 12-6 (LJ) potentials [89] were used to predict electrostatic interactions and repulsion-dispersion forces to model interatomic interactions between two atoms, respectively. Coulomb potential considers partial charges of two atoms to calculate their electrostatic interaction as follows:

$$U_{ij} = \frac{1}{4\pi\epsilon_0} \frac{q_i q_j}{r_{ij}} \quad (1)$$

where ϵ_0 , q_i and q_j represent the electric constant and the partial charges of atoms i and j , respectively. Functional form of the LJ potential depends on two parameters: σ is the magnitude parameter and ϵ is the energy parameter [89].

$$U_{LJ} = 4\epsilon_{ij} \left[\left(\frac{\sigma_{ij}}{r_{ij}} \right)^{12} - \left(\frac{\sigma_{ij}}{r_{ij}} \right)^6 \right] \quad (2)$$

Where U_{LJ} defines the intermolecular potential energy between two atoms (i and j), r is the distance from the center of mass of one particle to the center of mass of the other particle, ϵ_{ij} indicates how strongly two atoms attract each other and σ_{ij} defines a molecular

length scale related to the atomic diameter and controls the interaction scale. Moreover, the term of r^{12} and r^6 represents repulsive forces and attractive long-range forces, respectively. Lorentz-Berthelot combining rules are used to describe the interaction energy between two dissimilar unbonded atoms.[91] While the Lorentz rule[92] is performed by using an arithmetic mean of molecular lengths ($\sigma_{ij}=(\sigma_{ii}+\sigma_{jj})/2$), the Berthelot rule [93] is performed by using a geometric mean of well depths ($\epsilon_{ij}=\sqrt{\epsilon_{ii}\cdot\epsilon_{jj}}$).

Crystal structures of uremic toxin molecules were taken from PubChem database [94]. LJ 12-6 parameters of frameworks were taken from the Universal Force Field (UFF).[95] The Lorentz-Berthelot mixing rules were employed for pair-wise interactions [91]. Potential parameters of urea and creatinine were taken from DREIDING [96]. The validity of these force fields will be discussed in the next section. TIP4P/2005 H₂O model was used to model H₂O molecule [97]. Partial charge of each atom forming the bio-MOFs and guest molecules must be computed in order to calculate the electrostatic interactions. For uremic toxin molecules, geometry was optimized using density functional theory (DFT), and partial charges were calculated using the electrostatic potential (ESP) [98]. The partial charges of uremic toxins and water were shown in the appendix (**Table A2**). Since attractive force decreases as the distance between atoms increases, the cut-off distance was accepted as 13 Å to decrease the computational cost. Frameworks and adsorbates were assumed as rigid in all simulations. The lattice constant for each bio-MOF is extended to a length of at least 26 Å. Charge equilibration method (Qeq)[99] was used to estimate the initial partial atomic charges of atoms of bio-MOFs as implemented in RASPA. Electrostatic interactions between adsorbate molecules and the framework atoms were calculated by Ewald summation in simulations [100].

Henry's constants of adsorbates ($K_{H, \text{wat}}^0$, $K_{H, \text{ure}}^0$, $K_{H, \text{cre}}^0$, $K_{H, \text{p-cre}}^0$, $K_{H, \text{uric}}^0$ and $K_{H, \text{ind}}^0$) were calculated by Widom insertion method [89] at 298 K and infinite dilution. A total of 2×10^5 cycles with 10^5 cycles for initialization and the last 10^5 cycles for ensemble averages were used for computing Henry's constant of adsorbates and isosteric heat of adsorption Q_{st}^0 . GCMC method was used for single-component simulations of adsorbates at 310 K and 1 bar. Single-component GCMC simulations were performed for a total of 10^5 cycles with 5×10^3 cycles for both initialization and equilibration, and the last 9×10^4 cycles for ensemble averages. Mixture simulations were carried out for a total of 10^6 steps with the first 10^4 steps for equilibration. Water mole fractions in the bulk mixture were

set between 0.90-0.99 for urea/water and creatinine/water mixture, e.g., $X_{\text{water}}/X_{\text{urea}}$: 0.96/0.04) and were set between 0.90-0.98 for ternary and senary mixtures. Saturation vapor pressure of water was considered in mixture simulations for dilute solutions of uremic toxins. Saturation vapor pressure of water at 310 K was calculated using the Antoine equation.[101] GCMC simulations were also performed for co-adsorption of adsorbates at 0.063 bar, the vapor pressure of H₂O at 310 K. The saturated vapor pressure of H₂O was accepted as the total pressure because vapor pressure of urea (1.6×10^{-8} bar), [102] creatinine (2.7×10^{-4} bar) [103] and p-cresol (1.4×10^{-4} bar) [102] was assumed to have no contribution to the total pressure.

$$\log_{10}P = A - \frac{B}{T + C} \quad (3)$$

where A, B, and C being the Antoine coefficients [101]. Antoine equation parameters of urea and water is shown in **Table A3**. Those of creatinine, uric acid, p-cresol and indoxyl sulfate are not available in the literature.

3.4 Computational Screening of bio-MOFs

To perform GCMC simulations, one needs critical temperature, critical pressure, and acentric factor of adsorbates in the molecule file to calculate the fugacity coefficient. In the literature, critical constants (CCs) were only found for urea and p-cresol. Since CCs of creatinine are not available in literature, CCs of urea were also used for creatinine in simulations. However, there are several methods to predict the CCs such as Klincewicz, Lydersen and Joback in the literature. The Joback method is less complex and more accurate than other methods used for predictions of CCs. The Joback method is particularly good for estimating the critical temperature and needs the normal boiling point to calculate it. If the normal boiling point of pure component is unavailable, it can also predict the normal boiling point with an error of 2.4 % [104]. However, if an experimental boiling point is available, it is recommended to use it directly because the accuracy of estimated T_c is strongly dependent on the normal boiling point. Using an experimental boiling point gives a more accurate result with an error of 1.1 % [104-106]. For this reason, CCs for uric acid and indoxyl sulfate were estimated by Joback method. **Table 2** shows comparison of the uremic toxin's CCs estimated by the Joback method and their CCs reported in the literature.

Table 2. Comparison of critical constants estimated for uremic toxins using Joback method with those obtained from the literature [107].

		T_c (K)	P_c (bar)	T_b (K)	ω
Urea	Literature	638.13	77.53	438.1 ± 23	0.613
	Joback*	638.13	77.35	421.21	0.547
	Joback**	663.72	77.35	438.1	0.547
Creatinine	Literature	#	#	457.45 ± 23	#
	Joback*	832.12	59.17	563.04	0.572
	Joback**	676.07	59.17	457.45	0.572
P-cresol	Literature	704.65	51.5	475.05	0.507
	Joback*	696.68	50.30	466.86	0.464
	Joback**	708.91	50.30	475.05	0.464
Uric acid	Literature	#	#	1136.15	#
	Joback*	1055.41	84.79	756.21	1.0982
	Joback**	1585.68	84.79	1136.15	1.0982
Indoxyl sulfate	Literature	#	#	#	#
	Joback*	851.62	65.99	640.58	1.419
	Joback**	#	#	#	#

*: estimated normal boiling point by Joback method.

**: experimental normal boiling point.

#: not available

In Joback method, the critical temperature, T_c, is determined by equation 4:

$$T_c = T_b \times \left[0.584 + 0.965 \times \sum T_{c,i} - \left(\sum T_{c,i} \right)^2 \right]^{-1} \text{ (K)} \quad (4)$$

where $\sum T_{c,i}$ is the contribution of group i for critical temperature. T_b is the normal boiling point. The experimental or accurate normal boiling point is not available for uric acid and indoxyl sulfate, the normal boiling point thus can determine by Joback method as in equation 5:

$$T_b = 198 + \sum T_{b,i} \text{ (K)} \quad (5)$$

where $\sum T_{b,i}$ is the contribution of group i for the normal boiling point. Critical pressure, P_c, is determined by equation 6:

$$P_c = (0.113 + 0.0032 \times N_A - \sum P_{c,i}^{-2})^{-2} \text{ (bar)} \quad (6)$$

where N_A is the number of atoms in the molecular structure, including hydrogens, $\sum P_{c,i}$ is the contribution of group i for the critical pressure.

Lee-Kesler method can be used to estimate the acentric factor, (ω).

$$\theta = T_b/T_c \quad (7)$$

$$\alpha = -\ln(P_c) - 5.92714 + 6.09648/\theta + 1.28862 \times \ln(\theta) - 0.169347 \times \theta^6 \quad (8)$$

$$\beta = 15.2518 - 15.6875/\theta - 13.4721 \times \ln(\theta) + 0.43577 \times \theta^6 \quad (9)$$

$$\omega = \alpha/\beta \quad (10)$$

Interaction parameters of bio-MOF atoms and adsorbates in the simulations were obtained from UFF and DREIDING, respectively. These force fields were selected based on the comparison of our predictions with experiments for the urea uptake in MIL-100(Fe). As seen in **Table 3**, simulations were conducted using different force fields (UFF, Optimized Potentials for Liquid Simulations (OPLS) [108] and DREIDING). We selected UFF for the bio-MOF atoms and DREIDING for the uremic toxins' atoms based on the good agreement between our predictions (691.9 mg/g) and experiments (692 mg/g) [109].

Table 3. Comparison of predictions obtained from simulations with different force fields for urea uptake in MIL-100(Fe) at 1 bar and 310 K.

Force field used for bio-MOF	Force field used for urea	Amount of urea (mg/g)	Amount of urea (wt%)
UFF	UFF	726.2	72.6
UFF	DREIDING	691.9	69.2
UFF	OPLS	972.9	97.3
DREIDING	DREIDING	697.3	69.7
DREIDING	OPLS	957.4	95.7

In this thesis, several metrics including ideal adsorption selectivity (S^0) calculated at infinite dilution, 298 K, adsorption selectivity (S_{ads}) calculated at 1 bar and 310 K, and isosteric heat of adsorption (Q_{st}) were considered to evaluate the adsorption-based uremic toxin separation performance of materials. K_{Henry} (Henry's law constants) of adsorbates obtained from MC simulation results were used to calculate S^0 of bio-MOFs. $S_{\text{ads, ure/wat}}^0$, $S_{\text{ads, cre/wat}}^0$, $S_{\text{ads, cre/ure}}^0$, $S_{\text{ads, p-cre/wat}}^0$, $S_{\text{ads, ind/wat}}^0$, $S_{\text{ads, uric/wat}}^0$, $S_{\text{ads, uric/ure}}^0$ and $S_{\text{ads, uric/cre}}^0$ were computed using the ratios of $K_{\text{H,wat}}^0$, $K_{\text{H,ure}}^0$, $K_{\text{H,cre}}^0$, $K_{\text{H,p-cre}}^0$, $K_{\text{H,ind}}^0$ and $K_{\text{H,uric}}^0$. After single-component adsorption simulations computed at 1 bar and 310 K, $S_{\text{ads, ure/wat}}$, $S_{\text{ads, cre/wat}}$, $S_{\text{ads, cre/ure}}$, $S_{\text{ads, p-cre/wat}}$, $S_{\text{ads, ind/wat}}$, $S_{\text{ads, uric/wat}}$, $S_{\text{ads, uric/ure}}$ and $S_{\text{ads, uric/cre}}$ were

calculated using the uptake ratios of N_{wat} , N_{ure} , N_{cre} , $N_{\text{p-cre}}$, N_{ind} and N_{uric} . Adsorption selectivity of bio-MOFs at mixture condition was defined as the ratio of adsorbed amounts of each component normalized by the bulk compositions [110]. All these selectivities can be shown as follows:

$$S_{\text{ads}, i/j}^0 = \frac{K_{\text{H}, i}^0}{K_{\text{H}, j}^0}, \quad S_{\text{ads}, i/j} = \frac{N_i}{N_j}, \quad S_{\text{ads}, i/j} = \frac{N_i/x_i}{N_j/x_j} \quad (11)$$

where, i is urea, creatinine, p-cresol, indoxyl sulfate or uric acid, j is water, urea or creatinine. N is the adsorbed amount of adsorbates and x is the bulk composition of adsorbates.

Isosteric heat of adsorption, a thermodynamic variable, is used to analyse adsorption strength of uremic toxins in bio-MOFs. Isosteric heat of adsorption represents the average binding energy of an adsorbed molecule and can be calculated from the ensemble average fluctuations. Isosteric heat of adsorption values of adsorbates were computed based on the average potential energy during simulation at infinite dilution (Q_{st}^0):

$$Q_{\text{st}}^0 = -\Delta H = \langle U_{\text{gh}} \rangle - \langle U_{\text{g}} \rangle - RT \quad (12)$$

where R and T are ideal gas constant, and temperature, respectively. $\langle U_{\text{gh}} \rangle$ represents the average potential energy of the guest molecule inside the bio-MOF and $\langle U_{\text{g}} \rangle$ is the average potential energy of the adsorbate in the reference state.

Uremic toxin concentrations increase in blood of patients due to the dysfunction of their kidney. **Table 4** shows the rates of uremic toxins accumulated in blood of healthy people and people with kidney disease. In addition, the lethal limit for patients is indicated as the maximum concentration (C_{max}) of uremic toxin accumulated in blood. To imitate real uremic toxin concentrations in blood, the percent component rate was calculated for each uremic toxin in ternary and senary mixtures as follows:

$$\text{Component rate \%} = \frac{C_{\text{max}, i}}{\sum C_{\text{max}}} \times 100 \quad (13)$$

Using the maximum concentrations of uremic toxins, urea and creatinine concentrations were found to be 95% and 5% in ternary mixture, respectively. Urea

(87%), which accumulated most in the blood, was considered with a higher ratio than other uremic toxins (creatinine (5%), uric acid (3%), p-cresol (1%) and indoxyl sulfate (4%)) in senary mixture.

Table 4. Concentrations of free water soluble and protein bound uremic toxins measured in blood of healthy people (C_N) and patients having kidney diseases (C_U , maximum C_{max}) [5].

Solute	C_N (mg/dl)	C_U (mg/dl)	C_{max} (mg/dl)	Group
Urea	<40.2	230±110	460	Carbamides, free water-soluble solutes
Uric acid	<6.72	8.33±4.45	14.67	Purines, free water-soluble solutes
Creatinine	<1.2	13.6±4.6	24	Guanidines, free water-soluble solutes
p-Cresol	0.06±0.1	2.01±0.44	4.07	Phenols, protein bound solutes
Indoxyl sulfate	0.06±0.55	5.3±9.16	23.6	Indoles, protein bound solutes

The radial distribution function $g(r)$ defines the probability of finding a particle at a distance r from a given particle. RDF, ($g_{ij}(r)$), can be expressed as:

$$g_{ij}(r) = \frac{N_{ij}(r, r+\Delta r)V}{4\pi r^2 \Delta r N_i N_j} \quad (14)$$

where r represents the distance between atom i and atom j , $N_{ij}(r, r+\Delta r)$ represents the number of j atoms in a shell from r to $r+\Delta r$ around the i atom, V represents the system volume, and N_i and N_j represent the numbers of i and j atoms, respectively. RDF analyses were done for single-component, binary (urea/water:10/90, creatinine/water: 10/90) and ternary (creatinine/urea/water:5/5/90, creatinine/urea/water: 0.5/9.5/90) mixture simulations of promising 6 bio-MOFs with the highest selectivity for urea/water and creatinine/water separations. RDF analysis was primarily performed between polar atoms of uremic toxins and polar atoms of bio-MOFs. In addition, it was examined to detect hydrogen bonds between uremic toxin atoms themselves and between uremic toxin atoms and H_2O atoms. RDF results were written every 10^4 cycles during GCMC simulations. 300 and 12 were used for RDF histogram size and RDF range, respectively.

CHAPTER IV

INVESTIGATION OF THE POTENTIAL OF BIO-MOF ADSORBENTS FOR UREA AND CREATININE SEPARATION

4.1 Motivation

Polymeric membranes in dialysis machines are currently used to separate uremic toxins from blood of patients with CKD. As an alternative to membranes, adsorption-based separation methods can be used to remove uremic toxins from blood. Recently, metal organic frameworks (MOFs) have been tested for separation of uremic toxins due to their highly porous and tuneable structures. In this work, we identify adsorption-based uremic toxin separation performances of 315 bio-MOFs by performing atomically detailed simulations and then first determined 122 hydrophobic bio-MOFs. 60 bio-MOFs were predicted to be the most suitable materials for uremic toxin separation based on the single-component GCMC simulation results at 1 bar, 310 K. Adsorption selectivities of bio-MOFs for urea/water, creatinine/water and creatinine/urea separations were calculated at both infinite dilution and 1 bar, 310 K. 6 promising bio-MOFs were identified for urea/water and creatinine/water separations. Results showed that bio-MOFs outperform traditional adsorbents such as zeolites, activated carbons and polymers in terms of creatinine and urea uptakes. We also performed simulations for binary and ternary mixtures to examine multi-component adsorption of uremic toxins within the pores of 6 bio-MOFs at 310 K. Our results will be highly useful for development of high-performance MOF adsorbents for uremic toxin separation.

4.2 Single-Component Urea and Creatinine Adsorption

Among 315 bio-MOFs, 122 hydrophobic bio-MOFs were identified using $K_{H, \text{water}}$ of ZIF-8, which is known to be hydrophobic. **Figure 8** shows relations between Henry's law constants and Q_{st}^0 values of the adsorbates with the structural properties of 60 bio-MOFs, which are optimum members for uremic toxin separation, at infinite dilution, 298 K. Their Henry's law constants and Q_{st}^0 values were given in **Table A4-A5**. $K_{H, \text{ure}}^0$ ranged from 1.03×10^{-5} to 1.74×10^{-3} mol/kg/Pa whereas $K_{H, \text{cre}}^0$ ranged from 1.93×10^{-10} and 3.59 mol/kg/Pa. $K_{H, \text{wat}}^0$ of bio-MOFs was in the range of 2.16×10^{-7} to 1.72×10^{-6} mol/kg/Pa. We could not observe a direct relationship between structural properties of bio-MOFs and their structural properties for urea and water adsorption. However, $K_{H, \text{cre}}^0$ was found to

be slightly related to pore diameters of bio-MOFs and $K_{H,cre}^0$ of bio-MOFs generally decreases as their PLDs, LCDs and porosities increase.

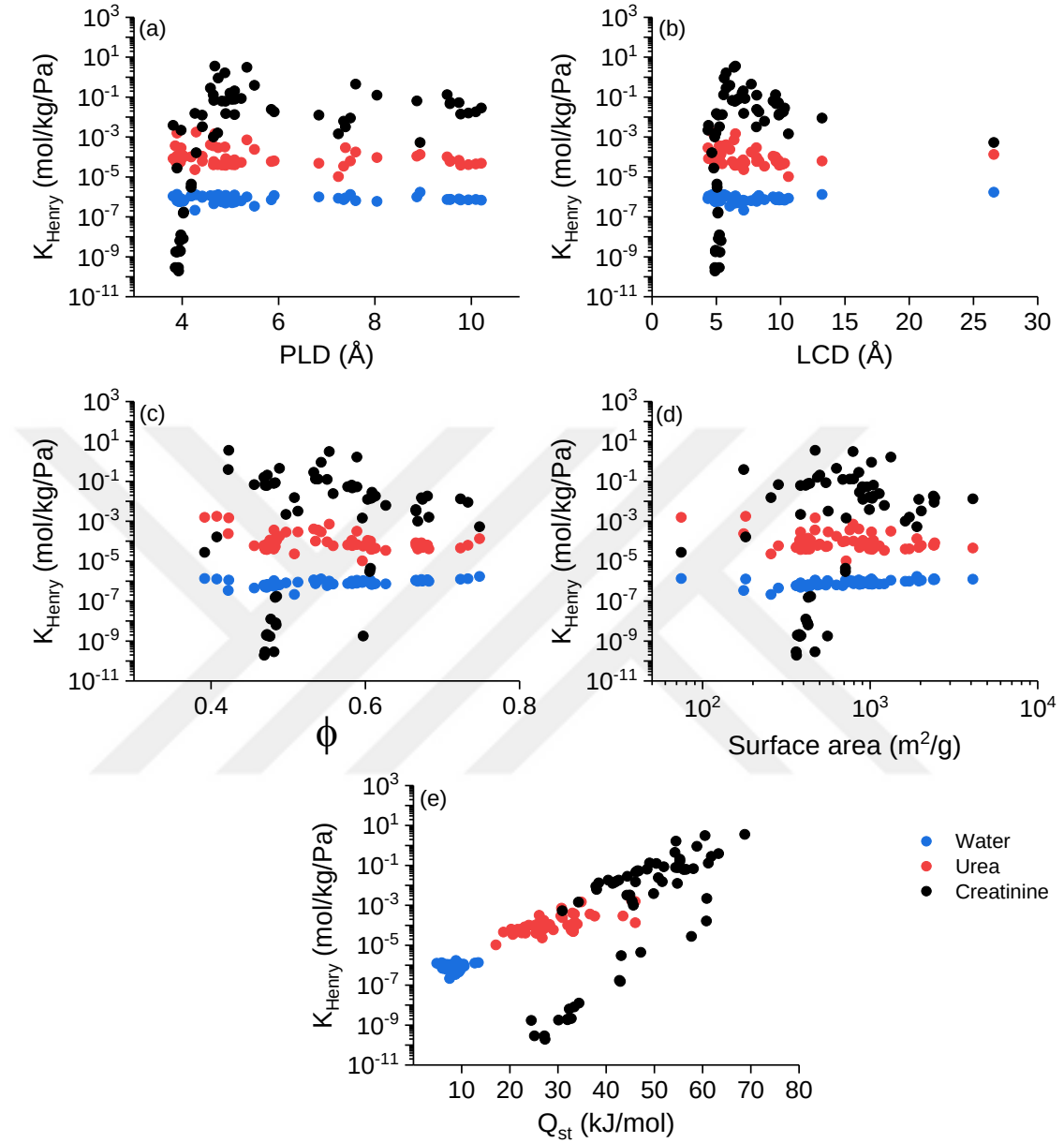


Figure 8. Relations between (a) PLDs, (b) LCDs, (c) porosities, (d) surface areas and (e) Q_{st}^0 values and Henry constants of 60 bio-MOFs at infinite dilution and 298 K.

In addition, as the $Q_{st}^0 = -\Delta H_{ads}$ values increase, Henry's law constants also increase. $Q_{st,cre}^0$ values for creatinine (from -24.45 to -68.76 kJ/mol) were found to be much higher than those computed for urea (from -17.13 to -46.05 kJ/mol), indicating the strong confinement of creatinine molecules within framework. The creatinine molecule ($C_4H_7N_3O$) is larger than the urea (CH_4N_2O), and the effect of LJ energy parameters (ϵ/k_B) is greater considering the difference in atomic numbers (4C, 7H and 3N). Therefore, van

der Waals interactions between bio-MOF atoms and creatinine molecule are much stronger than those occurred between bio-MOF atoms and urea molecule. Additionally, since the creatinine molecule has a higher dipole moment (7.62 Debye) than urea (5.21 Debye) based on the ab-initio calculation, [111] creatinine-MOF electrostatic interactions were found to be much stronger. Due to stronger interaction of bio-MOF atoms with the creatinine molecule, the average $Q_{st, cre}^0$ were found to be much higher for creatinine adsorption (46.60 kJ/mol) compared to urea (31.59 kJ/mol) and water (9.18 kJ/mol) adsorption.

The number of adsorbed urea, creatinine, and water molecules within the pores of 60 bio-MOFs were then predicted using single-component GCMC simulations at 1 bar and 310 K. **Figure 9** shows the top 10 materials (AJESAJ02, BAHLED, BEPMEQ, BEPMIU, CIGXIA, DEPJIR02, HAQSIE, PORLAL, SAFBAF and VEJZIU) with the highest uptake capacity for urea and creatinine at 1 bar, 310 K. Among 60 bio-MOFs, CIGXIA known as MIL-100 (Fe) exhibited the highest creatinine (730.4 mg/g) and urea (691.9 mg/g) uptakes due to its large surface area (1903.51 m²/g) and high pore volume (1.06 cm³/g). In the literature, the highest experimental urea uptake was also reported as 692 mg/g for MIL-100(Fe), [70] showing the good agreement between our predictions and experiments. Similar to MIL-100 (Fe), VEJZIU (ZIF-10) gave high creatinine (623.4 mg/g) and urea (651.6 mg/g) uptakes due to its high porosity (0.73). We observed that as the porosity increases, both urea and creatinine uptakes increase, indicating a linear relationship (R^2 :0.95 for urea adsorption; R^2 :0.96 for creatinine adsorption:) as shown in **Figure A1**. For example, BAHLED, BEPMEQ, BEPMIU and PORLAL have nearly the same porosity (~0.6) and they exhibit approximately similar uremic toxin uptakes (353.3, 306.3, 293.8 and 343.5 mg urea/g and 327, 310.3, 301.7 and 345.1 mg creatinine/g, respectively) as shown in **Figure 9**. On the other hand, although AJESAJ02, DEPJIR02, HAQSIE and SAFBAF have similar porosities (0.67-0.68), their adsorption amounts are quite different due to large differences in their surface areas (AJESAJ02: 2429.61 m²/g DEPJIR02: 989.69 m²/g HAQSIE: 1953.42 m²/g SAFBAF:2386.69 m²/g). Since DEPJIR02 has a very low surface area, it gave the lowest uremic toxin uptakes among these four bio-MOFs.

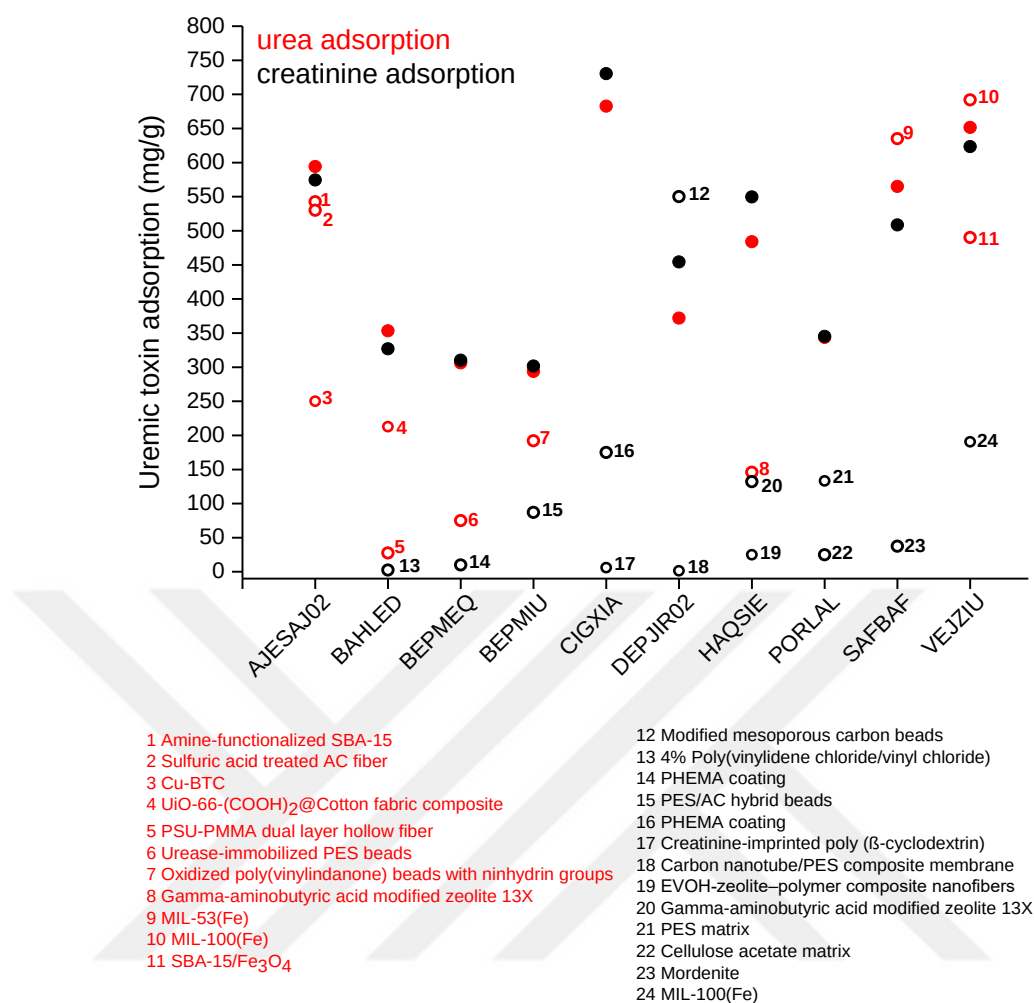


Figure 9. Comparison of the performances of the best 10 bio-MOFs with those of the materials reported in the literature for single-component creatinine and urea adsorption. CIGXIA is the REFCODE for MIL-100(Fe) used in simulations.

We also compared the performance of top 10 bio-MOFs with those of traditional adsorbents (unfilled symbols with numbers) in **Figure 9**. The data of traditional adsorbents studied for urea and creatinine adsorption with their corresponding studies were given in **Table A6**. Creatinine uptake capacities of promising bio-MOFs were found to be much higher than the materials for which the maximum creatinine uptakes are reported in the literature (carbon nanotubes, 25 mg/g; zeolites, 44 mg/g; activated carbon, 62.5 mg/g; zeolite-polymer composite nanofibers, 220 mg/g; and amine group-functionalized silica, 542.6 mg/g) [74]. As shown in **Figure 9**, creatinine uptake was low (≤ 175 mg/g) in most adsorbents except suspension-assisted colloidal silica templating treated mesoporous carbon beads (MCBs) [112]. The creatinine adsorption performance of MCBs is high (550 mg/g) due to their well-developed and interconnected mesoporous

channels. Similarly, many adsorbents exhibited low urea uptake, but sulfuric acid-treated activated carbon fiber [113] and mesoporous silica materials [22, 114] showed high adsorption capacity for urea, which was attributed to the strong hydrogen bonds between the amine groups of the urea and the adsorbents. Although some bio-MOFs exhibited lower urea uptake performances than amine group-containing adsorbents, several bio-MOFs such as AJESAJ02, MIL-100(Fe), SAFBAF and VEJZIU outperformed most of the traditional adsorbents studied so far, such as zeolites, activated carbons and polymers. For example, urea uptake in MIL-100(Fe) (692 mg/g) is much higher than the adsorbed urea amounts reported for various adsorbents in the literature. It is also important to note that although our predictions were in a good agreement with the experimental data for urea adsorption in MIL-100 (Fe), simulations overestimated the creatinine uptake in this bio-MOF. This was attributed to differences in material properties used in simulations and experiments. The surface area (1903.5 m²/g) of MIL-100(Fe) used in this work is much larger than the surface area (1598 m²/g) reported in the experimental study [71]. In addition, experimental study was performed in a Tyrode solution (pH 7.4) to mimic the mineral composition and pH of blood whereas simulations only consider the maximum theoretical uptake of creatinine in this bio-MOF without solvent molecules. However, although simulations overestimate the creatinine uptake in MIL-100(Fe), they revealed its potential for uremic toxin uptake, consisted with the literature. Overall, our results suggested that bio-MOFs can compete or even outperform these adsorbents in terms of uremic toxin uptake due to their large surface area and high porosity.

The selectivities calculated at 1 bar, 310 K were then compared with the ideal selectivities computed at infinite dilution, 298 K for 60 bio-MOFs; a) urea/water, b) creatinine/water and c) creatinine/urea separations in **Figure 10**. As shown in this figure, selectivities follow a different trend for urea and creatinine separations based on the operating condition. $S_{\text{ads, ure/wat}}$ was found to be much higher than $S_{\text{ads, ure/wat}}^0$ for most bio-MOFs (51) shown in **Figure 10(a)** whereas $S_{\text{ads, cre/wat}}$ was much lower than $S_{\text{ads, cre/wat}}^0$ for most bio-MOFs (42) shown in **Figure 10(b)**. This was attributed to significant difference in the values of $K_{\text{H, ure}}^0$ and $K_{\text{H, cre}}^0$. Since creatinine is more strongly adsorbed than urea, calculated $K_{\text{H, cre}}^0$ of bio-MOFs were much higher than $K_{\text{H, ure}}^0$ values, resulting in very high $S_{\text{ads, cre/wat}}^0$ for bio-MOFs. In **Figure 10(c)**, $S_{\text{ads, cre/ure}}$ was found to be almost 1 for most bio-MOFs (31) although their $S_{\text{ads, cre/ure}}^0$ vary. As we discussed above, both

creatinine and urea uptakes of bio-MOFs are dependent on the porosities of bio-MOFs. Since these 31 bio-MOFs have similar porosities, their urea and creatinine uptakes were quite similar, indicating a non-selective behaviour for creatinine/urea separation. On the other hand, remaining 12 bio-MOFs have poor creatinine uptakes due to their narrow pore dimensions (~ 4 Å of PLD and ~ 5 Å of LCD), suggesting that these bio-MOFs exhibit selectivity towards urea rather than creatinine.

We then ranked 60 bio-MOFs based on their selectivities calculated at infinite dilution and 1 bar, 310 K for both urea/water and creatinine/water separations and identified the best 10 candidates exhibiting high urea/water and creatinine/water selectivities at both conditions in **Table A7**. KEXDIB and NIHBIQ02 showed the highest urea/water selectivity at infinite dilution ($S_{\text{ads, ure/wat}}^0$: 713.9) and 1 bar, 310 K ($S_{\text{ads, ure/wat}}$: 6.00×10^3), respectively. For KEXDIB, $K_{\text{H, ure}}^0$ (7.0×10^{-3} mol/kg/Pa) was computed to be much higher than $K_{\text{H, wat}}^0$ (9.93×10^{-7} mol/kg/Pa), resulting in high ideal selectivity towards urea. This was attributed to interactions between urea and pyridine aromatic ring of KEXDIB, a dicyanamide based MOF since urea can make stacking and NH- π interactions with aromatic rings [115, 116]. In NIHBIQ02, a formate based MOF with Fe sites, almost negligible amount of water was adsorbed (~ 0.02 mg/g) compared to the amount of adsorbed urea (~ 135.3 mg/g), leading to a high adsorption selectivity towards urea at 1 bar. For creatinine/water separation, KEXDIB and CATDIL showed the highest creatinine/water selectivity at infinite dilution ($S_{\text{ads, cre/wat}}^0$: 3.10×10^6) and 1 bar, 310 K ($S_{\text{ads, cre/wat}}$: 6.99×10^3), respectively. Similar to urea adsorption, a strong interaction occurs between pyridine ring of KEXDIB and imidazole ring of creatinine validated by its high heat of adsorption for creatinine (-60.5 kJ/mol) due to the π -stacking and π - π interactions between aromatic rings [117]. CATDIL, a porphyrin-based MOF with Zn sites, has hexagonal channels surrounded by pyridine and pyrrole rings. In CATDIL, these hexagonal pores are filled with creatinine molecules and a very low amount of water was adsorbed (0.01 mg/g), leading to high selectivity towards creatinine. As shown in **Table A7**, 6 bio-MOFs namely BEPPOD, BEYSEF, CAYSIE, CAYSOK, KEXDIB and YUVSUE were found to be common in these two rankings. Therefore, we selected these 6 bio-MOFs for further examination.

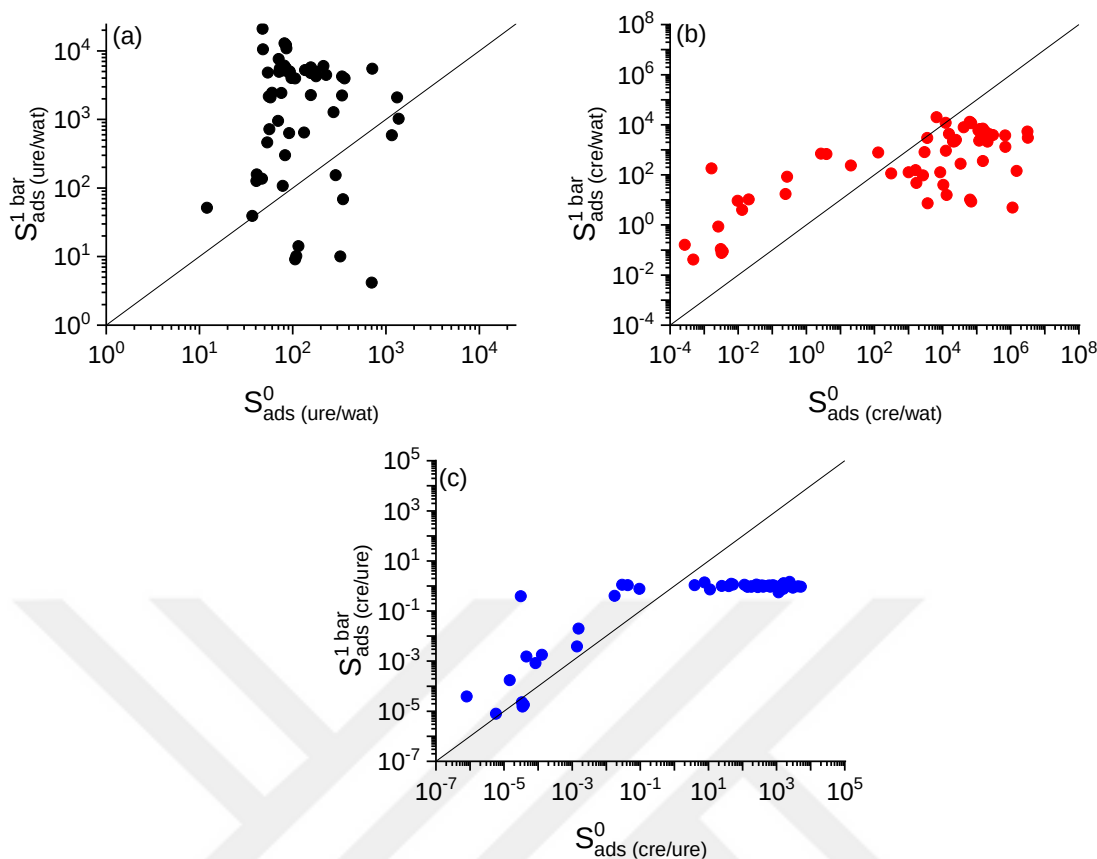


Figure 10. Comparison of ideal adsorption selectivities with the adsorption selectivities calculated at 1 bar, 310 K for (a) urea/water, (b) creatinine/water, (c) creatinine/urea separations.

4.3 Co-Adsorption of Uremic Toxins in Bio-MOFs

4.3.1 Binary Mixture

So far, we only discussed single-component uremic toxin adsorption within the pores of bio-MOFs. However, under experimental conditions, solvent molecules like water will be in the environment, which may affect the overall separation performance of materials. For this reason, we also computed the adsorbed amount of uremic toxins within the pores of bio-MOFs in the aqueous mixture at 310 K considering the vapor pressure of water. Due to the high computational cost of mixture uremic toxin simulations, we only considered the top 6 bio-MOFs, having the highest ideal and 1 bar adsorption selectivities for urea/water and creatinine/water separations as discussed above. **Figure 11** shows simulation results for 6 promising bio-MOFs at different water molar fractions (X_{wat}) of 0.90-0.99 in binary mixture.

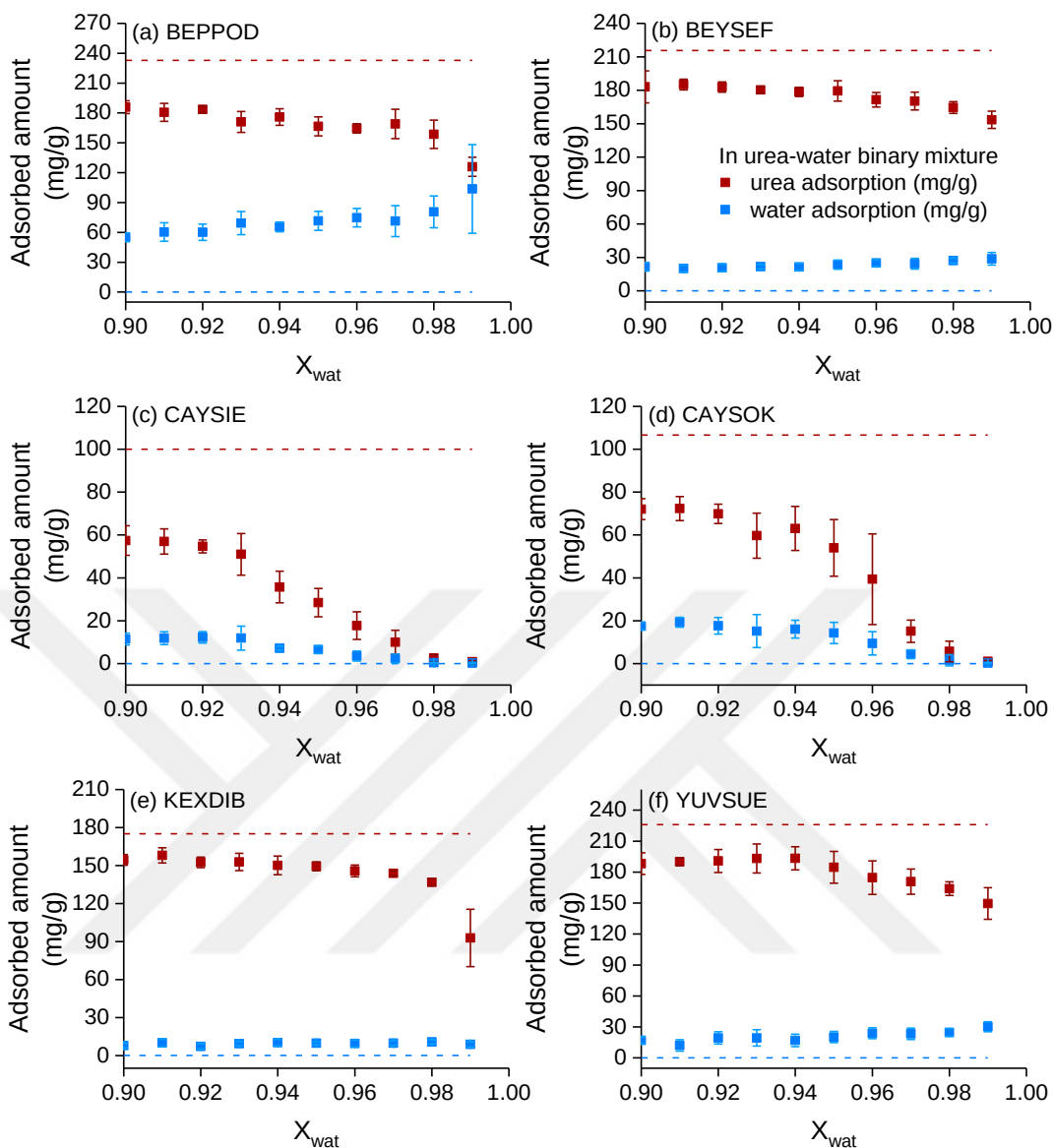


Figure 11. Urea-water binary mixture adsorption isotherms of the top 6 performing bio-MOFs at 310 K. The dashed red (blue) line shows the adsorbed amount of urea (water) calculated at 1 bar and 310 K. Error bars are demonstrated on each graph.

The adsorbed amount of urea and water in bio-MOFs at single-component condition were also shown with red and blue dashed lines, respectively in **Figure 11**. The amount of adsorbed urea in binary mixture decreases as the water amount in the mixture increases for all bio-MOFs in **Figure 11(a-f)**. This is expected since competitive adsorption occurs in the mixture. This decrease is significant for CAYSIE and CAYSOK as shown in **Figure 11(c-d)**. For example, when the water mole fraction is increased from 0.90 to 0.99, the adsorbed amount of urea in CAYSIE (CAYSOK) decreases from 57.41 (72.06) mg/g to 0.88 (1.03) mg/g. Since these materials have very low surface areas (485.08-501.54 m²/g) and pore volumes (0.39-0.40 cm³/g), there is not enough space for

the storage of urea molecules due to the increase in water molecules in the environment. Therefore, the amount of adsorbed urea decreased remarkably as the amount of water increased in the mixture.

Among the materials we studied, uremic toxin uptake performances of YUVSUE (bio-MOF-11) and BEYSEF (bio-MOF-12) were not significantly affected by the presence of water in the environment. This may be due to their Lewis-basic sites as N1 and amino groups [118]. GCMC snapshots also reveal that oxygen atoms of water molecules and hydrogen atoms of amino groups in these bio-MOFs trigger Lewis-acid and Lewis-base interactions (**Figure 12**).

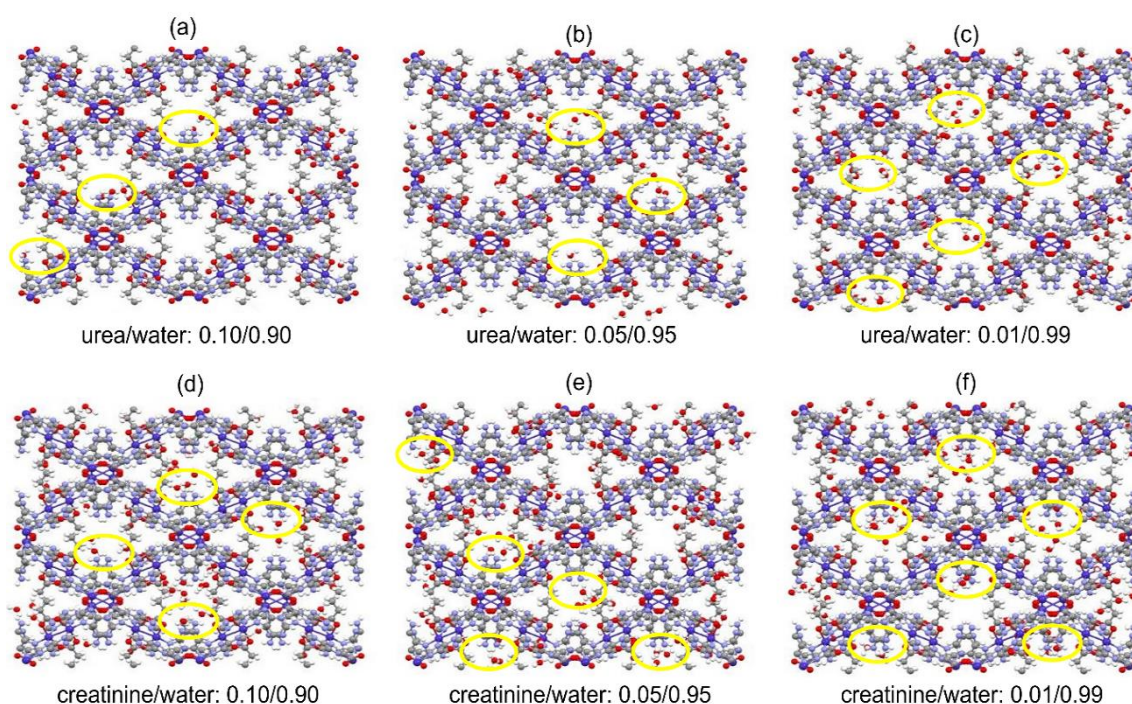


Figure 12. Snapshots of Bio-MOF-12 obtained from GCMC simulations for binary mixtures of (a) urea/water:0.10/0.90, (b) urea/water: 0.05/0.95, (c) urea/water: 0.01/0.99, (d) creatinine/water: 0.10/0.90, (e) creatinine/water: 0.05/0.95 and (f) creatinine/water: 0.01/0.99. For the elements of MOF, C, H, O, Co, N, the colours gray, white, red, dark blue and blue are used respectively. Urea and creatinine molecules were not shown for clarity.

Since there is a strong O-H bond between oxygen atom of urea and hydrogen atom of adenine, it is predicted that no serious decrease in the amount of urea is observed even if the amount of water increases in the mixture. For these reasons, bio-MOF-11 and bio-MOF-12 can be potential candidates for adsorption-based urea/water separation.

Figure 13 shows creatinine-water binary mixture adsorption isotherms of the top performing 6 bio-MOFs at 310 K. As shown in this figure, creatinine adsorption in these

bio-MOFs was not significantly affected by the presence of water, suggesting that the creatinine separation performance of materials does not change in the presence of water. The performance of BEYSEF (bio-MOF-12), KEXDIB and YUVSUE (bio-MOF-11) does not change much for both urea/water and creatinine/water separations, indicating that these materials can be promising for uremic toxin separations. We also note that the moisture stability of KEXDIB [119] is also important for practical uremic toxin separation. Another result is that water adsorption in bio-MOFs slightly increases at the mixture condition compared to that computed at single-component condition. All these 6 bio-MOFs have nitrogen containing rings in their structure. BEPPOD and KEXDIB contain only pyridine rings whereas CAYSIE and CAYSOK have pyrrole rings around the central metal atom in addition to pyridine. BEYSEF and YUVSUE have adenine rings. RDF analysis of these bio-MOFs showed that creatinine, urea and water molecules did not make any hydrogen bonds with the atoms of bio-MOFs. We observed that hydrogen bonds occur between the atoms of uremic toxins and water molecules. **Figure A2-A3** shows RDF analysis of uremic toxins in 6 bio-MOFs during single-component GCMC simulations. Creatinine has amino and methyl groups with an imidazole ring as well as polar atoms. Its polar atoms interact with hydrophilic water atoms, whereas its hydrophobic regions can interact with hydrophobic surfaces of bio-MOFs. Bio-MOFs have pyrrole and pyridine rings made up of hydrocarbons. The number of hydrocarbons in the structures determines the level of hydrophobic interaction. In other words, molecules with the highest number of carbons have the strongest hydrophobic interaction [120, 121]. A hydrophobic interaction occurs in the hydrophobic regions of creatinine and bio-MOFs by stacking and $\text{NH}-\pi$ interactions [116].

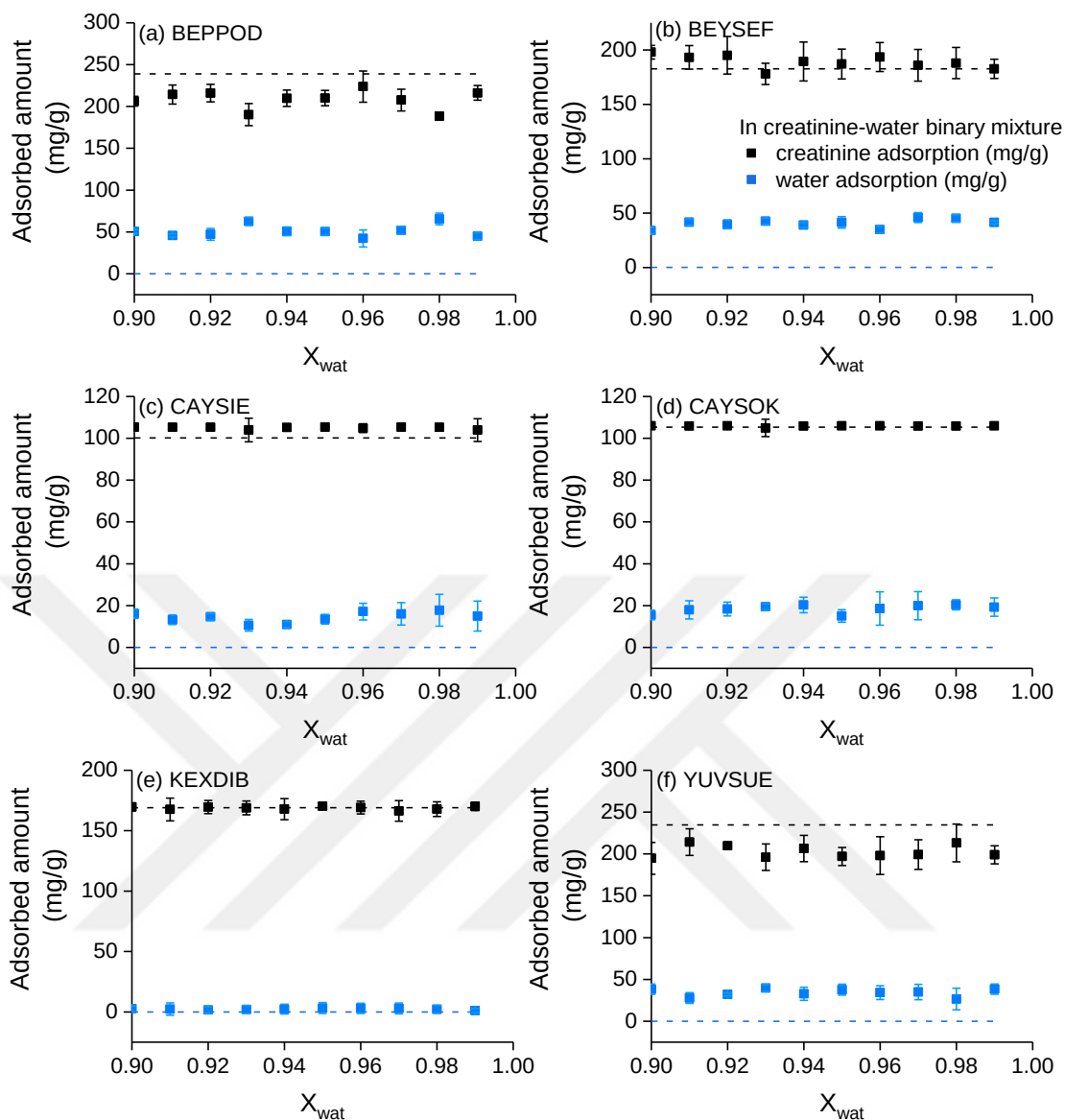


Figure 13. Creatinine-water binary mixture adsorption isotherms of the top performing 6 bio-MOFs at 310 K. The dashed black (blue) line shows the adsorbed amount of creatinine (water) calculated at 1 bar and 310 K. Error bars are demonstrated on each graph.

Varying amounts of uremic toxins due to interactions in single-component simulations were demonstrated by RDF analysis. Hydrogen bond forms between the electronegative atoms of urea (O) and creatinine (O, N). Dorota Swiatla-Wojcik [122] reviewed the definition of hydrogen bond for liquid water and the distance between the hydrogen and oxygen of water is defined as less than 2.5 Å. No hydrogen bond or interaction between bio-MOF atoms and uremic toxin atoms could be detected by RDF. However, it was shown that uremic toxin atoms also have an interaction with water in addition to the interaction between uremic toxin atoms themselves. Hydrogen bonds between atoms of adsorbates at single-component and binary mixture conditions were

shown in **Figure 14**. Distance between urea or creatinine atoms was found to be 2.58 Å, which is very close to the hydrogen bond criterion. For this reason, a hydrogen bond between the atoms of the urea or creatinine molecule was observed (**Figure 14(a-b)**). When BEPPOD are examined for both urea-water and creatinine-water binary mixture adsorption, the increase in the adsorbed amount of water in the mixture draws attention. As shown in **Figure 14(c-d)**, hydrogen bonds were formed between creatinine-water atoms (1.82 Å) and between urea-water atoms (1.82 Å) in the mixture. For this reason, it was predicted that the amount of adsorbed water increases within the pores of BEPPOD at mixture conditions. In summary, creatinine was strongly adsorbed in bio-MOFs due to hydrophobic interactions between creatinine molecule and hydrophobic regions of bio-MOFs. In addition, hydrogen bonding between polar atoms of creatinine and water molecule led to increase in water adsorption.

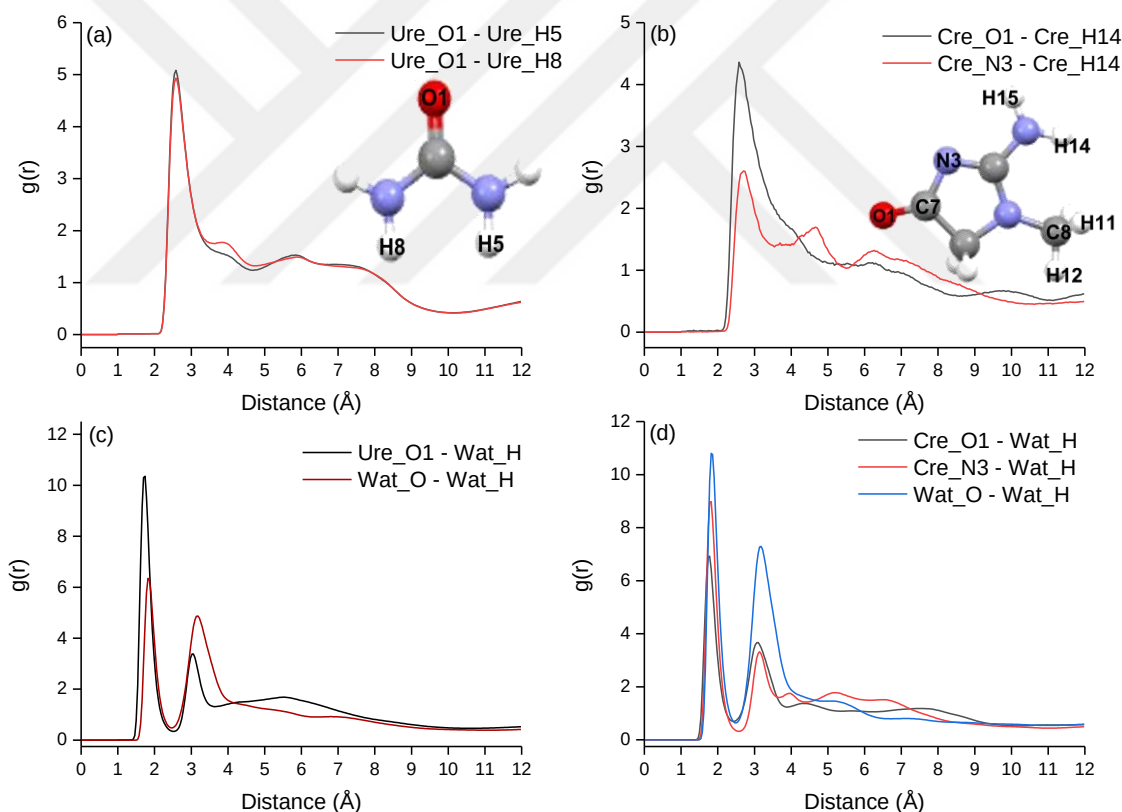


Figure 14. The radial distribution function of BEPPOD calculated during GCMC simulations for (a) single-component creatinine adsorption, (b) single-component urea adsorption, (c) creatinine-water binary mixture adsorption, and (d) urea-water binary mixture adsorption.

4.3.2. Ternary Mixture

Since uremic toxins are present in blood as a mixture, simulations were also performed for these 6 bio-MOFs (BEPPOD, BEYSEF, CAYSIE, CAYSOK, KEXDIB

and YUVSUE) at ternary mixture condition and results for equal molar concentrations of urea and creatinine were shown in **Figure 15**.

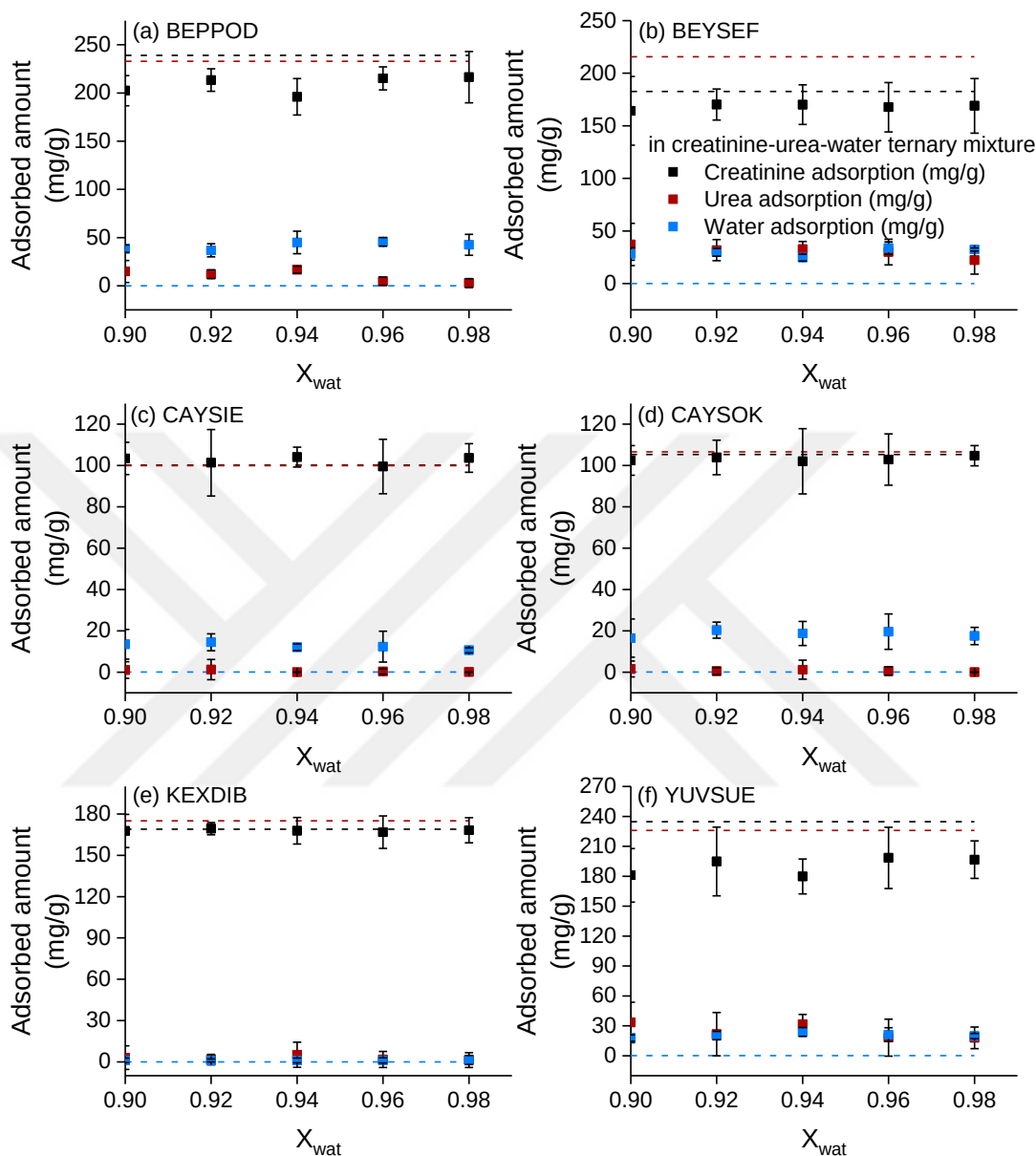


Figure 15. Creatinine-urea-water ternary mixture adsorption isotherms of the top performing 6 bio-MOFs at 310 K. The creatinine/urea concentration in the mixture was simulated as 50/50. The dashed black (blue) line shows the adsorbed amount of creatine (water) calculated at 1 bar and 310 K. Error bars are demonstrated on each graph.

Creatinine is more strongly adsorbed than urea in these bio-MOFs. As shown in **Figure 15**, the adsorbed amount of creatinine in bio-MOFs were found to be almost the same in the ternary mixture, indicating that the presence of urea and water does not significantly affect the adsorption of creatinine molecules. On the other hand, the adsorbed amount of urea decreased in the presence of creatinine and water molecules in

the system. For example, single-component urea adsorption in BEPPOD was calculated as 232.79 mg/g at 1 bar, 310 K whereas the adsorbed amount of urea in BEPPOD was calculated as 11.96 mg/g at a composition ratio of urea/creatinine/water: 0.04/0.04/0.92.

Figure 16 presents GCMC snapshots obtained from single-component and ternary mixture GCMC simulations for BEPPOD.

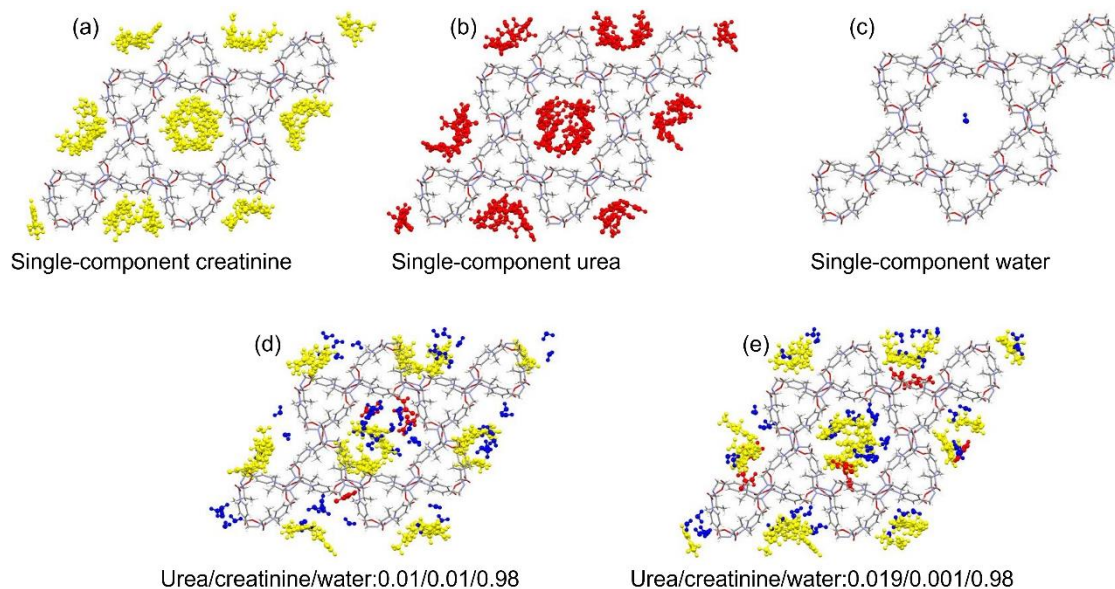


Figure 16. Snapshots of BEPPOD obtained from (a) single-component urea adsorption, (b) single-component creatinine adsorption, (c) single-component water adsorption, (d) urea/creatinine/water:0.01/0.01/0.98 mixture, and (e) urea/creatinine/water:0.019/0.001/0.98 ternary mixture GCMC simulations at 310 K. Yellow, red and blue represents creatinine, urea and water, respectively.

Although single-component urea (232.79 mg/g) and creatinine (238.93 mg/g) uptakes in BEPPOD are similar due to its large pores (LCD:9.62 Å, PLD:9.50 Å), at mixture condition the adsorbed amount of creatinine in this MOF was much higher than that of urea due to the competition between molecules. Similarly, urea adsorption in BEYSEF at ternary mixture condition (urea/creatinine/water: 0.02/0.02/0.96) was much lower (29.98 mg/g) than the single-component urea adsorption (215.71 mg/g) in this bio-MOF. The same situation also occurs in remaining materials. Competitive adsorption in the mixture causes decrease in adsorbed amount of urea molecules in these materials. Urea contains two amine groups attached to a carboxyl group, while creatinine contains a pyrazole ring and an amine group attached to the carboxyl group. Compared to results obtained from single-component GCMC simulations, adsorbed amount of urea and creatinine in bio-MOFs were found to be completely different. The pores of bio-MOFs

adsorb much more creatinine molecules which have more polar atoms and an imidazole ring than urea molecules in the mixture. This may be attributed to π - π interactions with the nitrogen-containing rings of bio-MOFs since a much higher binding energy was observed for the pyrrole and pyridine rings containing nitrogen atom compared to the benzene ring without nitrogen molecule [117]. This indicates that the nitrogen number affects the binding energy. For this reason, it was predicted that the imidazole structure would interact strongly with nitrogen-containing bio-MOF rings.

Since the amount of urea is higher than that of creatinine in patients suffering from kidney failure as shown in **Table 4**, we also computed the adsorbed amount of uremic toxins considering creatinine-urea concentration in the ternary mixture as 5/95 at 310 K. **Figure 17** shows creatinine-urea-water ternary adsorption isotherms of 6 bio-MOFs at 310 K. Dashed lines show the single-component creatinine and water adsorption amounts of the bio-MOFs calculated at 1 bar, 310 K. No significant change in creatinine adsorption was observed when the urea concentration increased in the mixture. However, BEYSEF (bio-MOF-12) and YUVSUE (bio-MOF-11) were more affected than the other materials. For example, the adsorbed amount of urea in BEYSEF (YUVSUE) increased from 31.74 (21.62 mg/g) mg/g to 63.64 mg/g (38.68 mg/g) when the bulk composition was changed from urea/creatinine/water: 0.04/0.04/0.92 to urea/creatinine/water: 0.076/0.004/0.92 at 310 K. The increase in adsorbed urea molecules in these two bio-MOFs was attributed to two reasons: (i) both materials have smaller LCDs (5.62 Å, 5.76 Å) than others (6.38 Å - 9.62 Å). The competition between uremic toxins gains more importance in narrow pores, where the adsorption is restricted by the repulsive forces [123]. (ii) BEYSEF and YUVSUE contain adenine in their structures. Since adenine has a pyrrole and a pyridine in its structure, the intermolecular affinity has enhanced between urea molecules and aromatic groups, [116] and urea has been strongly retained as a result of stacking and NH- π interactions with the adenine ring. Methyl, and amino groups in pores of BEYSEF were found to be favourite adsorption sites for uremic toxins. When the bulk composition of urea in the ternary mixture increased, urea molecules (5.6×6.3×3.0 Å) [5] managed to enter through the narrow pores of BEYSEF due to its smaller structure than creatinine (7.1×8.1×3.0 Å) [5]. In addition to the uptake of urea and creatinine in the pores of the bio-MOFs, a slight increase in the amount of water was observed in mixture simulations. It is assumed that this is because the simulations of the mixture are carried out considering the vapor pressure of water at 310 K (0.062 bar). In the literature, it has been emphasized

that the storage and condensation of water in the pores occurs at low relative pressure in materials [124].

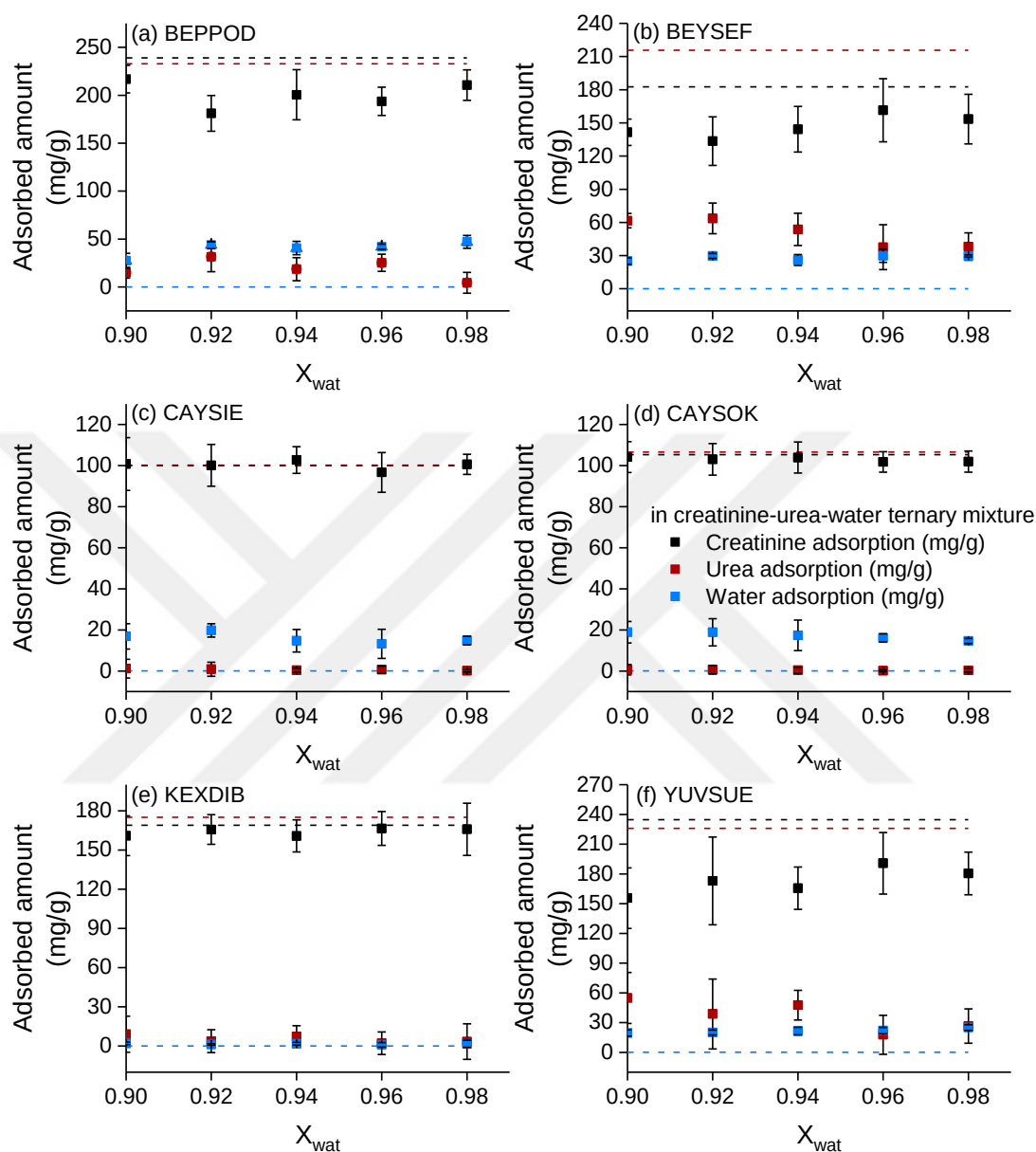


Figure 17. Creatinine-urea-water ternary mixture adsorption isotherms of the top performing 6 bio-MOFs at 310 K. The creatinine/urea concentration in the mixture was simulated as 5/95. The dashed black (blue) line shows the adsorbed amount of creatine (water) calculated at 1 bar and 310 K. Error bars are demonstrated on each graph.

In the presence of creatinine and urea, the interaction of water with uremic toxins through hydrogen bonding was also demonstrated by RDF analysis. **Figure 18** shows hydrogen bonding between water atoms and uremic toxin (urea and creatinine) atoms in ternary mixture simulations (urea/creatinine/water: 0.01/0.01/0.98 and urea/creatinine/water: 0.019/0.001/0.98) of BEPPOD. Distance between atoms of

adsorbates in ternary mixture simulations was measured by RDF to be approximately 1.74 Å, indicating hydrogen bonds between the polar atoms of urea and creatinine and the atoms of water (**Figure 18(a-b)**). While the molar ratio of urea and creatinine is equal, hydrogen bonding of urea and creatinine molecules with water is very close. On the other hand, with the increase in molar ratio of urea, a greater attraction occurred between urea and water molecules, and hydrogen bond between urea and water was higher compared to the previous situation. The increase of this hydrogen bond is clearly visible in GCMC snapshots in **Figure 18(c-d)**.

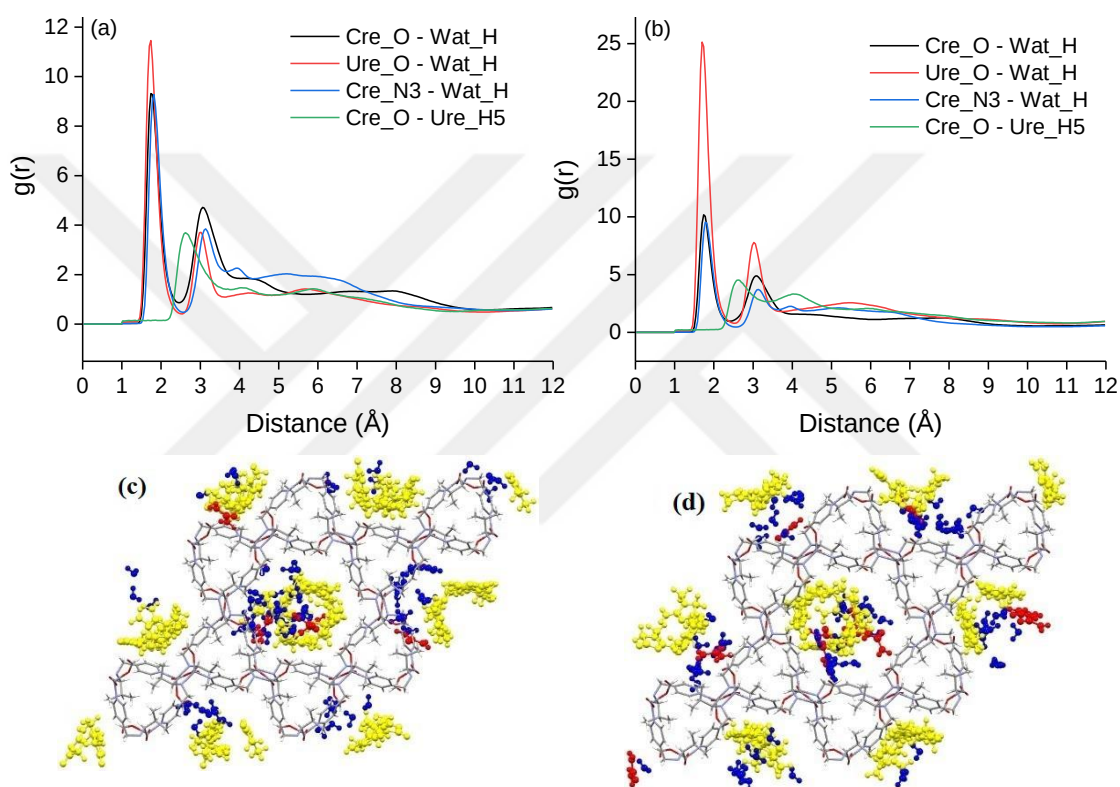


Figure 18. Comparison of interactions between uremic toxins and water atoms by RDF analyses in mixture simulation of BEPPOD and snapshots of adsorbates at ternary mixture simulations. (a, c) urea/creatinine/water: 0.01/0.01/0.98 and (b, d) urea/creatinine/water: 0.019/0.001/0.98 in ternary mixture condition.

The same analysis was also done for other bio-MOFs (BEYSEF, CAYSIE, CAYSOK, KEXDIB and YUVSUE) (**Figure A4-A8**), showing the hydrogen bonding between urea and water. However, in BEYSEF and YUVSUE, the number of hydrogen bond between urea and water decreases with increase in molar ratio of urea in the mixture (**Figure A4, A8**). This may be attributed to the fact that creatinine molecules interact more strongly with water molecules within the pores of these bio-MOFs and the amount of adsorbed water decreases with the decrease in creatinine molecules in the system. For

example, the single-component water adsorption in BEYSEF was computed as 0.04 mg/g at 1bar and 310 K, suggesting that the interaction of water molecules with the atoms of BEYSEF is weak. At binary mixture condition, the amount of adsorbed water in BEYSEF was found to be much higher in the creatinine/water mixture (45 mg/g) compared to the urea/water mixture (27 mg/g). In addition, the amount of adsorbed water was also high (32.6 mg/g) in the ternary mixture where urea and creatinine have equimolar bulk compositions of urea/creatinine/water: 0.01/0.01/0.98, indicating strong adsorption of water molecules with the creatinine in BEYSEF. Overall, the separation performance of bio-MOFs, especially BEYSEF, KEXDIB and YUVSUE did not dramatically change when ternary mixtures of uremic toxins were considered in simulations, indicating their potential for uremic toxin separation.



CHAPTER V

INVESTIGATION OF CO-ADSORPTION OF UREMIC TOXINS IN BIO-MOFS

5.1 Single-Component *P*-cresol and Uric Acid Adsorption

Figure 19 shows the relations between Henry's law constants and Q_{st}^0 values of the adsorbates with the structural properties of 60 bio-MOFs at infinite dilution, 298 K.

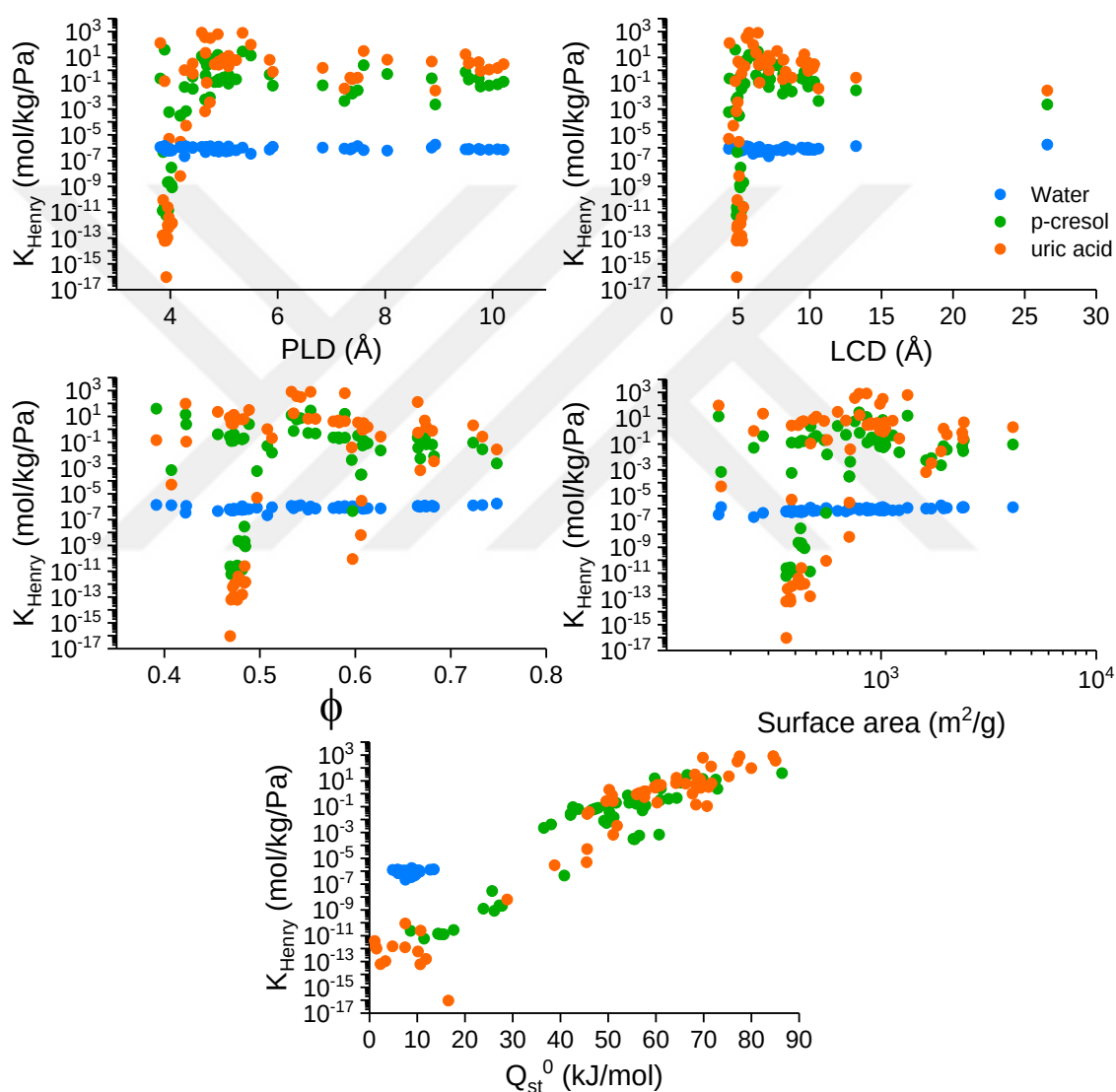


Figure 19. Relations between (a) PLDs, (b) the LCDs, (c) porosities, (d) surface areas and (e) Q_{st}^0 values and Henry constants of 60 bio-MOFs at 298 K.

$K_{H, p\text{-cre}}^0$ ranged from 5.82×10^{-12} to 38.71 mol/kg/Pa whereas $K_{H, uric}^0$ ranged from 9.34×10^{-17} and 794.60 mol/kg/Pa. $K_{H, wat}^0$ of bio-MOFs was in the range of 2.16×10^{-7} to 1.72×10^{-6} mol/kg/Pa. We could not observe a direct relationship between PLD, porosity

and SA of bio-MOFs and Henry constants of p-cresol, uric acid and water. However, $K_{H, \text{p-cre}}^0$ and $K_{H, \text{uric}}^0$ were found to be slightly related to the LCDs of bio-MOFs and $K_{H, \text{p-cre}}^0$ and $K_{H, \text{uric}}^0$ of bio-MOFs generally decrease with increasing their LCDs. In addition, Henry's law constants also increase as Q_{st}^0 values increase. While $Q_{\text{st, p-cre}}^0$ values ranged from -86.44 to -8.60 kJ/mol, $Q_{\text{st, uric}}^0$ values ranged from -85.09 to 16.53 kJ/mol. **Figure 20** shows uremic toxin adsorption in 60 bio-MOFs having different porosities. We observed that as porosity of bio-MOFs increases, uremic toxin uptakes generally increase, slightly indicating a linear relationship (R^2 :0.7 for p-cresol adsorption; R^2 :0.62 for uric acid adsorption) as shown in **Figure A9**. MIL-100 gives the highest uptake for both p-cresol (699.6 mg/g) and uric acid (993.3 mg/g) due to its very high porosity (0.75). Since p-cresol has an apolar structure, a hydrophobic interaction takes place between its benzene ring and aromatic ring of bio-MOFs. However, uric acid has a nitrogen-containing purine ring, which enhances electrostatic interactions between frameworks and uremic toxins. Due to its larger size, van der Waals interactions were also found to be much stronger, resulting in higher uric acid uptakes in bio-MOFs.

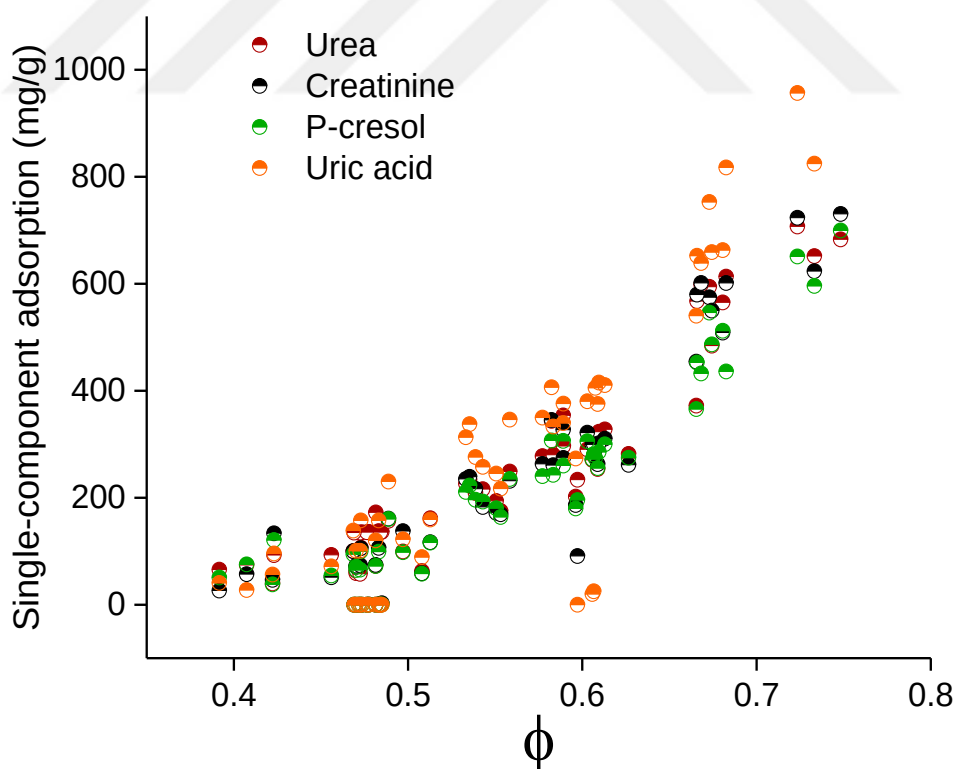


Figure 20. Relation between adsorbed amounts of uremic toxins of 60 bio-MOFs and their porosities at 1 bar, 310 K.

Single-component adsorption of p-cresol and uric acid were computed for 60 bio-MOFs at 1 bar, 310 K. **Figure 21** shows the top 10 bio-MOFs having the maximum adsorption of p-cresol and uric acid. MIL-100(Fe) (CIGXIA) and ZIF-10 (VEJZIU) exhibited the highest adsorption of p-cresol and uric acid due to their large pore diameters ($26.59 \times 8.94 \text{ \AA}$ and $13.23 \times 7.49 \text{ \AA}$), high PVs ($1.06 \text{ cm}^3/\text{g}$ and $0.98 \text{ cm}^3/\text{g}$) and large SAs ($1903.51 \text{ m}^2/\text{g}$ and $2410.51 \text{ m}^2/\text{g}$). Adsorption of p-cresol and uric acid in these bio-MOFs increased with the increase in their porosity from 0.67 to 0.75.

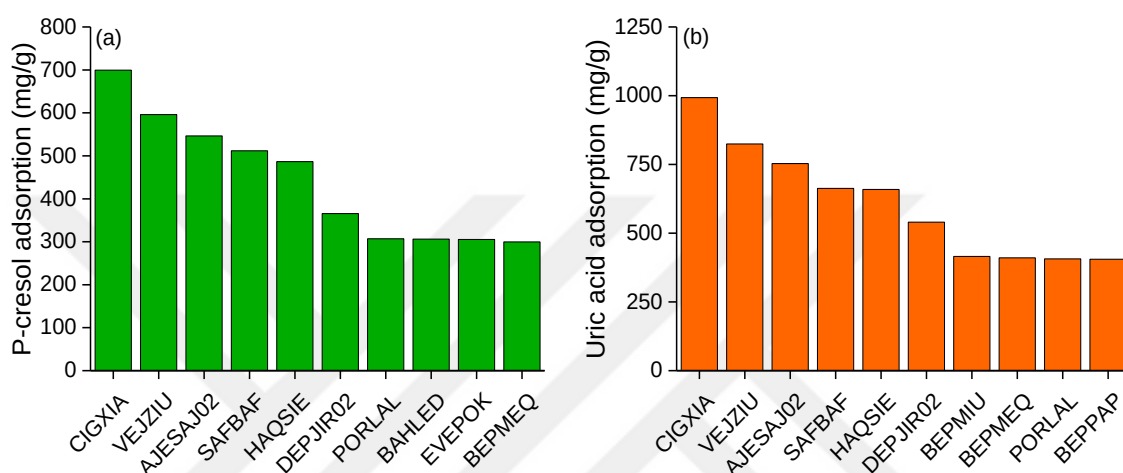


Figure 21. Top 10 bio-MOFs having the highest p-cresol and uric acid uptakes at 1 bar and 310 K.

To date, many adsorbents have been used for adsorption-based uremic toxin separation in the literature. **Table A6** shows the maximum adsorption amounts of uremic toxins in pristine and composite adsorbents. The adsorption of uric acid is generally high, while p-cresol is adsorbed low by conventional adsorbents. This is because p-cresol, which has a benzene ring, has a hydrophobic structure, and can interact effectively with adsorbents with hydrophobic surfaces [125]. However, uric acid contains a purine ring with polar atoms. Nitrogen-containing rings are known to interact more strongly than benzene rings [117]. Therefore, it is more attracted by porous adsorbents due to both its structure and molecular size. Among conventional adsorbents, Uric acid-imprinted poly(acrylamide-hydroxyethyl methacrylate) p(AAm-MMA) cryogel exhibited high uric acid adsorption of 687.6 mg/g while carbonylated hypercrosslinked chloromethylated poly(styrene-co-divinylbenzene) achieved the highest p-cresol uptake of 141.5 mg/g (**Table A6**). With their large surface area and high porosity, MOFs can compete or even outperform these adsorbents. For example, p-cresol (uric acid) adsorption amount of MIL-100 as 699.6 mg/g (993.31 mg/g) is much higher than the adsorbed p-cresol and uric

acid amounts reported in the literature. 31 hydrophobic bio-MOFs outperformed traditional adsorbents in terms of p-cresol uptake. In addition, MIL-100, VEJZIU and AJESAJO2 outperformed traditional adsorbents in terms of uric acid adsorption.

The selectivities calculated at 1 bar and 310 K were then compared with the ideal selectivities computed at infinite dilution, 298 K for 60 bio-MOFs for p-cresol/water, uric acid/water and uric acid/p-cresol separations in **Figure 22**.

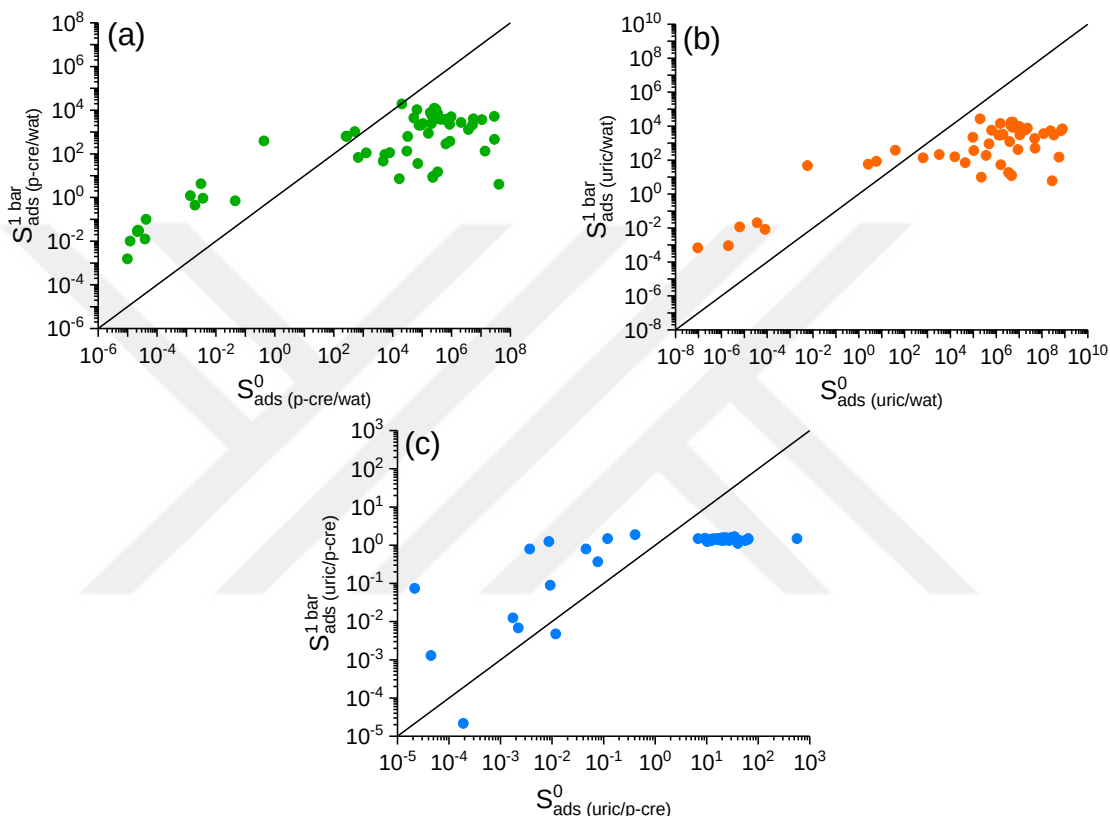


Figure 22. Comparison of ideal adsorption selectivities with the adsorption selectivities calculated at 1 bar, 310 K for (a) p-cresol/uric acid, (b) uric acid/water, (c) uric acid/p-cresol separations.

Similar to the analysis of urea and creatinine adsorption selectivities of bio-MOFs, $S_{ads, \text{p-cre/wat}}$ and $S_{ads, \text{uric/wat}}$ was found to be much lower than $S_{ads, \text{p-cre/wat}}^0$ and $S_{ads, \text{uric/wat}}^0$ for most bio-MOFs (48) shown in **Figure 22(a-b)**. This was attributed to significant difference in the values of $K_{H, \text{p-cre}}^0$ and $K_{H, \text{uric}}^0$. P-cresol and uric acid were strongly adsorbed within the pores of bio-MOFs. In **Figure 22(c)**, $S_{ads, \text{uric/p-cre}}$ was found to be almost 1 for most bio-MOFs because both p-cresol and uric acid uptakes of bio-MOFs were found to be similar, indicating a non-selective behaviour for uric acid/p-cresol separation. On the other hand, remaining 12 bio-MOFs have poor p-cresol and uric acid

uptakes due to their narrow pore dimensions (~ 4 Å of PLD and ~ 5 Å of LCD). **Figure A10** also shows uric acid/urea and uric acid/creatinine adsorption selectivities of bio-MOFs. Similar discussion was also valid for uric acid/urea and uric acid/creatinine adsorption selectivities of bio-MOFs.

5.2 Co-Adsorption of Uremic Toxins in Bio-MOFs

5.2.1 Binary Mixture

The effect of water on urea and creatinine adsorption was discussed in the previous chapter. Using a similar approach, the effect of water on p-cresol and uric acid adsorption was investigated in this section. **Figure 23** shows binary mixture adsorption isotherms of p-cresol for promising 6 bio-MOFs at different molar fractions of water (X_{wat} : 0.90-0.99) in the mixture.

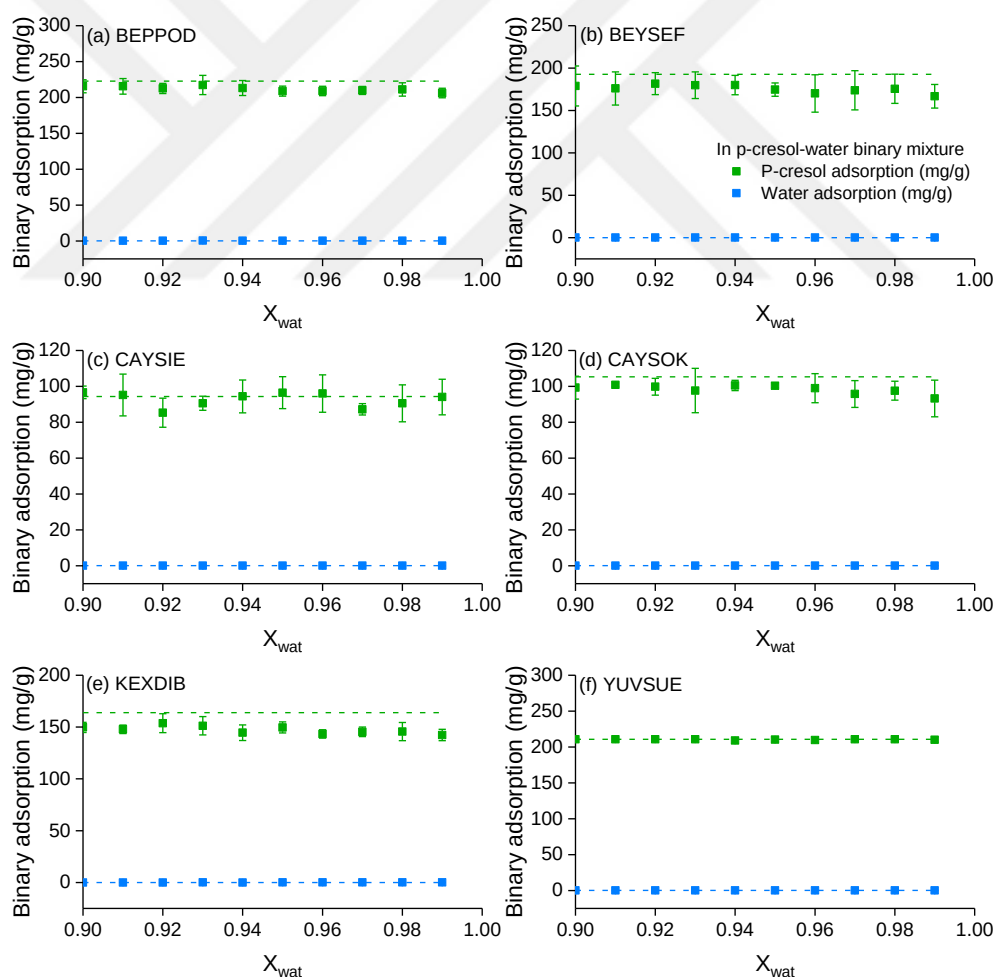


Figure 23. P-cresol-water binary mixture adsorption isotherms of the top performing 6 bio-MOFs at 310 K. The dashed green (blue) line shows the adsorbed amount of p-cresol (water) calculated at 1 bar and 310 K. Error bars are demonstrated on each graph.

The amount of adsorbed p-cresol in the binary mixture was not seriously affected even if the bulk compositions of water in the mixture increases for all bio-MOFs in **Figure 23(a-f)**. This is due to the hydrophobic nature of p-cresol. P-cresol has a strong hydrophobic interaction with MOFs with hydrophobic surfaces [125]. Although uric acid is a hydrophobic molecule, it also contains polar atoms in its structure. Therefore, it may have an interaction with water. **Figure 24** shows the uric acid-water binary mixture adsorption isotherms of promising 6 bio-MOFs.

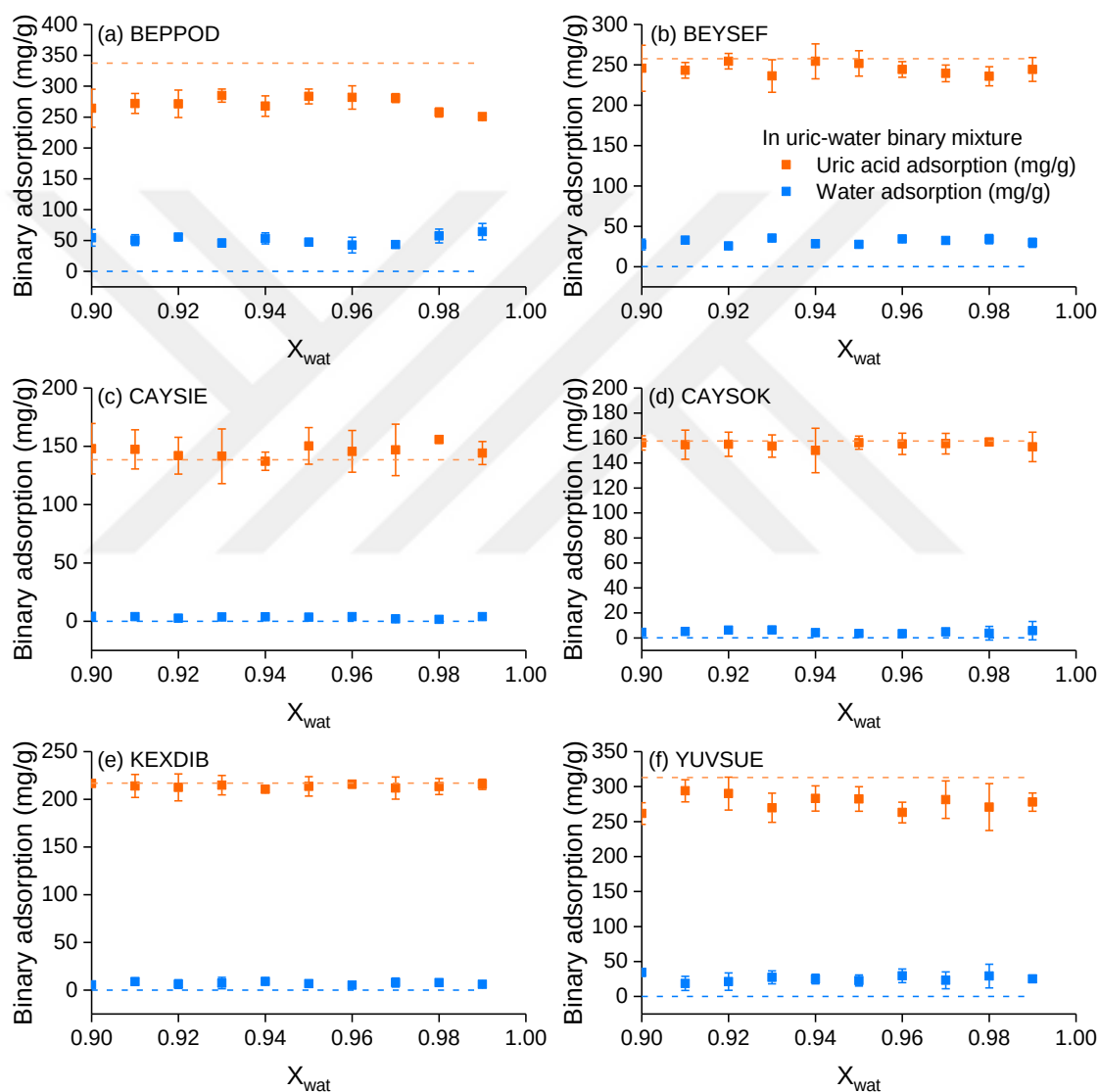


Figure 24. Uric acid-water binary mixture adsorption isotherms of the top performing 6 bio-MOFs at 310 K. The dashed orange (blue) line shows the adsorbed amount of uric acid (water) calculated at 1 bar and 310 K. Error bars are demonstrated on each graph.

The adsorption amounts of uric acid in CAYSIE, CAYSOK and KEXDIB having a similar PV of $\sim 0.40 \text{ cm}^3/\text{g}$ did not change in the presence of water, but the amount of adsorbed water increased in BEPPOD, BEYSEF and YUVSUE. Especially in BEPPOD,

as the amount of water increased, the adsorbed amount of uric acid dramatically decreased. This was attributed to BEPPOD's larger pore diameters ($9.62 \text{ \AA} \times 9.50 \text{ \AA}$) compared to those of the remaining five materials ($\sim 6.5 \text{ \AA} \times \sim 5 \text{ \AA}$). Large pore diameters allowed interaction between water molecules and uric acid molecules and water molecules could enter the pores.

5.2.2 Senary Mixture

Co-adsorption of uric acid, creatinine, urea, p-cresol, indoxyl sulfate and water was investigated in promising 6 bio-MOFs in **Figure 25**. Since simulations of large molecules require enormous computational time due to long equilibration process, indoxyl sulfate was only included in the senary mixture.

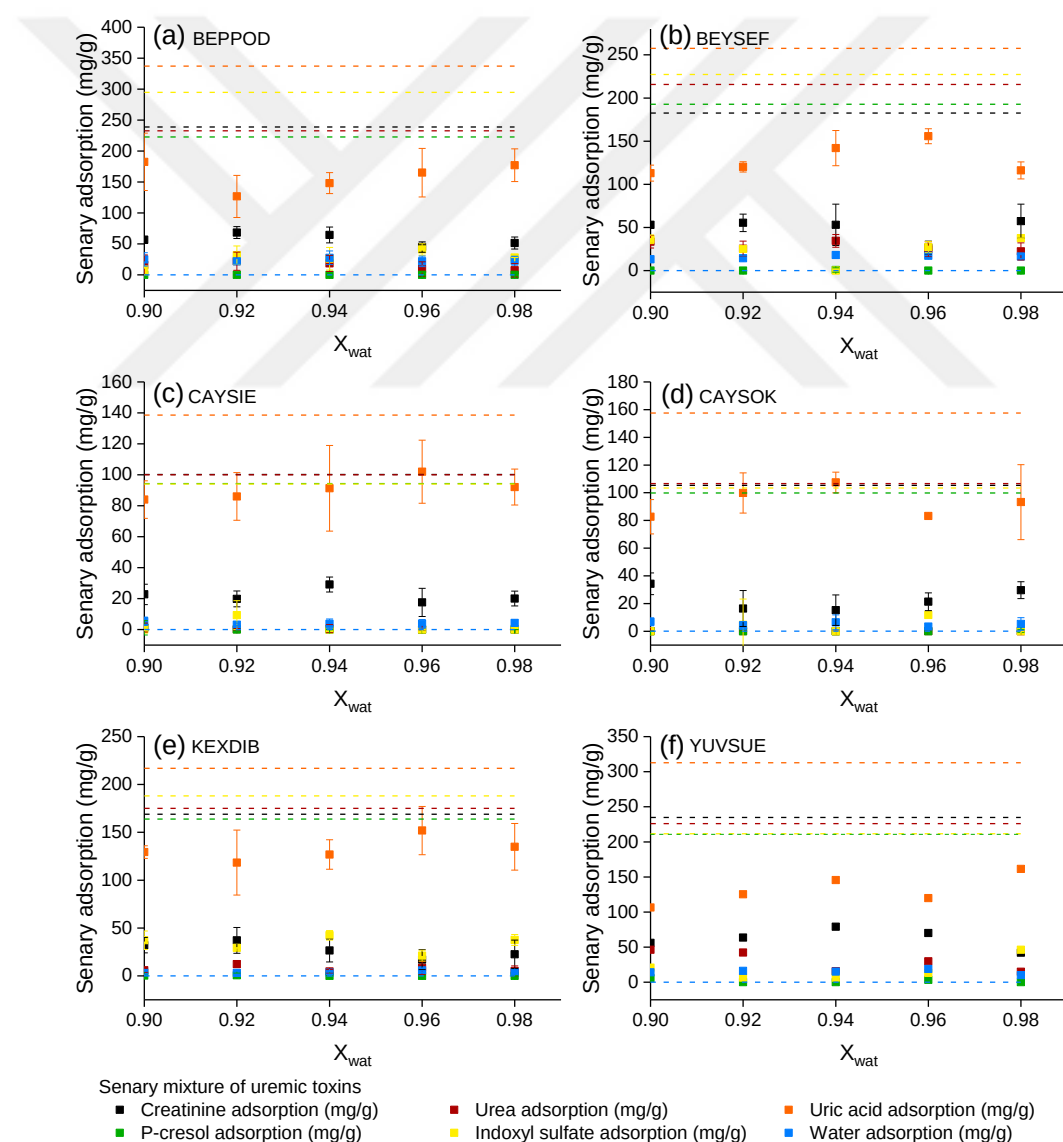


Figure 25. Senary mixture adsorption isotherms of the top performing 6 bio-MOFs at 310 K. The dashed orange, black, red, green, yellow, and blue line shows the adsorbed

amount of uric acid, creatinine, urea, p-cresol, indoxyl sulfate and water calculated at 1 bar and 310 K. Error bars are demonstrated on each graph.

Figure 25 shows the adsorbed amount of five uremic toxins in the presence of different mole fractions of water. In mixture adsorption, it is clearly seen that uric acid is strongly adsorbed in these 6 bio-MOFs. This was attributed to its favourable interactions with the framework triggered by its polar atoms and larger size. On the other hand, p-cresol, which was adsorbed in bio-MOFs at single-component and binary mixture conditions, was almost not adsorbed in bio-MOFs at senary mixture conditions. Since rings containing polar atoms such as pyridine and pyrazole have greater attractive strength than benzene rings [117], uric acid and creatinine were much strongly adsorbed within the pores of bio-MOFs. **Figure 26** presents GCMC snapshots obtained from single-component and mixture simulations for BEPPOD.

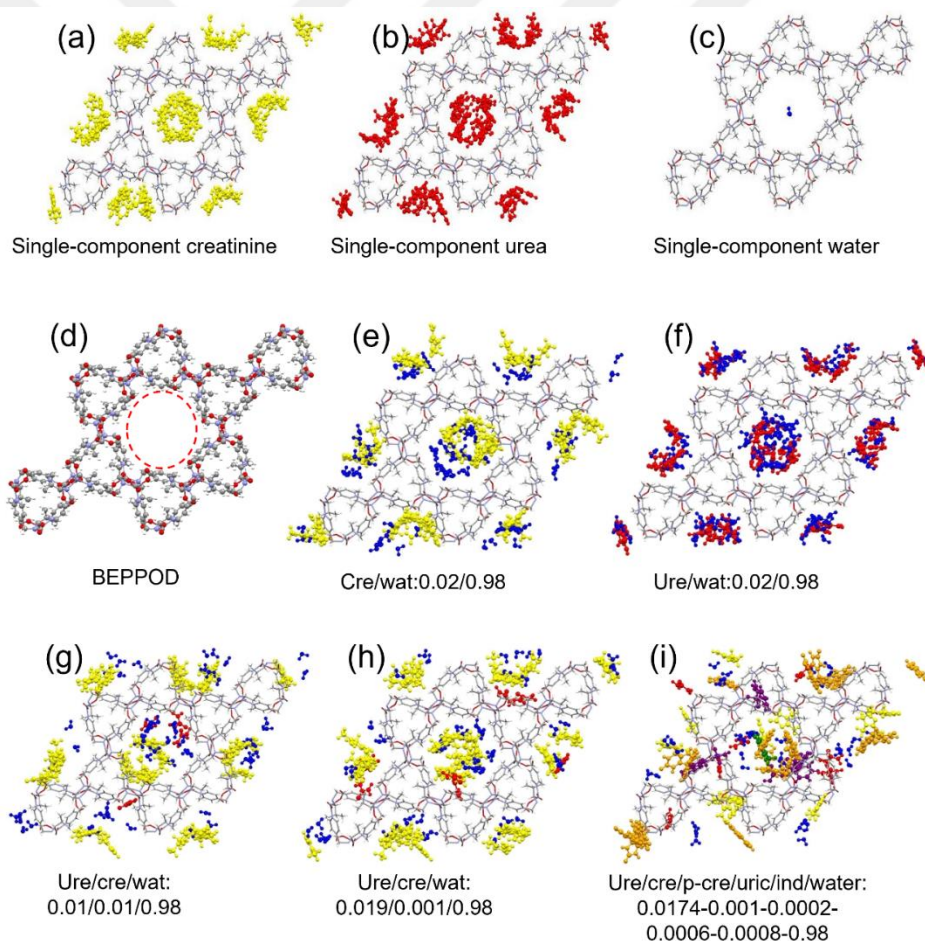


Figure 26. GCMC snapshots obtained from single-component (a-c), binary (e,f), ternary (g,h) and senary (i) mixture simulations of BEPPOD (d) at 310 K. Yellow, red, green, orange, purple and blue colours represent creatinine, urea, p-cresol, uric acid, indoxyl sulfate and water, respectively. The red line (in c) shows the favorite adsorption sites (amino and methyl groups).

Figure 26(a-d) shows favourable adsorption sites of BEPPOD for urea, creatinine, and water molecules. While urea and creatinine are adsorbed in large pores of BEPPOD, water cannot be adsorbed in BEPPOD, which has hydrophobic regions. However, as shown in **Figure 26(e-f)** water could enter the structure at binary mixture condition. As discussed before, this is because water forms hydrogen bonds with urea and creatinine molecules. At ternary mixture condition, the competition between uremic toxins increases and creatinine is adsorbed much strongly than urea (**Figure 26(g-h)**). Although molar fraction of uric acid was quite low in senary mixture, uric acid was strongly absorbed in bio-MOFs (**Figure 26(i)**) because uric acid ($C_5H_4N_4O_3$) is larger than creatinine ($C_4H_7N_3O$), and the effect of LJ energy parameters (ϵ/k_B) is greater considering the difference in atomic numbers (5C, 3O and 4N). Therefore, van der Waals interactions between bio-MOF atoms and uric acid molecule are much stronger than those occurred between bio-MOF atoms and creatinine molecule. Similar results were also found for CAYSIE, CAYSOK and KEXDIB (**Figure A11-A13**).

Figure 27 shows snapshots obtained from GCMC simulations at single-component, binary mixture, and ternary mixture conditions for BEYSEF at 310 K. **Figure 27(a-b)** shows that urea adsorption in this MOF (215.71 mg/g) is much higher than creatinine (182.66 mg/g) at single-component condition. Urea could also enter narrow pores ($5.62 \text{ \AA} \times 4.75 \text{ \AA}$) of BEYSEF due to its smaller molecular size (**Table A8**). In addition, water was not adsorbed in BEPPOD (**Figure 27(c)**). **Figure 27(d)** shows that methyl and amino groups within the pores of BEYSEF are favourite adsorption sites. Due to water-soluble properties of urea and creatinine, they interact with water, increasing the amount of water from 0.05 mg/g at single-component condition to 27.24 mg/g in urea/water and 45.16 mg/g in creatinine/water mixtures (**Figure 27(e-f)**). The methyl and amino groups may have $CH-\pi$ and $NH-\pi$ interactions in molecules with aromatic rings, respectively. Since $NH-\pi$ interaction is stronger than $CH-\pi$ interaction, [126] creatinine is closer to amino groups of BEYSEF as shown in **Figure 27(g)**. However, when the molar ratio of creatinine decreased, the amount of urea increased and a few creatinine molecules located near the amino groups of BEYSEF, as seen in **Figure 27(h)**. In senary mixture simulations, uric acids filled pores of BEYSEF due to its stronger interaction compared to that of creatinine. However, as seen from **Figure 27(i)**, creatinine managed to enter the structure by competing with uric acid. Similar results were also found for YUVSUE (**Figure A14**).

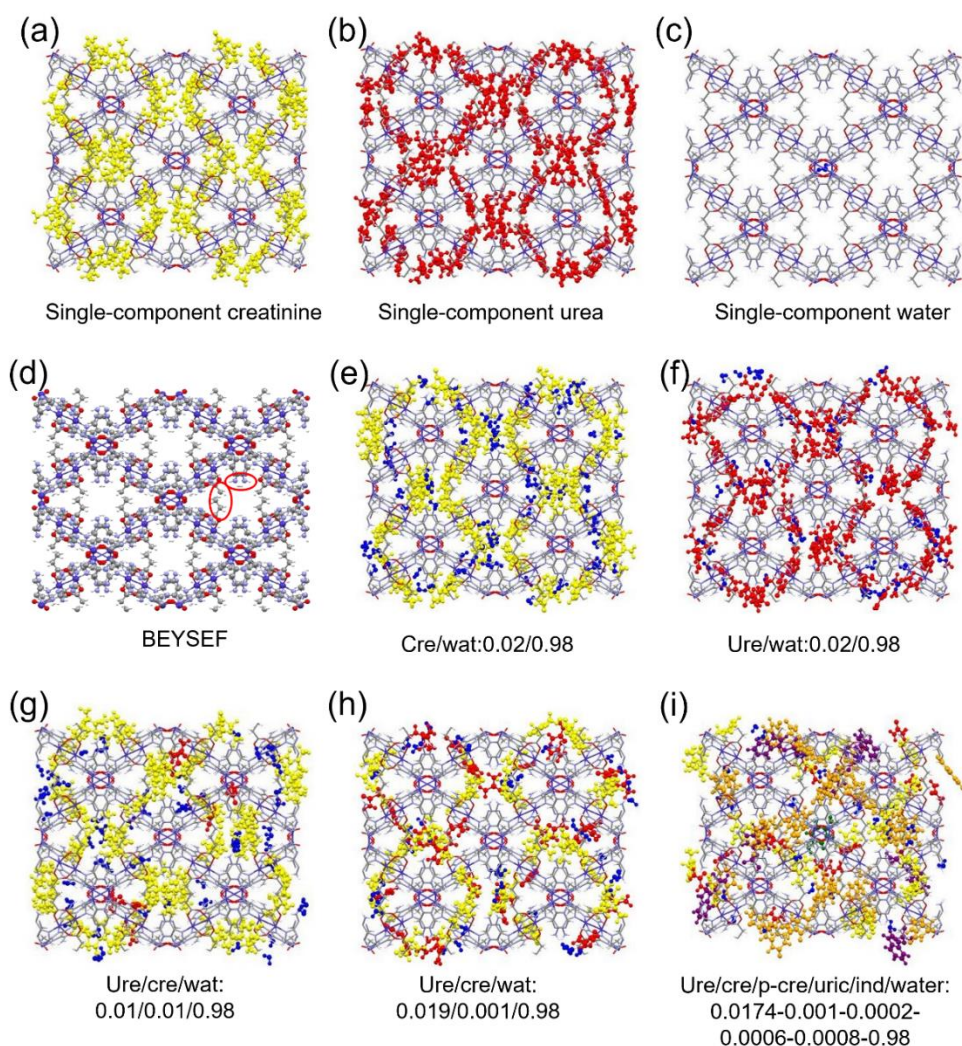


Figure 27. GCMC Snapshots obtained from single-component (a-c), binary-mixture (e,f), ternary-mixture (g,h) and senary-mixture (i) simulations of BEYSEF(d) at 310K. Yellow, red, and blue colours represents creatinine, urea and water, respectively. The red line (in c) shows the favorite adsorption sites (amino and methyl groups).

The results of single-component, binary, ternary, and senary mixture simulations for urea, creatinine, p-cresol, and uric acid adsorption in promising 6 bio-MOFs are compared in **Figure 28**. Since ternary mixture simulations were performed only for urea and creatinine molecules, results were given for urea and creatinine adsorption in **Figure 28(a-b)**. On the other hand, the data is not available in **Figure 28(c-d)** since ternary mixture simulations were not performed for p-cresol and uric acid molecules. The single-component uremic toxin adsorption in bio-MOFs gave highest uptakes as expected. Adsorption of uremic toxins, except urea, was not affected much in the presence water, although the mole fraction of water was high ($X_{\text{wat}}:0.98$). A very low urea adsorption in CAYSIE and CAYSOK was observed due to their hydrophobic regions surrounding metal atom. In ternary and senary mixture simulations, urea could not compete with other

uremic toxins. However, urea managed to enter the structure by making a dipole-dipole interaction with amino groups of BEYSEF and YUVSUE (**Figure 28(a)**). At binary mixture condition, creatinine adsorption was not affected by the presence of water in the mixture and the amount of adsorbed water in the structure increased. However, a weak competition was observed between uric acid and creatinine in senary mixture (**Figure 28(b)**), resulting in higher adsorbed uric acid amount in bio-MOFs.

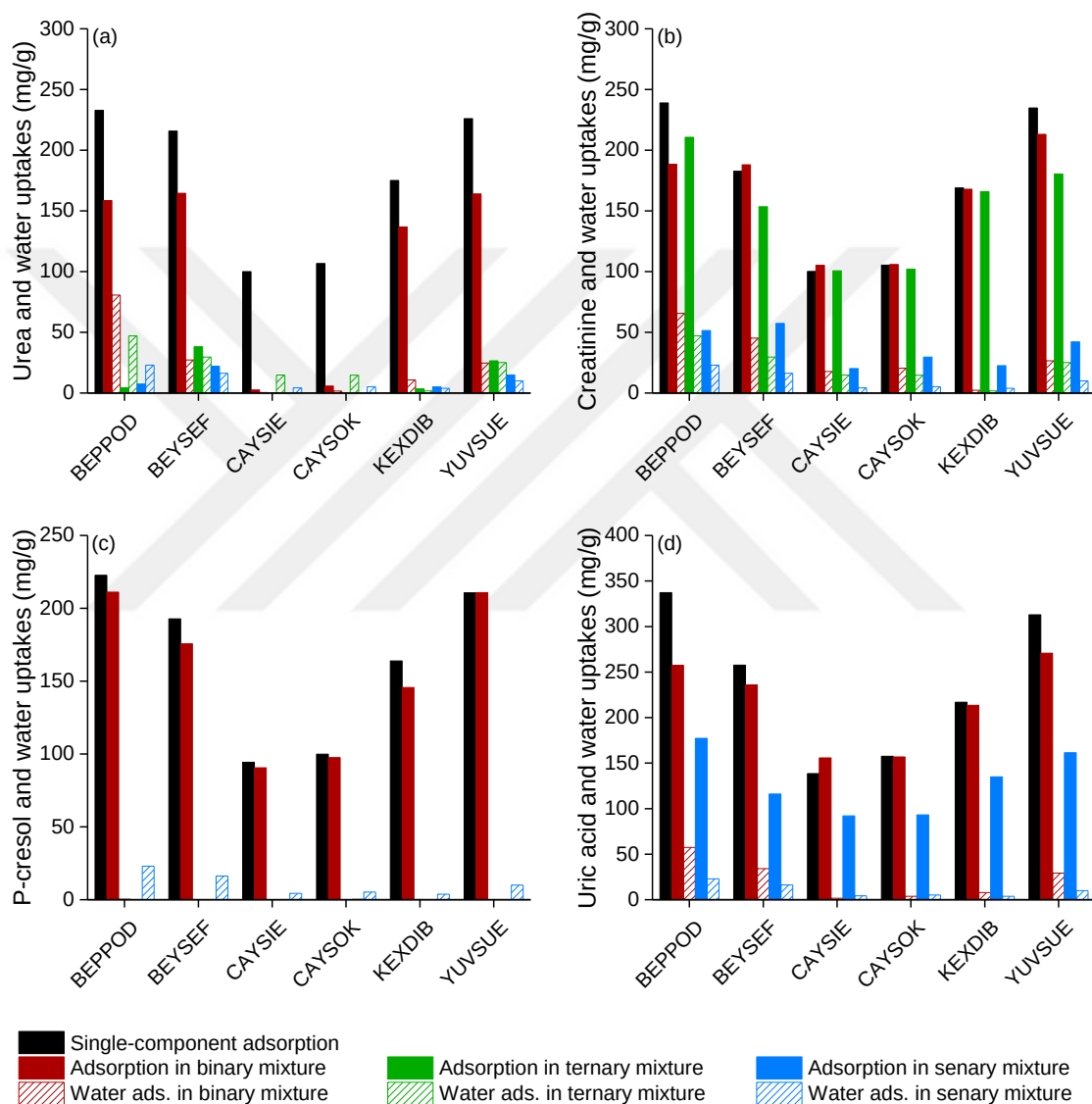


Figure 28. Comparison of GCMC simulations for urea, creatinine, p-cresol, and uric acid adsorption in promising 6 MOFs at single-component, binary, ternary, and senary mixture conditions. Striped bar represents the amount of water in that simulation.

P-cresol uptakes adsorbed in bio-MOFs at binary mixture condition was found to be very close to those obtained at the single-component adsorption condition because water could not enter the pores of hydrophobic bio-MOFs due to the hydrophobic nature

of p-cresol. In addition, since p-cresol could not compete with creatinine and uric acid in bio-MOFs, it could not be adsorbed in senary simulations (**Figure 28(c)**). Polar atoms (O, and N) and purine ring in the structure of uric acid are predicted to have higher attraction force in bio-MOFs because OH- π interaction is stronger than NH- π and CH- π interactions [126]. In addition, bio-MOFs exhibited higher selectivity towards uric acid because it has a higher oxygen number (O1, O2 and O3) than that of creatinine (O1), enhancing its electrostatic and van der Waals interactions. Therefore, adsorption of uric acid was not seriously affected by the presence water and other uremic toxins (**Figure 28(d)**).

Figure 29 shows RDF analysis obtained from single-component simulations of BEPPOD.

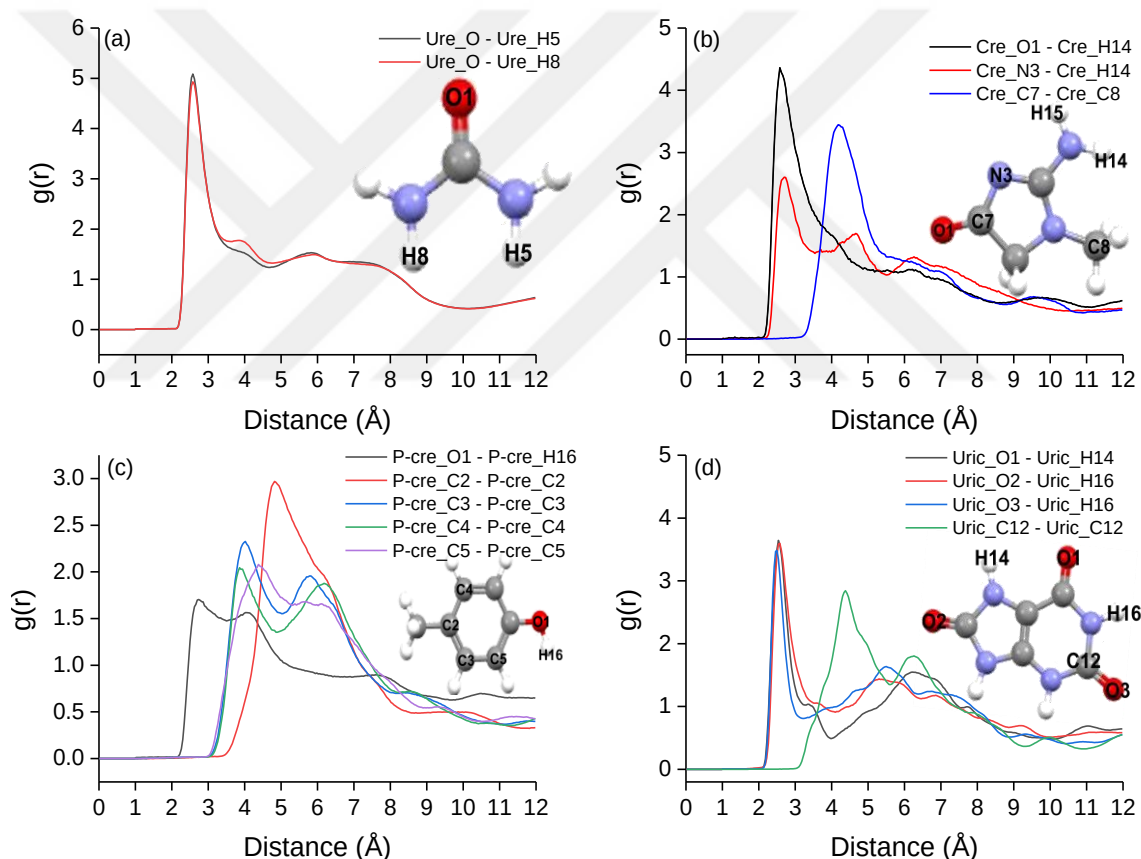


Figure 29. Interactions between atoms of uremic toxins computed at single-component condition. BEPPOD: (a) urea, (b) creatinine, (c) p-cresol and (d) uric acid.

The distance between atoms of urea, creatinine and uric acid was measured as 2.6 Å by RDF analysis. Although this value does not fall below the hydrogen bond criterion, it is quite close. Hydrogen bond between the atoms of p-cresol, which is a hydrophobic molecule, is weak. However, distance of the carbon atoms in the aromatic rings of creatinine, p-cresol and uric acid is remarkable. The distance between aromatic rings is

generally accepted as 3.5 Å for π - π bonding interactions [117]. However, when distance of carbon atoms is examined by RDF, distance between atoms is very close to 3.5 Å. This proximity may indicate the existence of a π - π interaction between molecules with aromatic rings. A slight increase in the amount of water was observed at binary mixture condition. **Figure 30** shows hydrogen bond of uremic toxin atoms with water atoms in BEPPOD. As shown in **Figure 30(a-b)**, urea and creatinine atoms form hydrogen bonds with water. However, in p-cresol/water mixture, the interaction between the p-cresol atom and the hydrogen atom of water was found to be weak (**Figure 30(c)**).

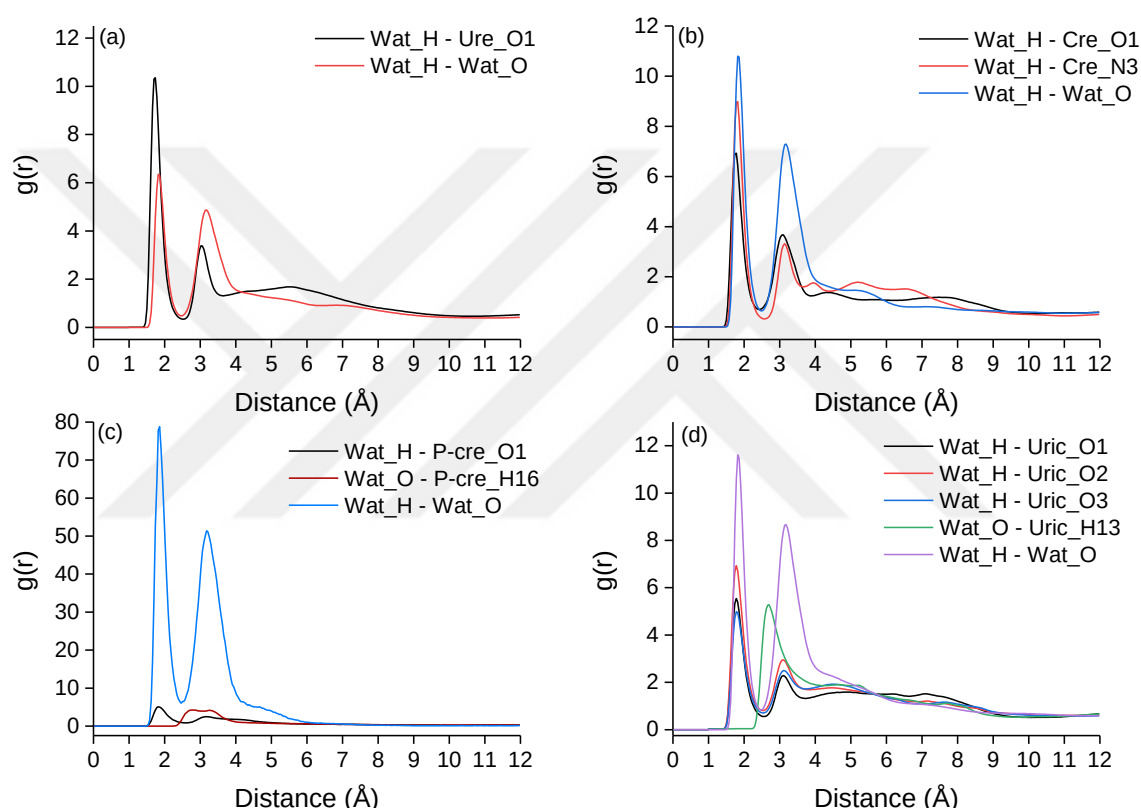


Figure 30. RDF plots obtained from GCMC simulations of BEPPOD at binary mixture condition. (a) urea, (b) creatinine, (c) p-cresol and (d) uric acid.

This can be attributed to the high carbon atom content of p-cresol. Atoms of water molecules, which managed to enter the structure with weak interaction of oxygen atom of p-cresol, made strong hydrogen bonds with each other. In addition, interaction between water and uric acid, which has three polar atoms, was also similar to that of urea and creatinine. In summary, the distance between the four uremic toxin atoms and the water atoms confirmed that they form hydrogen bonds with 1.8 Å. Thus, presence of uremic toxins affected water adsorption and increased BEPPOD's water uptake in mixture simulations.

CHAPTER VI

CONCLUSION

In this thesis, we examined the performance of 315 bio-MOFs for separation of uremic toxins (urea, creatinine, uric acid, p-cresol and indoxyl sulfate), which accumulates in blood of patients with CKD. We first identified hydrophobic bio-MOFs using the Henry's law constant of water. After structural analysis and single-component water adsorption simulations, 60 hydrophobic bio-MOFs were identified to be further used for uremic toxin separation. Ideal and single-component adsorption selectivities for urea/water, creatinine/water and creatinine/urea separations were calculated at both infinite dilution and 1 bar, 310 K. Although infinite dilution selectivities of bio-MOFs significantly differ, adsorption selectivities of bio-MOFs computed at 1 bar were found to be similar for most bio-MOFs due to the similar pore volumes of bio-MOFs. Promising 6 bio-MOFs (BEPPOD, BEYSEF, CAYSIE, CAYSOK, KEXDIB and YUVSUE) were identified based on their high urea/water and creatinine/water selectivities. We also performed highly costly binary and ternary mixture simulations to mimic a more realistic uremic toxin composition and results showed that the presence of water does not have a significant effect on creatinine uptakes of bio-MOFs. However, the amount of adsorbed water in bio-MOFs increased at mixture condition due to hydrogen bonds occurred between polar atoms of urea or creatinine and atoms of water. Co-adsorption of uric acid, p-cresol and indoxyl sulfate which are also accumulated in body were finally examined by performing GCMC simulations for uremic toxin separation. Results showed that uric acid adsorption in bio-MOFs is found to be much stronger than adsorption of the remaining uremic toxins due to its strong π - π interactions with the aromatic rings of bio-MOFs.

It is also important to note our assumptions used in this thesis:

- We first assume defect-free and perfect crystal structures of bio-MOFs in our simulations. However, bio-MOFs can have impurities or structural defects during their synthesis, which may affect their uremic toxin separation performances. The effect of impurities or defects can be investigated as a future work.
- Rigid framework assumption was done throughout in this thesis since structural flexibility has thought to be negligible effect on guest adsorption. However, since

uremic toxins are large molecules, flexible GCMC simulations can be also performed to recalculate the adsorbent performance metrics.

- We only considered water in the simulation environment to represent the fluid. However, many substances, including ions, proteins in the blood content. Therefore, in the future, tests of these bio-MOFs can be performed in a (phosphate buffered saline) PBS liquid. In addition, structural stability of bio-MOFs did not consider in this thesis. Experimental work is highly required to understand the structural stabilities of bio-MOFs in the presence of water and/or PBS liquid.

Overall, adsorption-based separation performance of bio-MOFs was assessed using computationally demanding GCMC simulations in this study. Results will be useful to develop new adsorbents for artificial kidney applications with the joint efforts of researchers evolved in various disciplines, including but not limited to chemistry, physics, material science, medicine, and engineering.

APPENDIX

Table A1. “Other” linkers and metals contained in bio-MOFs.

Linkers (Number of bio-MOFs)	Acetamide (2)	Cyclodextrin (24)	Muconate (19)	Thymine (9)
	Acetate (6)	Gallate (6)	Oxalate (4)	
	Biocompatible (53)	Glutamate (10)	Peptide (16)	
	Citrate (8)	Metalloporphyrin (8)	Succinate (44)	
Metals (Number of bio-MOFs)	Au (4)	Er (9)	Mo (3)	Sm (10)
	Ba (10)	Eu (6)	Na (14)	Sn (3)
	Ca (15)	Gd (12)	Nd (8)	Sr (8)
	Ce (3)	Hg (7)	Pb (5)	Tb (10)
	Cr (3)	K (23)	Pr (3)	Y (4)
	Cs (6)	La (4)	Rb (3)	Zr (18)
	Dy (7)	Li (6)	Ru (4)	Multiple Metals (66)

Table A2. Parameters for adsorbate molecules used in molecular simulations.

Adsorbent	Atoms	$\sigma(\text{\AA})$	$\epsilon/\text{kB (K)}$	$q(e^-)$
H ₂ O TIP4P/2005	O	3.159	93.20	0.0
	Imaginary atom	0.0	0.0	-1.113
	H	0.0	0.0	0.556
Urea (CH ₄ N ₂ O)	O1	3.033	48.19	-0.594
	N2-N3	3.263	38.97	-1.011
	C4	3.473	47.86	0.929
	H5-H8	2.846	7.65	0.425
	H6-H7	2.846	7.65	0.419
Creatinine (C ₄ H ₇ N ₃ O)	O1	3.033	48.19	-0.530
	N2	3.263	38.97	0.119
	N3	3.263	38.97	-0.709
	N4	3.263	38.97	-0.947
	C5	3.473	47.89	-0.620
	C6	3.473	47.89	0.644
	C7	3.473	47.89	0.745
	C8	3.473	47.89	-0.497
	H9-H10	2.846	7.65	0.209
	H11-H13	2.846	7.65	0.146
	H12	2.846	7.65	0.213
	H14	2.846	7.65	0.418
	H15	2.846	7.65	0.454
P-cresol (C ₇ H ₈ O)	O1	3.033	48.19	-0.535
	C2	3.473	47.89	0.299
	C3	3.473	47.89	-0.205
	C4	3.473	47.89	-0.288
	C5	3.473	47.89	-0.315
	C6	3.473	47.89	-0.180
	C7	3.473	47.89	0.307
	C8	3.473	47.89	-0.605
	H9	2.846	7.65	0.148
	H10-H11	2.846	7.65	0.159
	H12	2.846	7.65	0.165
	H13-H15	2.846	7.65	0.168
	H14	2.846	7.65	0.158
	H16	2.846	7.65	0.397

Uric acid (C ₅ H ₄ N ₄ O ₃)	O1	3.033	48.19	-0.484
	O2	3.033	48.19	-0.490
	O3	3.033	48.19	-0.507
	N4	3.263	38.97	-0.559
	N5	3.263	38.97	-0.437
	N6	3.263	38.97	-0.623
	N7	3.263	38.97	-0.573
	C8	3.473	47.89	0.501
	C9	3.473	47.89	-0.142
	C10	3.473	47.89	0.549
	C11	3.473	47.89	0.569
	C12	3.473	47.89	0.661
	H13	2.846	7.65	0.394
	H14	2.846	7.65	0.377
	H15	2.846	7.65	0.398
	H16	2.846	7.65	0.366
Indoxyl sulfate (C ₈ H ₇ NO ₄ S)	S1	3.590	173.22	0.569
	O2	3.033	48.19	-0.086
	O3	3.033	48.19	-0.452
	O4	3.033	48.19	-0.314
	O5	3.033	48.19	-0.322
	N6	3.263	38.97	-0.473
	C7	3.473	47.89	0.086
	C8	3.473	47.89	0.252
	C9	3.473	47.89	-0.001
	C10	3.473	47.89	-0.098
	C11	3.473	47.89	-0.215
	C12	3.473	47.89	-0.297
	C13	3.473	47.89	-0.162
	C14	3.473	47.89	-0.124
	H15	2.846	7.65	0.384
	H16	2.846	7.65	0.194
	H17	2.846	7.65	0.158
	H18	2.846	7.65	0.168
	H19	2.846	7.65	0.141
	H20	2.846	7.65	0.138
	H21	2.846	7.65	0.454

Table A3. Antoine equation parameters of components, in mmHg and °C units, at the temperature range of 1–99 °C.

Antoine equation parameters	Water[101]	Urea[127]
A	8.07131	10.44
B	1730.63	4579
C	233.426	-

Table A4. $K_{\text{Henry,water}}$, $K_{\text{Henry,urea}}$ and $K_{\text{Henry,creatinine}}$ values of 60 bio-MOFs. Standard deviations (σ) were also added for each data.

Biyo-MOFs	$K_{\text{Henry,water}}$ ve σ	$K_{\text{Henry,urea}}$ ve σ	$K_{\text{Henry,creatinine}}$ ve σ
ADATOQ	$7.14 \times 10^{-7} \pm 1.47 \times 10^{-9}$	$5.92 \times 10^{-5} \pm 3.85 \times 10^{-7}$	$2.42 \times 10^{-2} \pm 1.24 \times 10^{-3}$
AJESAJ02	$1.19 \times 10^{-6} \pm 6.38 \times 10^{-10}$	$8.28 \times 10^{-5} \pm 2.58 \times 10^{-7}$	$1.49 \times 10^{-2} \pm 5.13 \times 10^{-4}$
AJESAJ03	$1.10 \times 10^{-6} \pm 9.76 \times 10^{-10}$	$6.16 \times 10^{-5} \pm 1.73 \times 10^{-7}$	$3.27 \times 10^{-3} \pm 2.16 \times 10^{-4}$
ATIBOU01	$6.26 \times 10^{-7} \pm 1.30 \times 10^{-9}$	$1.11 \times 10^{-4} \pm 1.88 \times 10^{-6}$	$1.53 \times 10^{-7} \pm 8.81 \times 10^{-8}$
ATIBOU02	$6.25 \times 10^{-7} \pm 1.88 \times 10^{-9}$	$1.11 \times 10^{-4} \pm 8.15 \times 10^{-7}$	$1.71 \times 10^{-7} \pm 1.69 \times 10^{-7}$
ATICAH	$6.10 \times 10^{-7} \pm 1.35 \times 10^{-9}$	$9.55 \times 10^{-5} \pm 1.17 \times 10^{-6}$	$1.24 \times 10^{-8} \pm 7.63 \times 10^{-9}$
BAHLED	$1.10 \times 10^{-6} \pm 2.07 \times 10^{-9}$	$3.17 \times 10^{-4} \pm 6.64 \times 10^{-7}$	$1.64 \pm 1.93 \times 10^{-2}$

BEPLUF	$7.93 \times 10^{-7} \pm 1.73 \times 10^{-9}$	$6.75 \times 10^{-5} \pm 1.55 \times 10^{-7}$	$5.25 \times 10^{-2} \pm 1.14 \times 10^{-3}$
BEPMAM	$7.62 \times 10^{-7} \pm 9.59 \times 10^{-10}$	$6.53 \times 10^{-5} \pm 2.88 \times 10^{-7}$	$5.34 \times 10^{-2} \pm 4.72 \times 10^{-4}$
BEPMEQ	$7.40 \times 10^{-7} \pm 1.94 \times 10^{-9}$	$4.46 \times 10^{-5} \pm 1.86 \times 10^{-7}$	$1.84 \times 10^{-2} \pm 2.47 \times 10^{-4}$
BEPMIU	$7.12 \times 10^{-7} \pm 4.30 \times 10^{-10}$	$4.12 \times 10^{-5} \pm 1.87 \times 10^{-7}$	$1.59 \times 10^{-2} \pm 2.39 \times 10^{-4}$
BEPNIV	$5.91 \times 10^{-7} \pm 1.65 \times 10^{-9}$	$9.27 \times 10^{-5} \pm 3.33 \times 10^{-7}$	$1.24 \times 10^{-1} \pm 3.34 \times 10^{-3}$
BEPNOB	$7.40 \times 10^{-7} \pm 2.13 \times 10^{-9}$	$6.03 \times 10^{-5} \pm 2.91 \times 10^{-7}$	$4.65 \times 10^{-2} \pm 1.98 \times 10^{-3}$
BEPNUH	$6.77 \times 10^{-7} \pm 1.22 \times 10^{-9}$	$4.78 \times 10^{-5} \pm 1.65 \times 10^{-7}$	$2.83 \times 10^{-2} \pm 4.51 \times 10^{-4}$
BEPPAP	$6.94 \times 10^{-7} \pm 3.31 \times 10^{-10}$	$3.84 \times 10^{-5} \pm 2.48 \times 10^{-7}$	$1.41 \times 10^{-2} \pm 1.94 \times 10^{-4}$
BEPPIX	$6.43 \times 10^{-7} \pm 1.23 \times 10^{-9}$	$1.76 \times 10^{-4} \pm 6.43 \times 10^{-7}$	$4.5 \times 10^{-1} \pm 1.86 \times 10^{-2}$
BEPPOD	$7.38 \times 10^{-7} \pm 1.27 \times 10^{-9}$	$1.00 \times 10^{-4} \pm 3.98 \times 10^{-7}$	$1.33 \times 10^{-1} \pm 2.6 \times 10^{-3}$
BEYSEF	$1.28 \times 10^{-6} \pm 4.31 \times 10^{-9}$	$2.93 \times 10^{-4} \pm 9.10 \times 10^{-7}$	$8.91 \times 10^{-1} \pm 2.08 \times 10^{-2}$
CATDEH	$5.54 \times 10^{-7} \pm 2.29 \times 10^{-9}$	$3.95 \times 10^{-5} \pm 3.86 \times 10^{-7}$	$6.31 \times 10^{-2} \pm 9.18 \times 10^{-3}$
CATDIL	$5.02 \times 10^{-7} \pm 6.98 \times 10^{-10}$	$4.08 \times 10^{-5} \pm 2.19 \times 10^{-7}$	$7.72 \times 10^{-2} \pm 4.04 \times 10^{-3}$
CAYRIE	$5.49 \times 10^{-7} \pm 2.22 \times 10^{-9}$	$4.00 \times 10^{-5} \pm 2.67 \times 10^{-7}$	$7.79 \times 10^{-2} \pm 3.11 \times 10^{-3}$
CAYROK	$4.89 \times 10^{-7} \pm 1.36 \times 10^{-9}$	$3.81 \times 10^{-5} \pm 6.18 \times 10^{-8}$	$6.13 \times 10^{-2} \pm 4.25 \times 10^{-3}$
CAYSIE	$6.35 \times 10^{-7} \pm 1.65 \times 10^{-9}$	$6.16 \times 10^{-5} \pm 5.28 \times 10^{-7}$	$1.59 \times 10^{-1} \pm 8.24 \times 10^{-3}$
CAYSOK	$6.81 \times 10^{-7} \pm 2.03 \times 10^{-9}$	$7.22 \times 10^{-5} \pm 8.15 \times 10^{-7}$	$2.06 \times 10^{-1} \pm 5.48 \times 10^{-3}$
CAYYEG	$6.31 \times 10^{-7} \pm 1.80 \times 10^{-9}$	$5.33 \times 10^{-5} \pm 5.51 \times 10^{-7}$	$8.55 \times 10^{-2} \pm 2.71 \times 10^{-3}$
CAZGIT	$1.34 \times 10^{-6} \pm 9.24 \times 10^{-9}$	$1.56 \times 10^{-3} \pm 4.90 \times 10^{-5}$	$2.75 \times 10^{-5} \pm 5.12 \times 10^{-5}$
CERDUY	$9.87 \times 10^{-7} \pm 1.51 \times 10^{-9}$	$4.07 \times 10^{-5} \pm 1.79 \times 10^{-7}$	$1.61 \times 10^{-3} \pm 1.12 \times 10^{-4}$
CERDUY01	$9.88 \times 10^{-7} \pm 1.51 \times 10^{-9}$	$4.04 \times 10^{-5} \pm 1.38 \times 10^{-7}$	$9.97 \times 10^{-4} \pm 7.48 \times 10^{-5}$
CETHEQ	$7.26 \times 10^{-7} \pm 1.20 \times 10^{-9}$	$3.40 \times 10^{-5} \pm 1.38 \times 10^{-7}$	$6.21 \times 10^{-3} \pm 1.16 \times 10^{-4}$
COPVOU	$2.16 \times 10^{-7} \pm 5.71 \times 10^{-10}$	$2.29 \times 10^{-5} \pm 8.87 \times 10^{-8}$	$1.51 \times 10^{-2} \pm 1.31 \times 10^{-3}$
DEPJIR02	$1.09 \times 10^{-6} \pm 1.54 \times 10^{-9}$	$8.22 \times 10^{-5} \pm 7.31 \times 10^{-7}$	$3.86 \times 10^{-3} \pm 3.37 \times 10^{-4}$
EVEPOK	$9.46 \times 10^{-7} \pm 1.29 \times 10^{-9}$	$1.09 \times 10^{-4} \pm 4.26 \times 10^{-7}$	$1.26 \times 10^{-2} \pm 1.78 \times 10^{-3}$
EXOJAC	$1.27 \times 10^{-6} \pm 3.12 \times 10^{-9}$	$1.74 \times 10^{-3} \pm 7.21 \times 10^{-5}$	$1.65 \times 10^{-4} \pm 2.35 \times 10^{-4}$
FAFBUL	$1.12 \times 10^{-6} \pm 4.22 \times 10^{-9}$	$1.48 \times 10^{-3} \pm 7.60 \times 10^{-6}$	$3.59 \pm 4.56 \times 10^{-1}$
HAQSIE	$1.01 \times 10^{-6} \pm 8.47 \times 10^{-10}$	$4.83 \times 10^{-5} \pm 2.06 \times 10^{-7}$	$1.24 \times 10^{-2} \pm 3.34 \times 10^{-4}$
IJOMOJ02	$5.97 \times 10^{-7} \pm 1.08 \times 10^{-9}$	$5.50 \times 10^{-5} \pm 9.32 \times 10^{-7}$	$1.85 \times 10^{-9} \pm 2.16 \times 10^{-9}$
IJOMOJ04	$6.00 \times 10^{-7} \pm 1.18 \times 10^{-9}$	$5.58 \times 10^{-5} \pm 1.76 \times 10^{-6}$	$1.96 \times 10^{-9} \pm 2.56 \times 10^{-9}$
IJOMOJ06	$5.91 \times 10^{-7} \pm 2.05 \times 10^{-9}$	$4.91 \times 10^{-5} \pm 7.36 \times 10^{-7}$	$2.85 \times 10^{-10} \pm 4.39 \times 10^{-10}$
IJOMOJ07	$5.96 \times 10^{-7} \pm 6.49 \times 10^{-10}$	$5.52 \times 10^{-5} \pm 7.49 \times 10^{-7}$	$2.11 \times 10^{-9} \pm 1.35 \times 10^{-9}$
IQEWOQ	$6.23 \times 10^{-7} \pm 1.27 \times 10^{-9}$	$9.70 \times 10^{-5} \pm 1.50 \times 10^{-6}$	$8.16 \times 10^{-9} \pm 4.17 \times 10^{-9}$
IREBAJ	$8.18 \times 10^{-7} \pm 2.96 \times 10^{-9}$	$2.84 \times 10^{-4} \pm 4.68 \times 10^{-6}$	$2.18 \times 10^{-3} \pm 3.78 \times 10^{-3}$
IZUMUM	$1.08 \times 10^{-6} \pm 2.05 \times 10^{-9}$	$3.65 \times 10^{-4} \pm 4.25 \times 10^{-6}$	$1.28 \times 10^{-1} \pm 2.61 \times 10^{-2}$
KEXDIB	$9.93 \times 10^{-7} \pm 1.70 \times 10^{-9}$	$7.09 \times 10^{-4} \pm 2.46 \times 10^{-6}$	$3.07 \pm 4.15 \times 10^{-2}$
MIL-100	$1.72 \times 10^{-6} \pm 1.0610^{-8}$	$1.35 \times 10^{-4} \pm 4.05 \times 10^{-5}$	$5.33 \times 10^{-4} \pm 6.28 \times 10^{-6}$
NEJBAF	$1.10 \times 10^{-6} \pm 1.96 \times 10^{-9}$	$1.01 \times 10^{-4} \pm 1.55 \times 10^{-6}$	$2.97 \times 10^{-6} \pm 5.11 \times 10^{-6}$
NEJBAF01	$1.10 \times 10^{-6} \pm 1.65 \times 10^{-9}$	$1.01 \times 10^{-4} \pm 3.26 \times 10^{-7}$	$4.34 \times 10^{-6} \pm 5.31 \times 10^{-6}$
NEJBAF02	$1.06 \times 10^{-6} \pm 1.77 \times 10^{-9}$	$5.68 \times 10^{-5} \pm 1.42 \times 10^{-6}$	$1.76 \times 10^{-9} \pm 8.82 \times 10^{-10}$
NIHBIQ01	$6.48 \times 10^{-7} \pm 1.02 \times 10^{-9}$	$1.14 \times 10^{-4} \pm 2.48 \times 10^{-6}$	$1.69 \times 10^{-9} \pm 1.77 \times 10^{-10}$
NIHBIQ02	$6.58 \times 10^{-7} \pm 2.21 \times 10^{-9}$	$1.41 \times 10^{-4} \pm 1.78 \times 10^{-6}$	$6.40 \times 10^{-9} \pm 5.78 \times 10^{-9}$
OREZES	$4.46 \times 10^{-7} \pm 8.96 \times 10^{-10}$	$5.89 \times 10^{-5} \pm 3.92 \times 10^{-7}$	$6.79 \times 10^{-2} \pm 5.57 \times 10^{-3}$
PORLAL	$9.98 \times 10^{-7} \pm 3.94 \times 10^{-9}$	$1.09 \times 10^{-4} \pm 6.58 \times 10^{-7}$	$6.40 \times 10^{-2} \pm 1.82 \times 10^{-3}$
QEKKEY	$1.24 \times 10^{-6} \pm 7.13 \times 10^{-10}$	$4.57 \times 10^{-5} \pm 1.55 \times 10^{-7}$	$1.31 \times 10^{-2} \pm 3.32 \times 10^{-5}$
SAFBAF	$1.18 \times 10^{-6} \pm 8.87 \times 10^{-10}$	$6.41 \times 10^{-5} \pm 2.82 \times 10^{-7}$	$1.81 \times 10^{-2} \pm 4.29 \times 10^{-4}$
SEGCUD	$3.40 \times 10^{-7} \pm 1.14 \times 10^{-9}$	$2.40 \times 10^{-4} \pm 5.18 \times 10^{-7}$	$3.85 \times 10^{-1} \pm 2.70 \times 10^{-2}$
VEJZIU	$1.32 \times 10^{-6} \pm 1.78 \times 10^{-9}$	$6.30 \times 10^{-5} \pm 2.23 \times 10^{-7}$	$8.84 \times 10^{-3} \pm 3.77 \times 10^{-5}$
XACZEH	$8.53 \times 10^{-7} \pm 1.89 \times 10^{-9}$	$1.03 \times 10^{-5} \pm 1.69 \times 10^{-8}$	$1.45 \times 10^{-3} \pm 2.67 \times 10^{-5}$
XEHDOG	$8.90 \times 10^{-7} \pm 2.28 \times 10^{-9}$	$2.89 \times 10^{-4} \pm 2.42 \times 10^{-5}$	$3.23 \times 10^{-3} \pm 4.61 \times 10^{-4}$
XEHSEJ	$1.07 \times 10^{-6} \pm 3.75 \times 10^{-9}$	$3.61 \times 10^{-4} \pm 4.27 \times 10^{-6}$	$2.89 \times 10^{-10} \pm 4.27 \times 10^{-10}$
XOHFIK	$5.92 \times 10^{-7} \pm 1.96 \times 10^{-9}$	$4.85 \times 10^{-5} \pm 1.04 \times 10^{-6}$	$1.93 \times 10^{-10} \pm 1.69 \times 10^{-10}$
YUVSUE	$1.14 \times 10^{-6} \pm 3.90 \times 10^{-9}$	$4.10 \times 10^{-4} \pm 3.72 \times 10^{-6}$	$2.84 \times 10^{-1} \pm 6.45 \times 10^{-2}$

Table A5. $Q^0_{st,water}$, $Q^0_{st,urea}$ and $Q^0_{st,creatinine}$ values of 60 bio-MOFs. Standard deviations (σ) were also added for each data.

Biyo-MOFs	$Q^0_{st,su} \text{ ve } \sigma$	$Q^0_{st,üre} \text{ ve } \sigma$	$Q^0_{st,kreatinin} \text{ ve } \sigma$
ADATOQ	$-7.30 \pm 1.19 \times 10^{-2}$	$-25.77 \pm 4.89 \times 10^{-2}$	$-50.81 \pm 4.36 \times 10^{-1}$
AJESAJ02	$-6.02 \pm 2.31 \times 10^{-3}$	$-23.14 \pm 1.19 \times 10^{-2}$	$-46.09 \pm 8.15 \times 10^{-2}$

AJESAJ03	$-6.06 \pm 1.85 \times 10^{-3}$	$-22.85 \pm 1.33 \times 10^{-2}$	$-44.90 \pm 1.63 \times 10^{-1}$
ATIBOU01	$-8.90 \pm 3.18 \times 10^{-3}$	$-33.11 \pm 2.36 \times 10^{-2}$	-42.95 ± 1.46
ATIBOU02	$-8.87 \pm 2.61 \times 10^{-3}$	$-33.02 \pm 7.26 \times 10^{-3}$	-42.75 ± 4.31
ATICAH	$-8.90 \pm 3.40 \times 10^{-3}$	$-32.92 \pm 3.41 \times 10^{-2}$	-34.37 ± 1.61
BAHLED	$-6.90 \pm 1.82 \times 10^{-3}$	$-26.13 \pm 5.82 \times 10^{-3}$	$-54.49 \pm 1.61 \times 10^{-2}$
BEPLUF	$-6.66 \pm 7.05 \times 10^{-3}$	$-22.73 \pm 1.26 \times 10^{-2}$	$-46.72 \pm 2.07 \times 10^{-1}$
BEPMAM	$-6.65 \pm 4.08 \times 10^{-3}$	$-22.53 \pm 1.56 \times 10^{-2}$	$-46.53 \pm 1.11 \times 10^{-1}$
BEPMEQ	$-6.11 \pm 5.36 \times 10^{-3}$	$-21.11 \pm 1.58 \times 10^{-2}$	$-42.63 \pm 1.51 \times 10^{-1}$
BEPMIU	$-6.07 \pm 6.24 \times 10^{-3}$	$-20.88 \pm 1.37 \times 10^{-2}$	$-42.09 \pm 1.52 \times 10^{-1}$
BEPNIV	$-7.00 \pm 7.70 \times 10^{-3}$	$-24.89 \pm 1.85 \times 10^{-2}$	$-50.42 \pm 1.27 \times 10^{-1}$
BEPNOB	$-6.54 \pm 8.84 \times 10^{-3}$	$-22.24 \pm 1.47 \times 10^{-2}$	$-46.16 \pm 3.18 \times 10^{-1}$
BEPNUH	$-6.24 \pm 9.05 \times 10^{-3}$	$-21.56 \pm 1.96 \times 10^{-2}$	$-44.40 \pm 1.08 \times 10^{-1}$
BEPPAP	$-6.07 \pm 3.12 \times 10^{-3}$	$-20.73 \pm 1.97 \times 10^{-2}$	$-41.73 \pm 9.36 \times 10^{-2}$
BEPPIX	$-7.71 \pm 3.72 \times 10^{-3}$	$-27.06 \pm 1.24 \times 10^{-2}$	$-54.26 \pm 3.73 \times 10^{-1}$
BEPPOD	$-6.80 \pm 2.74 \times 10^{-3}$	$-23.94 \pm 1.63 \times 10^{-2}$	$-49.01 \pm 1.81 \times 10^{-1}$
BEYSEF	$-9.36 \pm 8.00 \times 10^{-3}$	$-30.62 \pm 2.99 \times 10^{-2}$	$-58.84 \pm 1.19 \times 10^{-1}$
CATDEH	$-9.73 \pm 1.13 \times 10^{-2}$	$-26.24 \pm 2.42 \times 10^{-2}$	$-56.61 \pm 7.49 \times 10^{-1}$
CATDIL	$-9.13 \pm 9.86 \times 10^{-3}$	$-25.54 \pm 2.32 \times 10^{-2}$	$-54.88 \pm 2.80 \times 10^{-1}$
CAYRIE	$-9.32 \pm 1.38 \times 10^{-2}$	$-25.45 \pm 3.07 \times 10^{-2}$	$-54.42 \pm 1.35 \times 10^{-1}$
CAYROK	$-9.30 \pm 9.04 \times 10^{-3}$	$-25.97 \pm 1.61 \times 10^{-2}$	$-56.07 \pm 3.35 \times 10^{-1}$
CAYSIE	$-9.57 \pm 1.04 \times 10^{-2}$	$-26.90 \pm 4.28 \times 10^{-2}$	$-55.29 \pm 1.40 \times 10^{-1}$
CAYSOK	$-9.61 \pm 2.00 \times 10^{-2}$	$-27.22 \pm 5.28 \times 10^{-2}$	$-55.28 \pm 1.76 \times 10^{-1}$
CAYYEG	$-9.12 \pm 5.05 \times 10^{-3}$	$-26.30 \pm 5.08 \times 10^{-2}$	$-51.95 \pm 1.23 \times 10^{-1}$
CAZGIT	$-13.49 \pm 7.01 \times 10^{-3}$	$-46.02 \pm 1.37 \times 10^{-1}$	-57.70 ± 5.27
CERDUY	$-6.02 \pm 3.78 \times 10^{-3}$	$-22.50 \pm 1.12 \times 10^{-2}$	$-45.39 \pm 1.47 \times 10^{-1}$
CERDUY01	$-6.23 \pm 3.34 \times 10^{-3}$	$-23.27 \pm 9.16 \times 10^{-3}$	$-45.65 \pm 2.75 \times 10^{-1}$
CETHEQ	$-6.29 \pm 7.94 \times 10^{-3}$	$-20.63 \pm 1.90 \times 10^{-2}$	$-38.03 \pm 1.40 \times 10^{-1}$
COPVOU	$-7.54 \pm 5.83 \times 10^{-3}$	$-26.72 \pm 3.98 \times 10^{-2}$	$-51.62 \pm 8.41 \times 10^{-1}$
DEPJIR02	$-7.54 \pm 3.62 \times 10^{-3}$	$-28.39 \pm 3.18 \times 10^{-2}$	$-49.84 \pm 3.86 \times 10^{-1}$
EVEPOK	$-7.65 \pm 1.32 \times 10^{-3}$	$-28.26 \pm 1.21 \times 10^{-2}$	$-54.78 \pm 5.81 \times 10^{-1}$
EXOJAC	$-12.73 \pm 8.18 \times 10^{-3}$	$-45.24 \pm 1.73 \times 10^{-1}$	-60.80 ± 6.46
FAFBUL	$-10.41 \pm 5.48 \times 10^{-3}$	$-34.84 \pm 7.72 \times 10^{-3}$	$-68.76 \pm 4.08 \times 10^{-1}$
HAQSIE	$-5.62 \pm 5.75 \times 10^{-3}$	$-20.71 \pm 2.66 \times 10^{-2}$	$-41.33 \pm 2.43 \times 10^{-1}$
IJOMOJ02	$-9.12 \pm 1.60 \times 10^{-3}$	$-33.06 \pm 7.24 \times 10^{-2}$	-31.99 ± 3.92
IJOMOJ04	$-9.13 \pm 2.77 \times 10^{-3}$	$-33.08 \pm 8.39 \times 10^{-2}$	-32.01 ± 5.17
IJOMOJ06	$-9.18 \pm 2.75 \times 10^{-3}$	$-33.11 \pm 7.21 \times 10^{-2}$	-27.22 ± 7.41
IJOMOJ07	$-9.13 \pm 1.04 \times 10^{-3}$	$-33.10 \pm 3.13 \times 10^{-2}$	-32.76 ± 2.45
IQEWOQ	$-8.89 \pm 5.00 \times 10^{-3}$	$-32.77 \pm 2.05 \times 10^{-2}$	-33.38 ± 5.12
IREBAJ	$-10.12 \pm 5.62 \times 10^{-3}$	$-37.62 \pm 3.28 \times 10^{-2}$	-60.87 ± 5.26
IZUMUM	$-9.30 \pm 4.12 \times 10^{-3}$	$-33.41 \pm 4.05 \times 10^{-2}$	-61.21 ± 1.30
KEXDIB	$-8.53 \pm 6.66 \times 10^{-3}$	$-30.74 \pm 1.45 \times 10^{-2}$	$-60.51 \pm 7.98 \times 10^{-2}$
MIL-100	$-8.85 \pm 3.65 \times 10^{-2}$	-46.04 ± 2.74	$-30.91 \pm 1.11 \times 10^{-1}$
NEJBAF	$-8.92 \pm 1.56 \times 10^{-3}$	$-32.02 \pm 3.47 \times 10^{-2}$	-43.13 ± 7.70
NEJBAF01	$-8.92 \pm 1.50 \times 10^{-3}$	$-32.02 \pm 2.72 \times 10^{-2}$	-47.18 ± 5.15
NEJBAF02	$-9.32 \pm 3.95 \times 10^{-3}$	$-32.76 \pm 9.70 \times 10^{-2}$	-30.11 ± 3.56
NIHBIQ01	$-9.23 \pm 4.09 \times 10^{-3}$	$-34.01 \pm 6.41 \times 10^{-2}$	-24.45 ± 4.23
NIHBIQ02	$-9.02 \pm 3.97 \times 10^{-3}$	$-33.48 \pm 4.55 \times 10^{-2}$	-32.37 ± 4.63
OREZES	$-9.44 \pm 4.42 \times 10^{-3}$	$-29.05 \pm 2.63 \times 10^{-2}$	$-58.10 \pm 2.85 \times 10^{-1}$
PORLAL	$-7.40 \pm 9.88 \times 10^{-3}$	$-25.61 \pm 3.10 \times 10^{-2}$	$-48.48 \pm 2.75 \times 10^{-1}$
QEKKEY	$-4.88 \pm 1.28 \times 10^{-3}$	$-18.70 \pm 7.11 \times 10^{-3}$	$-38.46 \pm 1.14 \times 10^{-3}$
SAFBAF	$-5.71 \pm 6.06 \times 10^{-3}$	$-20.30 \pm 2.61 \times 10^{-2}$	$-40.42 \pm 2.50 \times 10^{-1}$
SEGCUD	$-8.75 \pm 3.68 \times 10^{-3}$	$-30.94 \pm 8.82 \times 10^{-2}$	$-63.30 \pm 2.33 \times 10^{-1}$
VEJZIU	$-5.90 \pm 5.01 \times 10^{-3}$	$-21.61 \pm 3.80 \times 10^{-2}$	$-37.87 \pm 1.36 \times 10^{-1}$
XACZEH	$-9.96 \pm 2.21 \times 10^{-2}$	$-17.13 \pm 1.34 \times 10^{-2}$	$-34.27 \pm 9.70 \times 10^{-2}$
XEHDOG	$-10.55 \pm 1.50 \times 10^{-2}$	$-43.50 \pm 4.38 \times 10^{-1}$	-44.31 ± 1.84
XEHSEJ	$-9.98 \pm 3.22 \times 10^{-3}$	$-36.66 \pm 3.00 \times 10^{-2}$	-25.11 ± 3.62
XOHFIK	$-9.20 \pm 2.70 \times 10^{-3}$	$-33.19 \pm 6.59 \times 10^{-2}$	-27.32 ± 2.77
YUVSUE	$-9.17 \pm 8.17 \times 10^{-3}$	$-33.01 \pm 1.81 \times 10^{-2}$	-61.81 ± 1.37

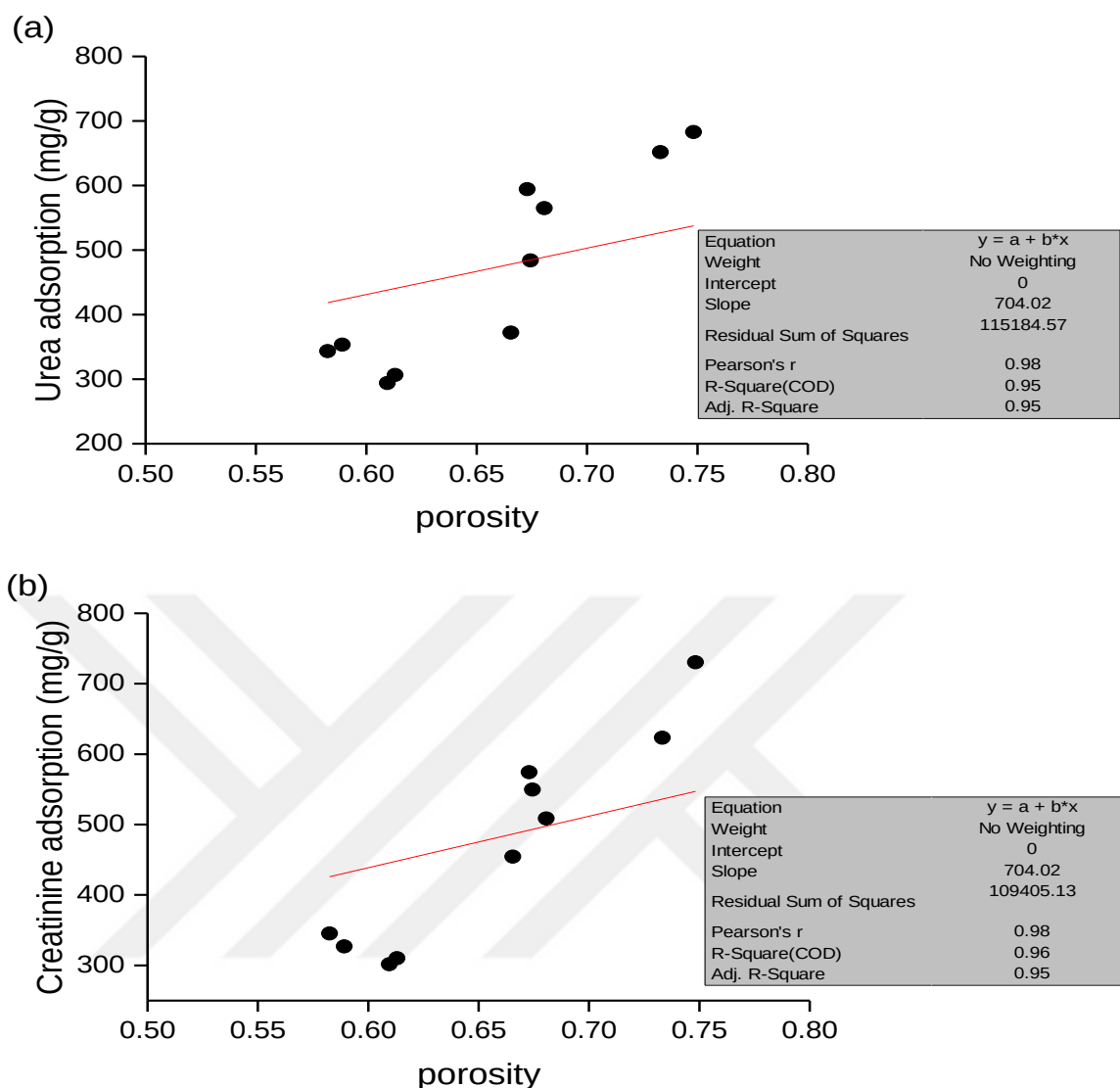


Figure A1. Relations between (a) urea and (b) creatinine adsorption and porosity of bio-MOFs.

Table A6. Uremic toxin removal performance of traditional adsorbents taken from the literature [9].

Adsorbent Type	Maximum removal capacity of uremic toxins in adsorbent	References
Activated carbon (AC)		
Sulfuric acid-treated activated carbon fiber	530 mg urea/g	[113]
4% poly (vinylidene chloride/vinyl chloride)	2.5 mg creatinine/g	[128]
Poly (hydroxyethyl methacrylate) coating	10 mg creatinine/g	[129]
Poly (ether sulfone)/activated carbon (PES-AC) hybrid beads	87 mg creatinine/g	[17]
Poly (hydroxyethyl methacrylate) coating	175 mg creatinine/g	[130]
Suspension-assisted colloidal silica templating treated mesoporous carbon beads	550 mg creatinine/g	[112]

Co-deposition with alginate	2.03 mg uric acid/g	[131]
NH ₃ deposition	333.1 mg uric acid/g	[132]
Polyvinylpyrrolidone coating	3.8 mg p-cresol sulfate/g and 4.4 mg indoxyl sulfate/g	[133]
Zeolite		
Gamma-aminobutyric acid modified zeolite 13X	146 mg urea/g and 132 mg creatinine/g	[49]
Poly (ethylene-co-vinyl alcohol) (EVOH)-zeolite-polymer composite nanofibers	25 mg creatinine/g	[55]
Mordenite	37.5 mg creatinine/g and 3.7 mg indoxyl sulfate/g	[5]
Silicalite	106 mg p-cresol/g	[12]
Mesoporous silica		
SBA-15/Fe ₃ O ₄ nanocomposites	490 mg urea/g	[114]
Amine-functionalized SBA-15	542.6 mg urea/g	[22]
Polymer		
Polysulfone-poly (methyl methacrylate) dual layer hollow fiber	27.6 mg urea/g	[134]
Urease-immobilized polyethersulfone beads	75.1 mg urea/g	[13]
Oxidized poly (vinylindanone) beads with ninhydrin groups	192 mg urea/g	[135]
Creatinine-imprinted poly (tetraethoxysilanol) sol-gel	0.8 mg creatinine/g	[136]
Creatinine-imprinted poly (β- cyclodextrin)	6 mg creatinine/g	[137]
Heparin-mimicking polymers grafted carbon nanotube/poly (ethersulfone) composite membrane	1.4 mg creatinine/g	[138]
Cellulose acetate matrix	25 mg creatinine/g and 13 mg indoxyl sulfate/g	[139]
Polyethersulfone matrix	133.3 mg creatinine/g and 108.7 mg p-cresol/g	[14]
Poly(acrylonitrile) membrane	0.3 mg p-cresol/g	[12]
Polyamide membrane	21 mg p-cresol/g	[12]
Polysulfone membrane	37.3 mg p-cresol/g	[12]
Carbonylated hypercrosslinked chloromethylated poly(styrene-co- divinylbenzene)	141.5 mg p-cresol/g	[140]
Uric acid-imprinted poly(acrylamide-hydroxyethyl methacrylate) p(AAm-MMA) cryogel	687.6 mg uric acid/g	[141]
Poly(cyclodextrins)	45 mg indoxyl sulfate/g	[59]
Metal-Organic Framework (MOF)		
MIL-53 (Fe)	635 mg urea/g	[70]
MIL-100(Fe)	692 mg urea/g	[73]
Cu ₃ (BTC) ₂	250 mg urea/g	[71]
MIL-100(Fe)	190.5 mg creatinine/g	[74]
UiO-66-(COOH) ₂ @Cotton fabric composite	212.8 mg creatinine/g	[72]
NU-1000	26.5 mg p-cresol/g	[72]

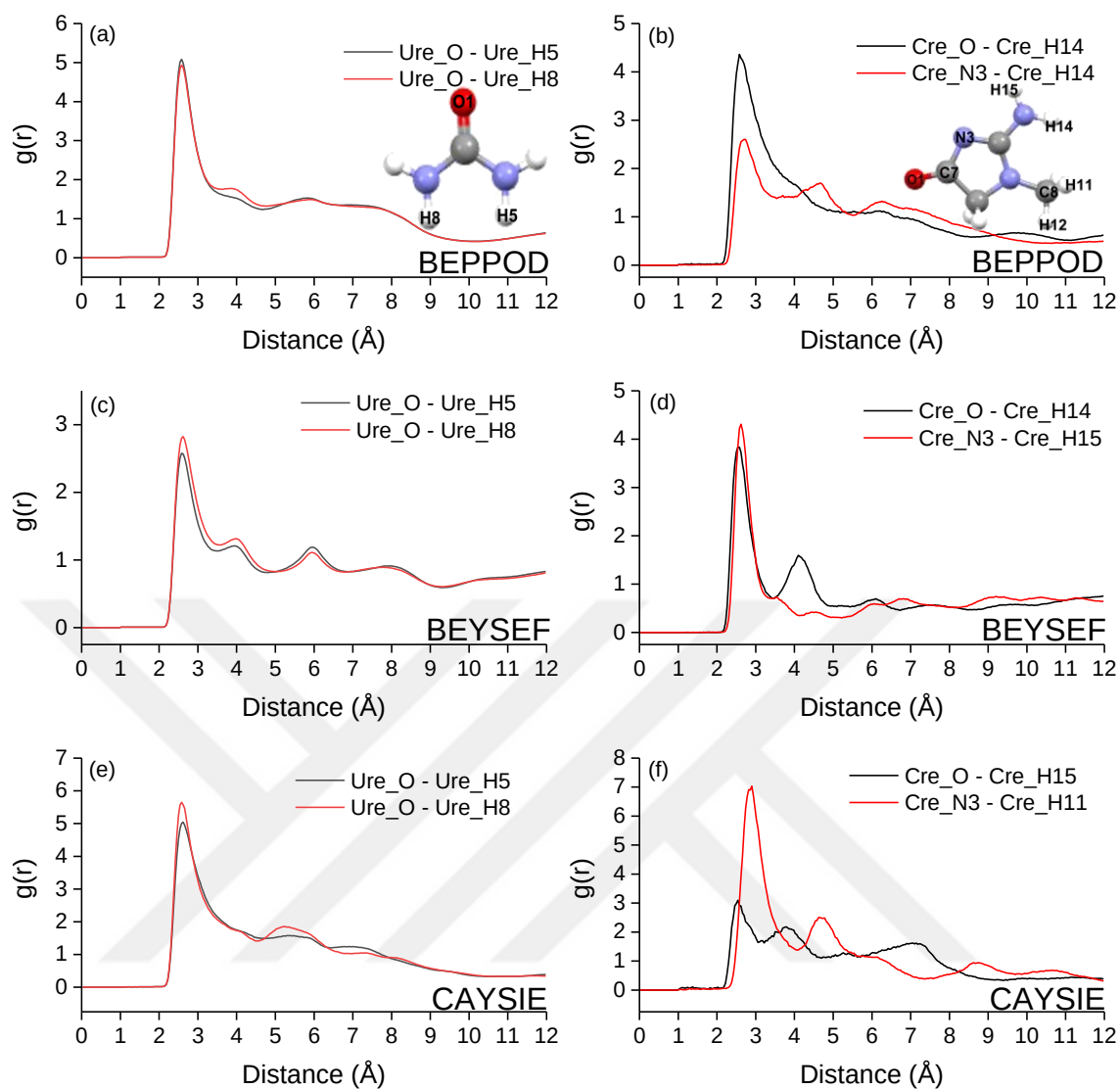


Figure A2. RDF analysis during single-component urea (a, c, e) and creatinine (b, d, f) adsorption simulations of BEPPOD, BEYSEF and CAYSIE.

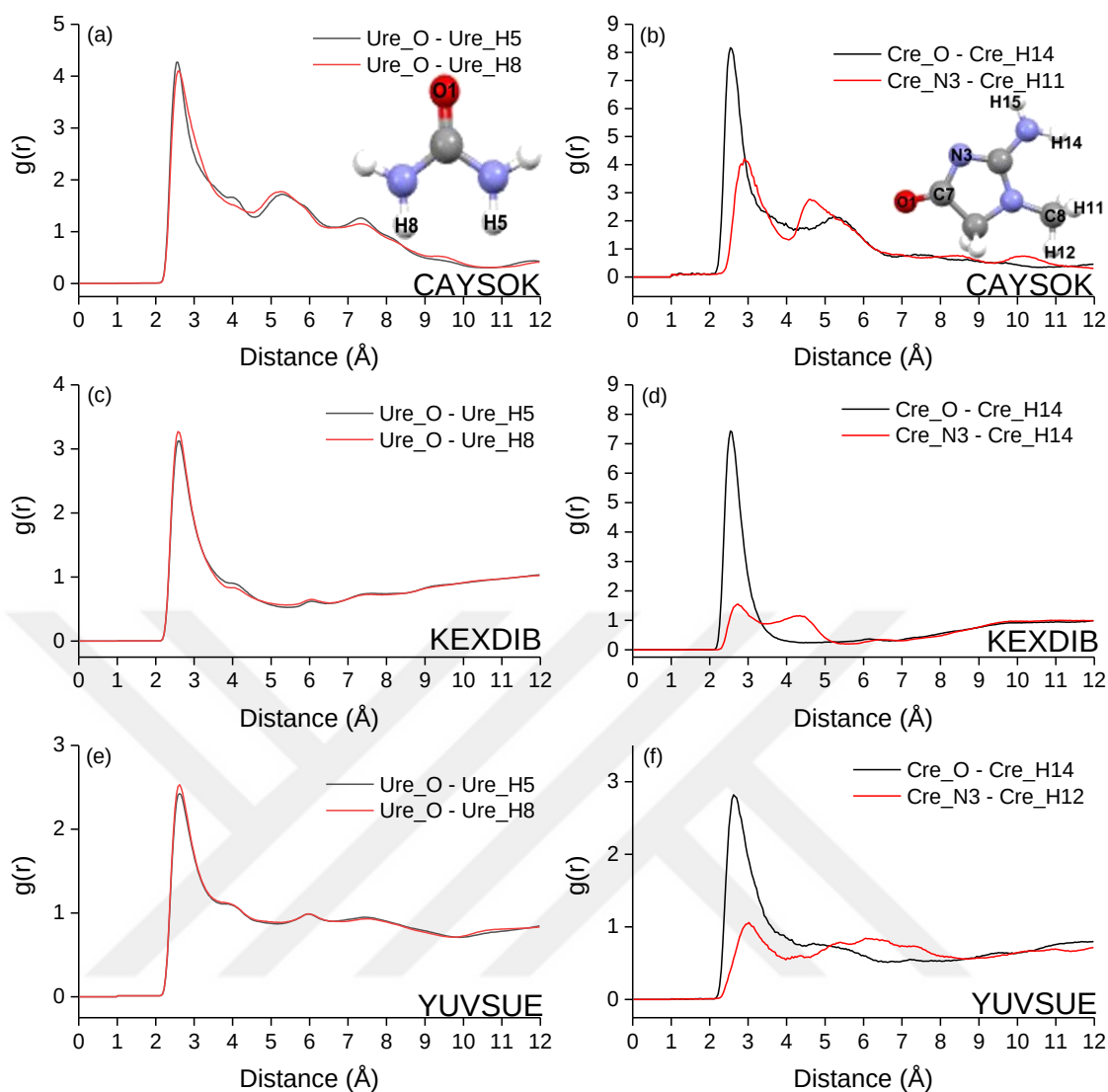


Figure A3. RDF analysis during single-component urea (a, c, e) and creatinine (b, d, f) adsorption simulations of CAYSOK, KEXDIB and YUVSUE.

Table A7. The best 10 bio-MOFs having the highest selectivity for urea/water and creatinine/water separations at infinite dilution and 1 bar, 310 K.

Based on $S_{\text{ads, ure/wat}}^0$ and $S_{\text{ads, ure/wat}}$		Based on $S_{\text{ads, cre/wat}}^0$ and $S_{\text{ads, cre/wat}}$	
ATIBOU01	176.83 and 4.52×10^3	BEPPOD	1.80×10^5 and 5.39×10^3
ATICAH	156.54 and 5.77×10^3	BEYSEF	6.94×10^5 and 3.76×10^3
BEPPOD	135.97 and 5.25×10^3	CATDIL	1.54×10^5 and 6.99×10^3
BEYSEF	228.14 and 4.45×10^3	CAYRIE	1.42×10^5 and 5.64×10^3
CAYSIE	97.00 and 4.02×10^3	CAYROK	1.25×10^5 and 6.70×10^3
CAYSOK	106.05 and 3.96×10^3	CAYSIE	2.50×10^5 and 4.03×10^3
KEXDIB	713.9 and 5.50×10^3	CAYSOK	3.02×10^5 and 3.91×10^3
NIHBIQ02	214.09 and 6.00×10^3	CAYYEG	1.36×10^5 and 4.33×10^3
XEHSEJ	337.92 and 4.22×10^3	KEXDIB	3.10×10^6 and 5.31×10^3
YUVSUE	360.71 and 3.95×10^3	YUVSUE	2.50×10^5 and 4.10×10^3

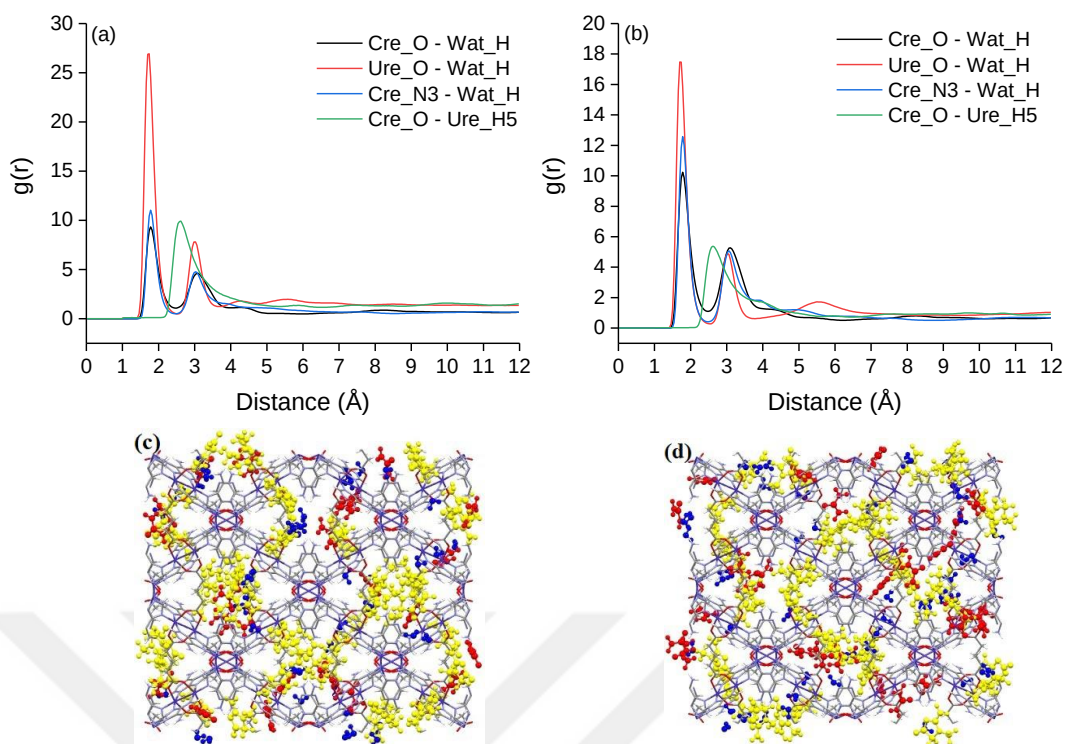


Figure A4. Comparison of RDF analyses (a,b) and GCMC snapshots of BEYSEF (c,d) obtained from ternary mixture GCMC simulations at different bulk compositions (a, c) urea/creatinine/water: 0.01/0.01/0.98 and (b, d) urea/creatinine/water: 0.019/0.001/0.98.

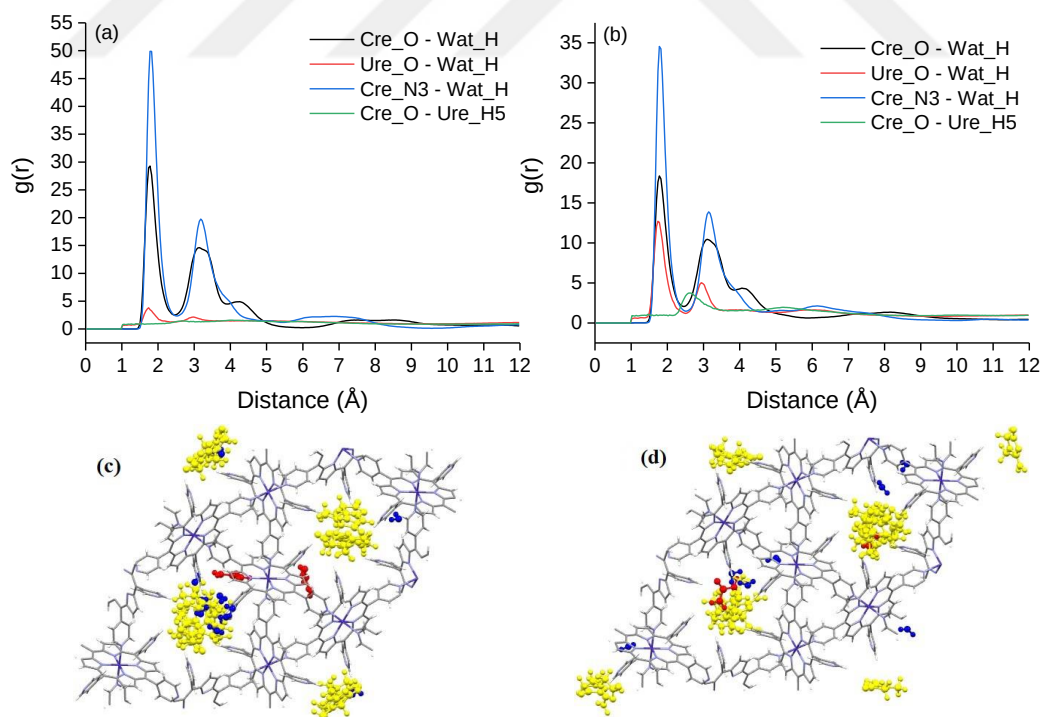


Figure A5. Comparison of RDF analyses (a,b) and GCMC snapshots of CAYSIE (c,d) obtained from ternary mixture GCMC simulations at different bulk compositions (a, c) urea/creatinine/water: 0.01/0.01/0.98 and (b, d) urea/creatinine/water: 0.019/0.001/0.98.

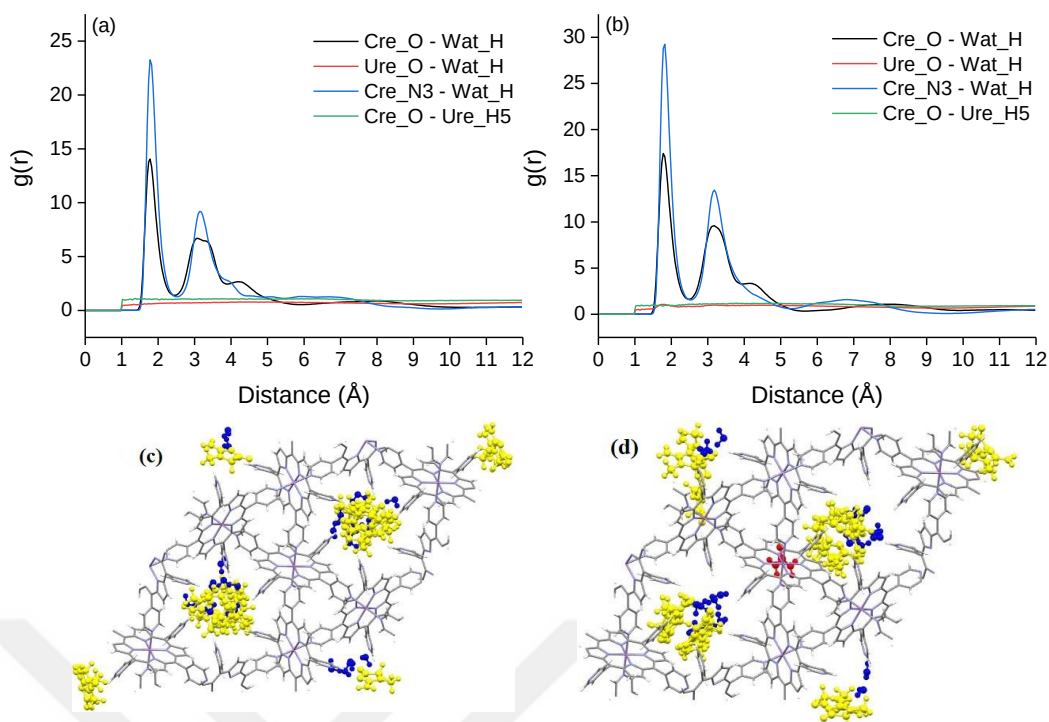


Figure A6. Comparison of RDF analyses (a,b) and GCMC snapshots of CAYSOK (c,d) obtained from ternary mixture GCMC simulations at different bulk compositions (a, c) urea/creatinine/water: 0.01/0.01/0.98 and (b, d) urea/creatinine/water: 0.019/0.001/0.98.

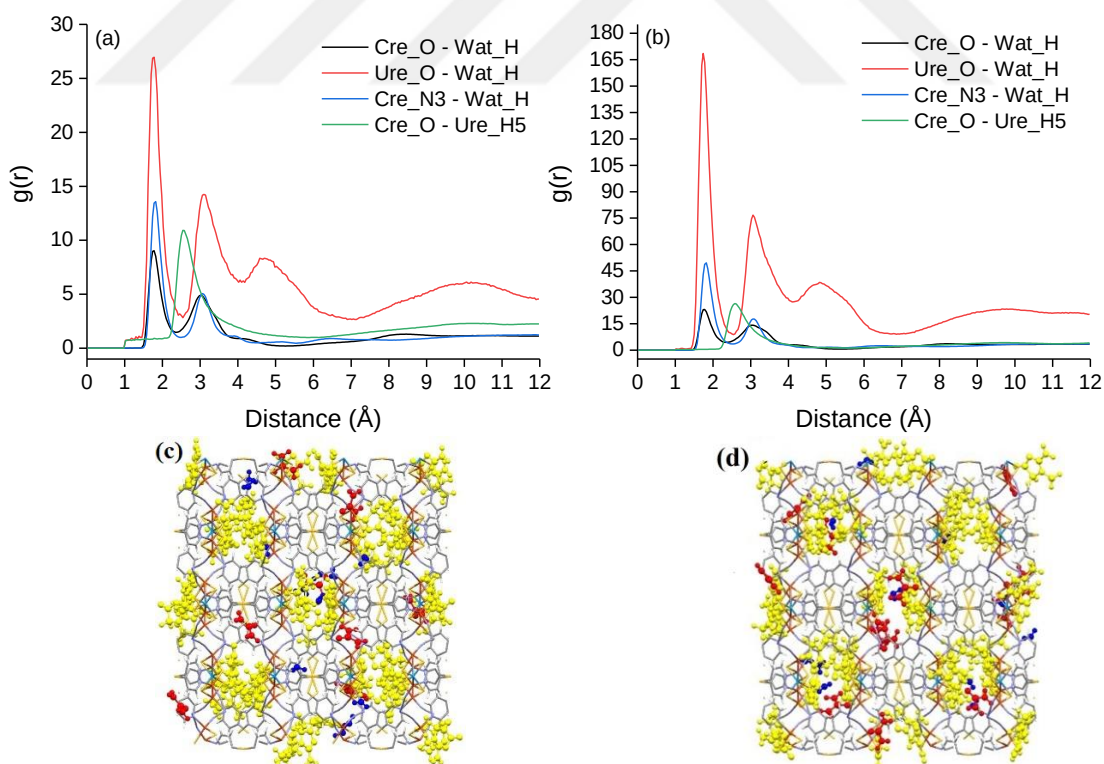


Figure A7. Comparison of RDF analyses (a,b) and GCMC snapshots of KEXDIB (c,d) obtained from ternary mixture GCMC simulations at different bulk compositions (a, c) urea/creatinine/water: 0.01/0.01/0.98 and (b, d) urea/creatinine/water: 0.019/0.001/0.98.

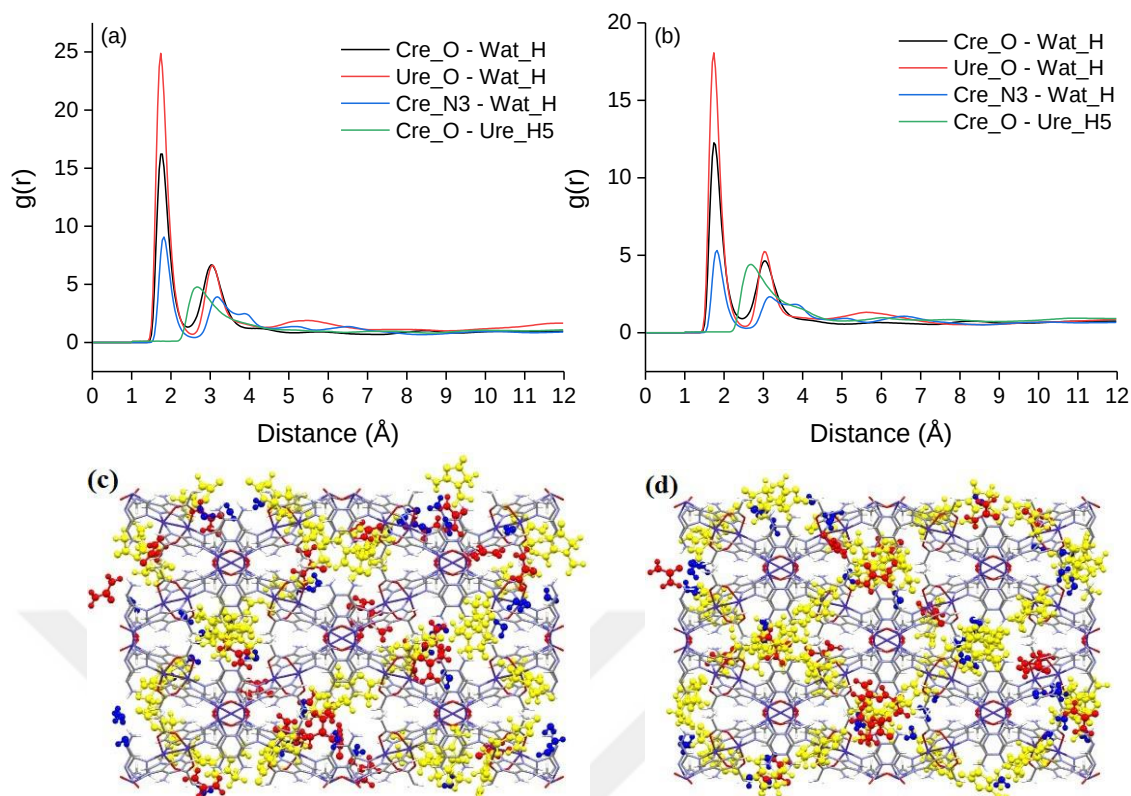
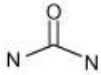
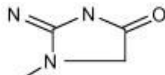
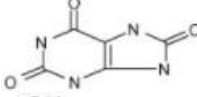
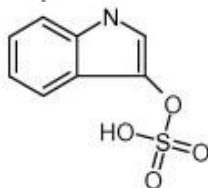


Figure A8. Comparison of RDF analyses (a,b) and GCMC snapshots of YUVSUE (c,d) obtained from ternary mixture GCMC simulations at different bulk compositions (a, c) urea/creatinine/water: 0.01/0.01/0.98 and (b, d) urea/creatinine/water: 0.019/0.001/0.98.

Table A8. Molecular weight and size of uremic toxins.

Solute	Formula	Structure	MW/g.mol ⁻¹	Size/Å		
				x	y	z
Ure	CH ₄ N ₂ O		60	5.6	6.3	3.0
Creatinine	C ₄ H ₇ N ₃ O		113	7.1	8.1	3.0
Uric Acid	C ₅ H ₄ N ₄ O ₃		168	7.7	1.0	3.0
P-cresol	C ₇ H ₈ O		108	6.6	7.6	3.9
Indoxyl Sulfate	C ₈ H ₇ NO ₄ S		251	7.9	1.1	5.4

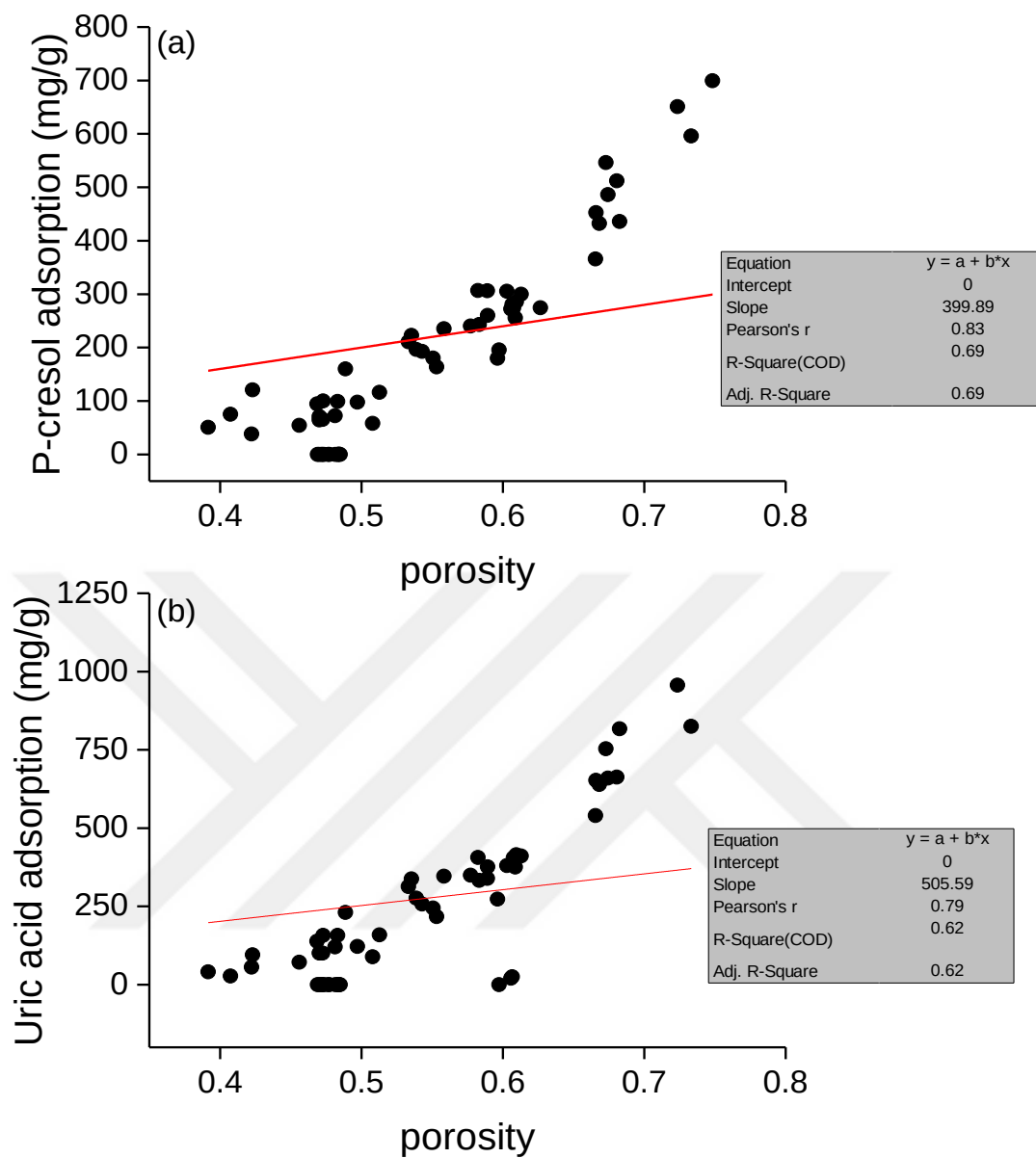


Figure A9. Relations between (a) p-cresol and (b) uric acid adsorption and porosity of bio-MOFs.

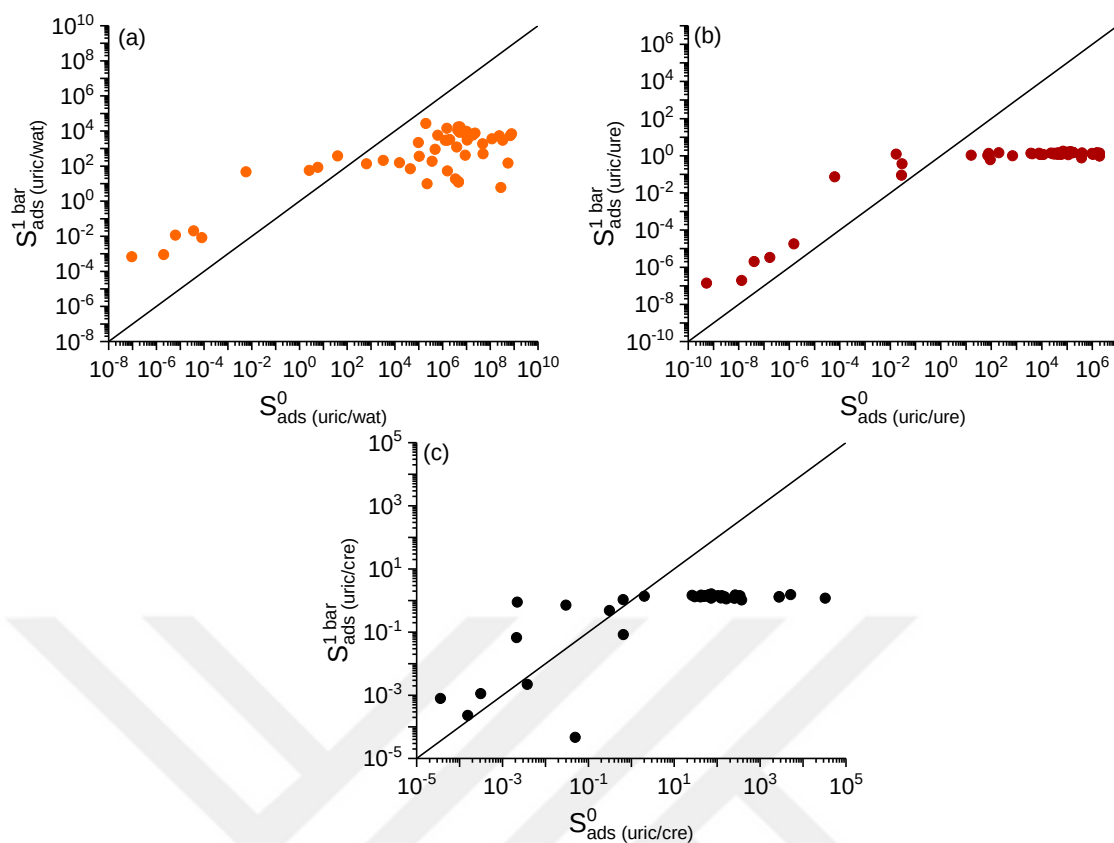


Figure A10. Comparison of ideal adsorption selectivities with the adsorption selectivities calculated at 1 bar, 310 K for a) uric acid/water, b) uric acid/urea, c) uric acid/creatinine separations.

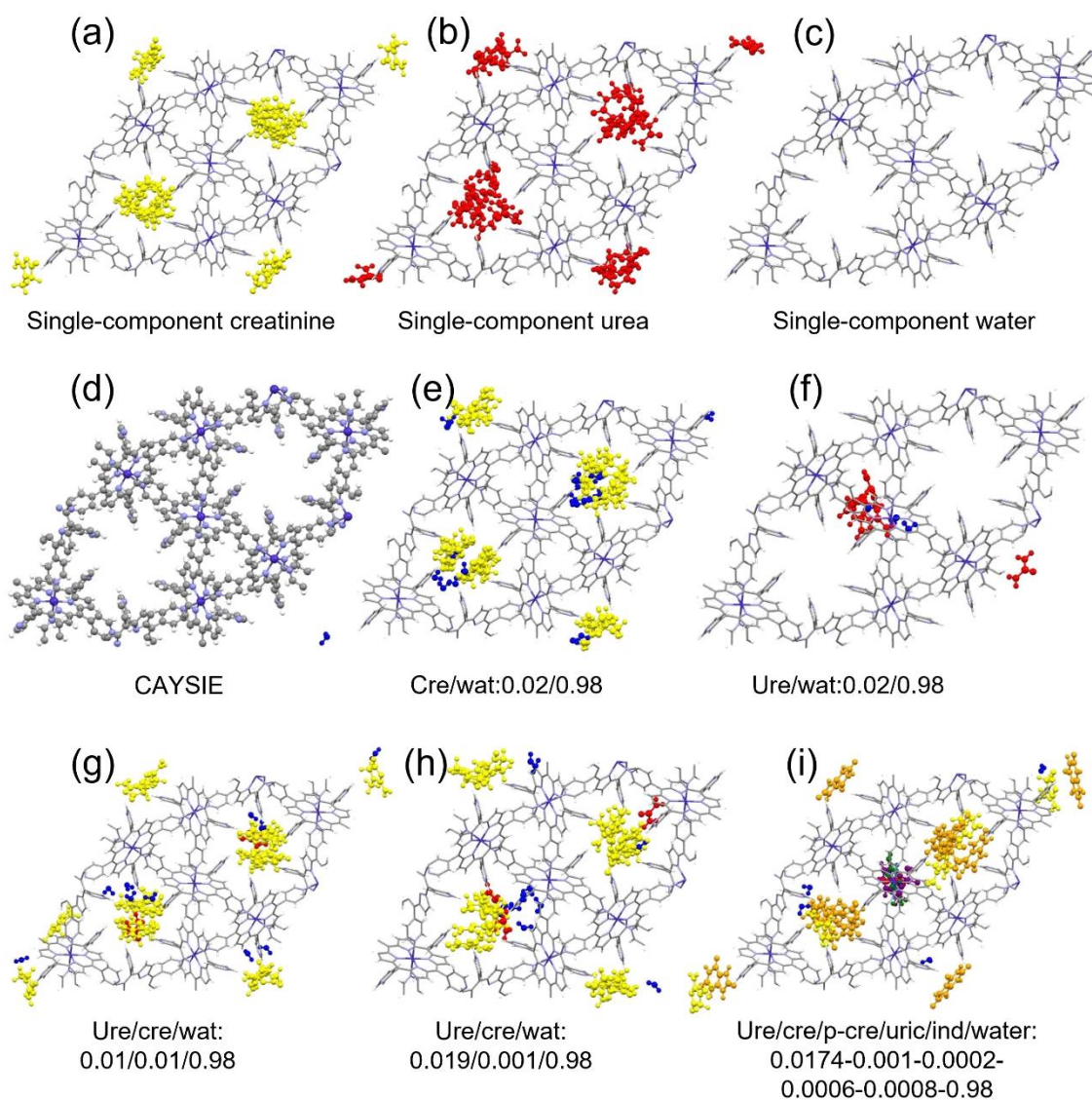


Figure A11. GCMC Snapshots obtained from single-component (a-c), binary mixture (e-f), ternary mixture (g-h) and senary mixture (i) simulations of CAYSIE (d) at 310K. Yellow, red, green, orange, purple and blue represents creatinine, urea, p-cresol, uric acid, indoxyl sulfate and water, respectively. The red line (in c) shows the favorite adsorption sites (amino and methyl groups).

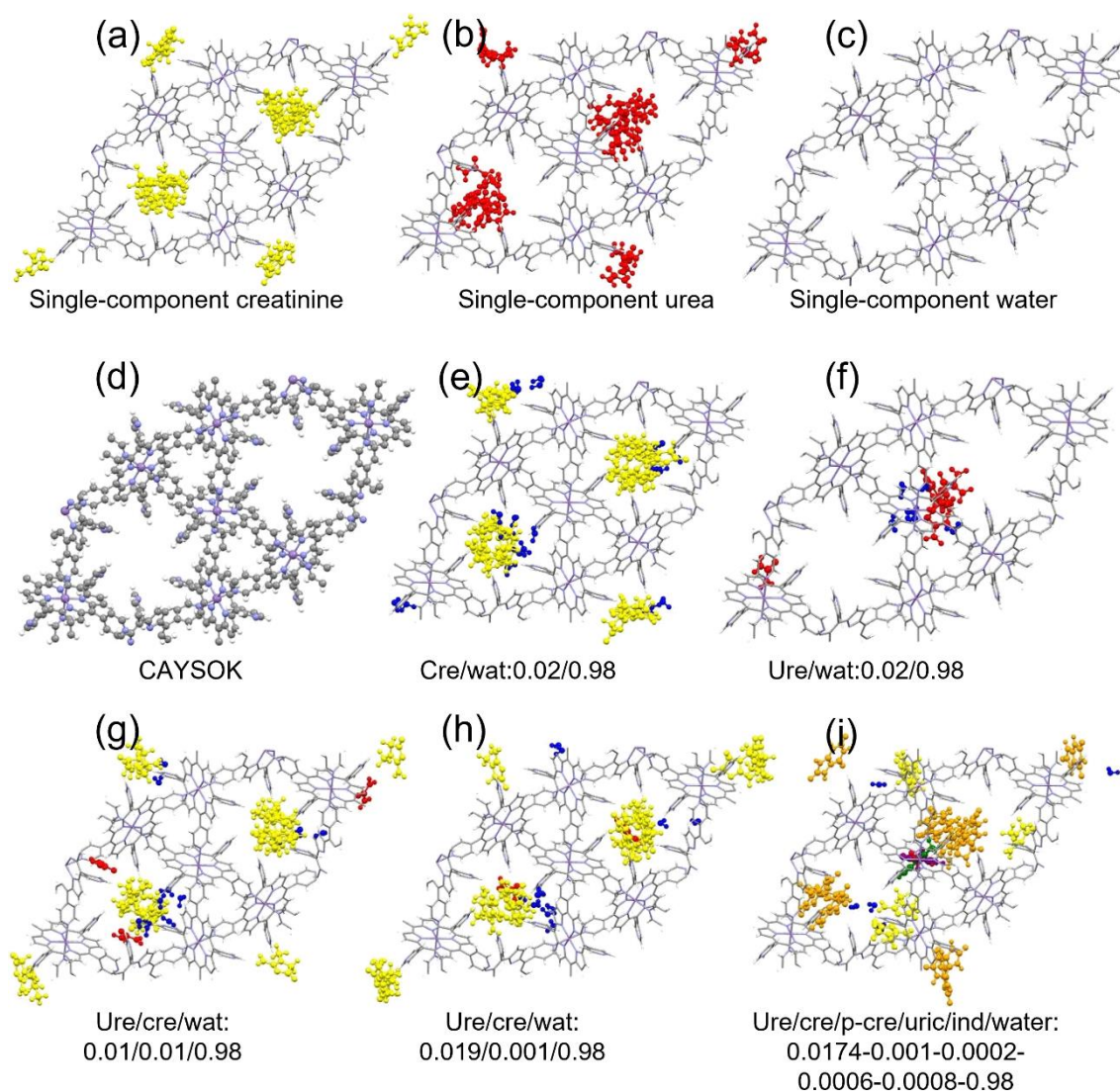


Figure A12. GCMC Snapshots obtained from single-component (a-c), binary mixture (e-f), ternary mixture (g-h) and senary mixture (i) simulations of CAYSOK (d) at 310K. Yellow, red, green, orange, purple and blue represents creatinine, urea, p-cresol, uric acid, indoxyl sulfate and water, respectively. The red line (in c) shows the favorite adsorption sites (amino and methyl groups).

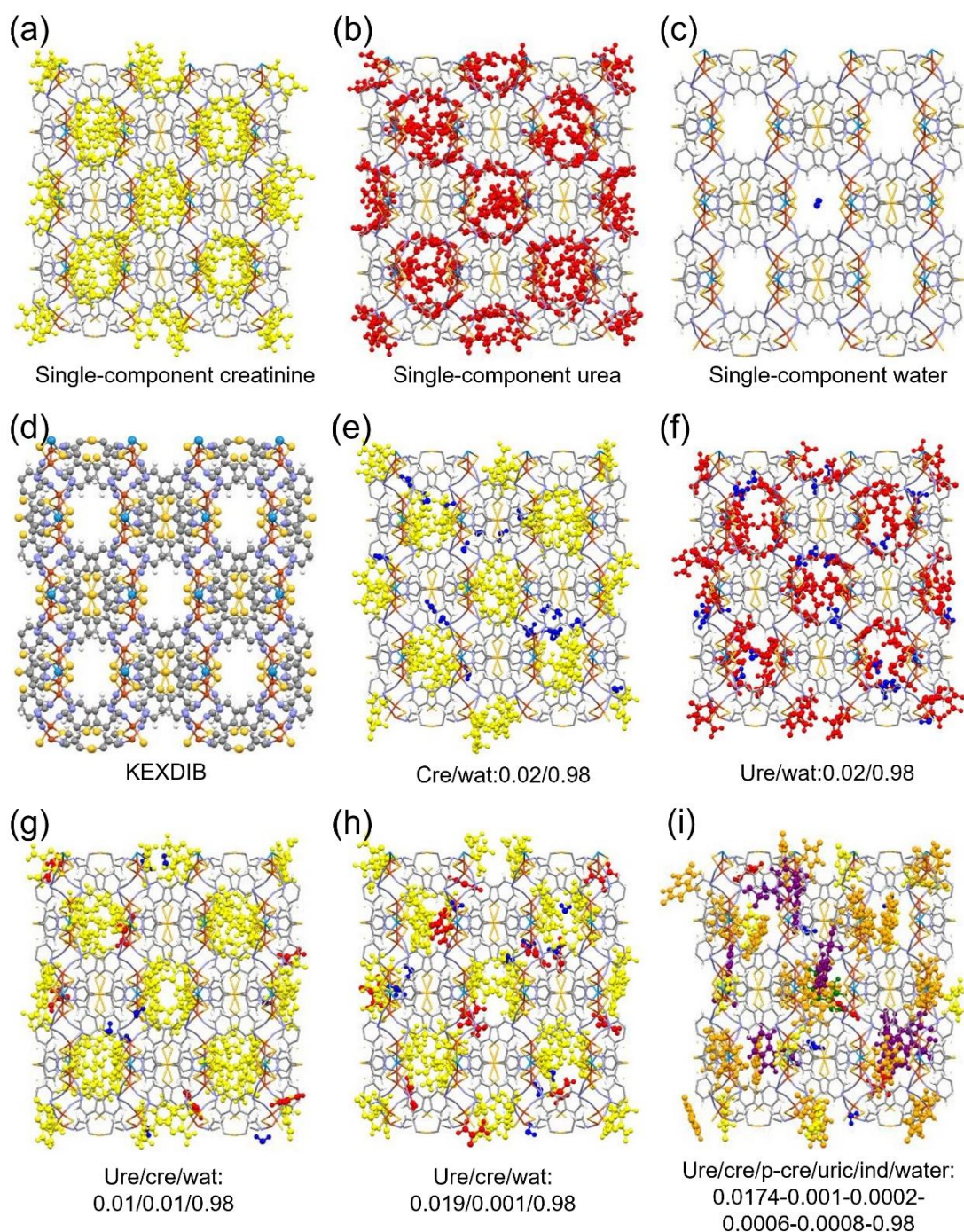


Figure A13. GCMC Snapshots obtained from single-component (a-c), binary mixture (e-f), ternary mixture (g-h) and senary mixture (i) simulations of KEXDIB (d) at 310K. Yellow, red, green, orange, purple and blue represents creatinine, urea, p-cresol, uric acid, indoxyl sulfate and water, respectively. The red line (in c) shows the favorite adsorption sites (amino and methyl groups).

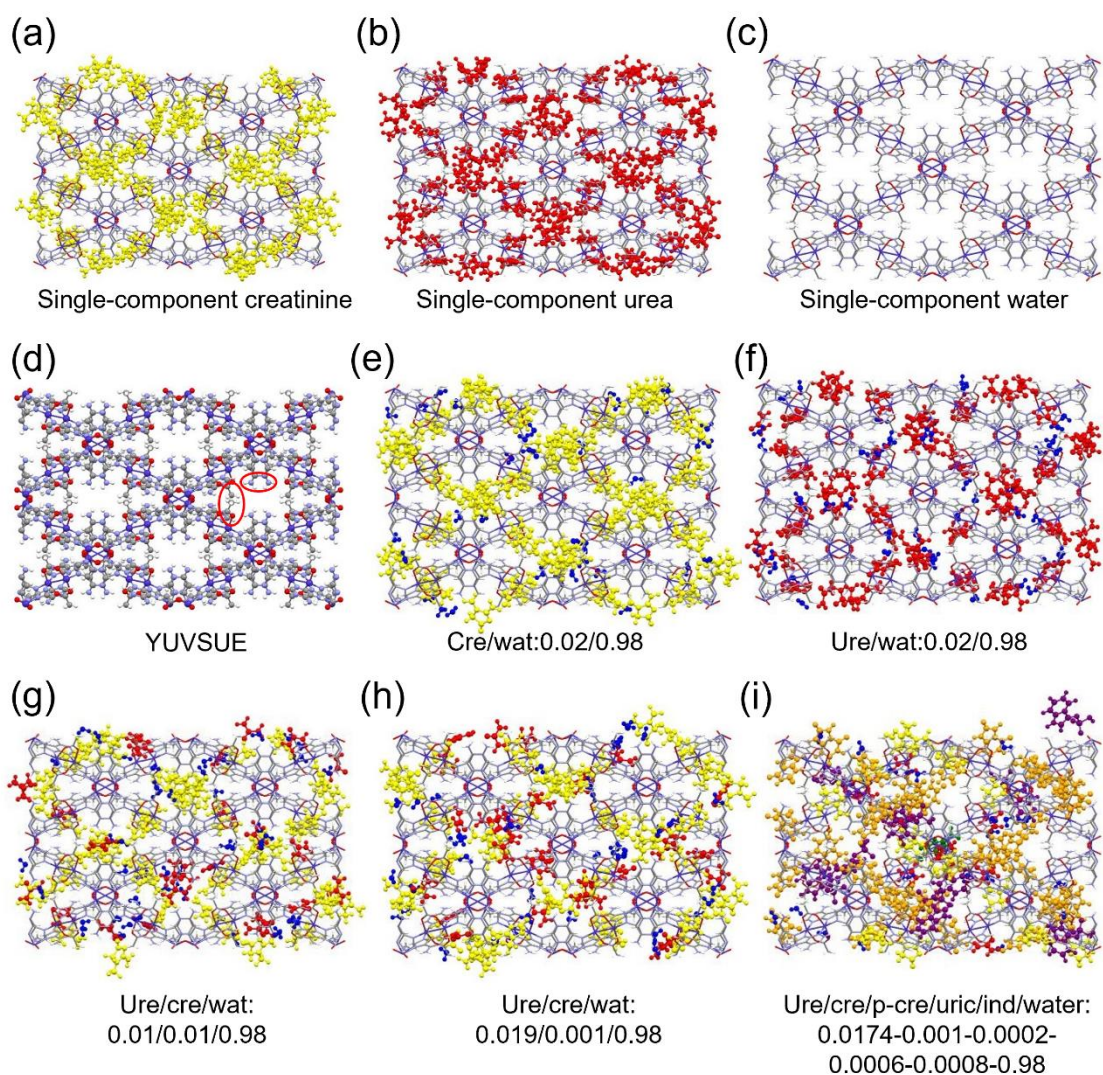


Figure A14. GCMC Snapshots obtained from single-component (a-c), binary mixture (e-f), ternary mixture (g-h) and senary mixture (i) simulations of YUVSUE (d) at 310K. Yellow, red, green, orange, purple and blue represents creatinine, urea, p-cresol, uric acid, indoxyl sulfate and water, respectively. The red line (in c) shows the favorite adsorption sites (amino and methyl groups).

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