Theoretical insight into the deep eutectic solvent based on choline chloride: Malic acid and its role in the transport performance of the antibiotic ciprofloxacin from water

S. Saraee[1], F. Moosavi[1,*]
[1]*Department of Chemistry, Faculty of Sciences, Ferdowsi University of Mashhad, 9177948974, Mashhad, Iran*
Corresponding Author's E-mail: moosavibaigi@um.ac.ir

Abstract
The presence of medicinal compounds (MCs) including antibiotics (ANTs) in water sources is a threat to the health of the environment and human. In line with this environmental and health issue, natural deep eutectic solvents (NADES) can play a useful role in transporting or removing MCs from water sources. Solubility and transport of ciprofloxacin (CFX) by a NADES based on choline chloride as hydrogen bond acceptor (HBA) and malic acid as hydrogen bond donor (HBD) with a molar ratio of 1:1 was studied using the classical molecular dynamics. The results of radial distribution functions and spatial distribution functions showed that structural properties of CFX have different trends in water under the influence of interaction with HBD and HBA. The presence of NADES in the water reduced the number of CFX around the water and removed it from the accumulation state. The diffusion coefficient of CFX in the presence of NADES is associated with an increase that confirms the departure of CFX from the accumulation state. The analysis of the hydrogen bond (HB) network showed that the retention time of HB for CFX…CFX interactions does not necessarily follow the number of HBs and the interaction in the presence NADES is of instantaneous type.

Keywords: Natural Deep Eutectic Solvent, Molecular Dynamics, Micropollutant, Ciprofloxacin, Hydrogen Bond Network.

Introduction
A natural deep eutectic solvent (NADES) is one of the types of deep eutectic solvents (DESs) compatible with the environment and has unique physicochemical properties including low cost and ease of synthesis and application [1, 2], low melting point [3], low volatility, high thermal stability [4], low toxicity [5], low vapor pressure, biodegradability [6], and recyclability in various processes such as purification and extraction. In addition, according to the diversity in the use of components in the structure of DES, adjustability and designing the structure can be added to these unique features. Consequently, a special DES can be prepared and used according to the intended purpose and application.
DESs are closely related to ionic liquids (ILs) in some properties, such as viscosity, density, melting point, and surface tension [7]. In any case, ILs require detailed toxicological studies and face limitations in terms of toxicity, biodegradability, and structural stability against moisture in various applied and industrial fields. Also, ILs are associated with high cost of

synthesis, which is due to the expensive raw materials and long preparation and purification steps [8].

The health of water resources and the availability of clean water has become one of the main concerns in recent years; in other words, the presence of micropollutants in water systems causes many environmental and health problems. Among micropollutants, medicinal compounds (MCs), including antibiotics (ATNs), have a special place. The presence of ANTs in water not only has negative effects on the human body, but also causes drug resistance against human pathogens [9, 10]. To remove ANTs from water sources, experimental studies have been carried out that consider diverse factors in the extraction process [11, 12]. The selection of DES with specific structural and physicochemical properties to improve the extraction of ANTs, including tetracyclines, sulfonamides, quinolones, and beta-lactams, has been described by Chen et al. [13].

The purpose of the current research is to introduce new aspects and to investigate the behavior of solubility, removal, or transfer of ciprofloxacin (CFX) as an antibiotic micropollutant from water with the help of NADES. In this regard, molecular dynamics (MD) simulation as a powerful tool is performed. By MD computation without the need to perform expensive experiments in laboratories, it is possible to investigate the behavior of systems from a molecular point of view and comment on their macroscopic properties. In this way, valuable suggestions can be made to solve the challenge related to water hygiene by introducing an efficient and environmentally friendly solvent. The expansion of research and the introduction of DES as a suitable solvent requires a complete understanding of their mechanism of action and properties. Considering the presence of micropollutants caused by ANTs in water resources and their importance in public health, the upcoming research aims to introduce NADES with a completely theoretical approach to reduce bacterial resistance and improve human health.

Simulation details

Figure 1 shows the optimized structures of NADES and CFX at B3LYP/6-311++G (d, p) level of theory that were applied as input structure for MD simulations performed by DL_POLY2.17 [14] the system contain 150: 150: 150: 5 species of HBA: HBD: water: CFX, respectively, as well as a system without NADES, i.e., CFX in water. AMBER [15] force field was used to investigate the potential of inter- and intra-molecular interactions and the TIP3P model was used to model water molecules.

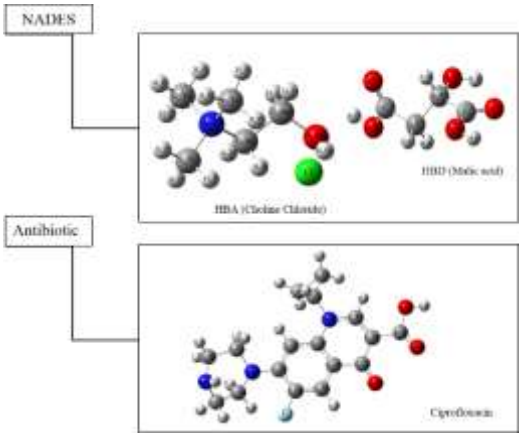

Figure 1. Optimized structures of studied NADES and CFX.

The cut-off radius, which is at most half the length of the simulation box, and the Ewald summation method were used to investigate short-range and long-range interactions, respectively. The simulation was first performed in NPT ensemble at a temperature of 298.15 K and a pressure of 1 atm to reach equilibrium in terms of density and temperature. Then, the simulation continued in the NVT ensemble at the same temperature to achieve the complete equilibrium of the system. The Brandsen thermostat and barostat were applied to control temperature and pressure, respectively, at considered ones. The time step equal to 1 fs was considered and the Leapfrog algorithm was used to achieve the correct dynamics. In order to collect the necessary data, the simulation was continued for 2 other nanoseconds in NVE ensemble.

Results and Discussion

To have insight into the behavior of NADES in the face of water-insoluble CFX the pair correlations of all species including choline cation (Ch.), chloride anion (Cl), malic acid (Ma), water (W), and CFX were under investigation by considering the radial distribution functions (RDFs). Figure 2 compares the RDF of the species.

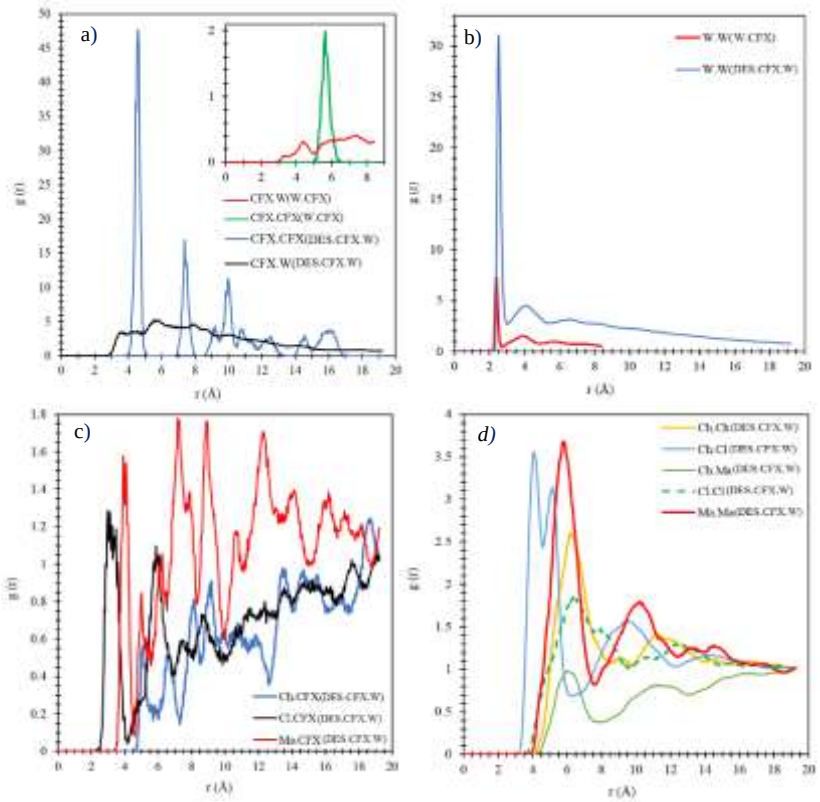

Figure 2. Center-of-mass RDFs for reported molecular pairs. a) CFX…CFX and CFX…W, b) W…W, c) CFX…NADES, d) Interaction of solvent components with each other.

As Figure 2a demonstrates, ANT aggregation is more pronounced in NADES. The CFX distance in water is approximately 5.641 Å while it is observed at 4.594 Å in the presence of mixture of water and NADES. However, its correlation with water has been weakened through the presence of ChCl.Ma DES that leads to the reduction in the number of water solvents around CFX from 1.315 to 0.696. From the other side of view, the goal NADES intensifies water… water (W…W) interaction that shed lights on the CFX freedom from water cage, as Figure 2b

displays. According to Figures 2c and 2d, it can be understandable that due to the interaction with CFX, anion plays as a bridge to connect CFX to HBD. In spite of ion-dipole interaction between CFX and NADES, dipole-dipole interaction has a major effect of CFX capture by NADES. The number of HBD (Ma) around each CFX is 0.007 that is greater than the coordination number of anion and cation with CFX (0.003 and 0.003). As a result, among NADES precursors, the HBD (Ma) component has a strong interaction with CFX attributed to the presence of more active functional groups (hydroxyl and carbonyl groups) in the HBD structure in comparison to the HBA.

The spatial distribution functions (SDFs) associated with the spatial distribution of W around the CFX are given in Figure 3. The W molecules around CFX in the presence of DES are observed to be more concentrated than in the W.CFX system, which indicates the transfer of interaction to closer distances compared to the W.CFX system. This is in agreement with the RDF results.

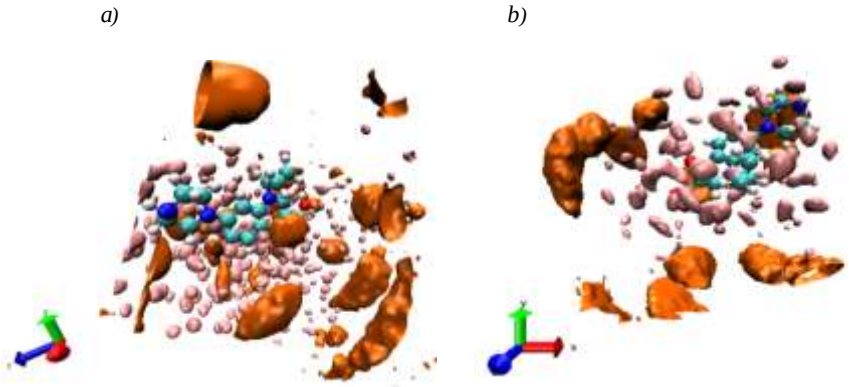

Figure 3. SDFs related to water (pink) and CFX (orange) components around CFX in the systems a) system of water and CFX; b) system containing DES, CFX, and W.

Root means square deviation (RMSD) analysis is considered as a measure to determine the amount of structure change in each component of the system. In the complex system containing DES, CFX, and W, the structure of CFX, according to Figure 4, enjoys the lowest RMSD that confirms its interaction with NADES and structurally stable during the simulation time. However, W shows the highest RMSD values the confirm its free movement. The other species, DES, have the middle values of RMSD. This observation confirms the synergistic effect of DES components in constructive and improving transmission of CFX by NADES.

The dynamic behavior and amount of displacement of CFX in each system were evaluated according to mean square displacement (MSD) analysis. Based on the MSD variation with simulation time, the values of diffusion coefficient (D) related to CFX in two systems were calculated. D of CFX 0.292×10^{-12} m^2s^{-1} is out of its accumulation mode in the presence of water and DES indicating the improvement of CFX transfer in the system. As it is clear from Figure 5, the distances between CFX molecules in the presence of water and DES are greater than pure water, which is a confirmation of its successful transfer from water to DES. It is noticeable that NADES has improved the solubility of CFX in comparison to pure water.

At last, examining the average number of HB and its lifetime demonstrate the highest number of HB between water molecules due to the transfer of CFX into target DES and the HB network between CFX and water breaks due to the presence of NADES.

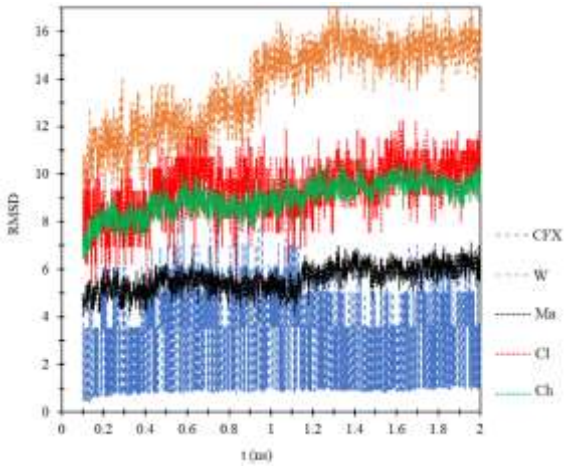

Figure 4. RMSD of each component of HBD, HBA, CFX, and water in the DES.CFX.W system.

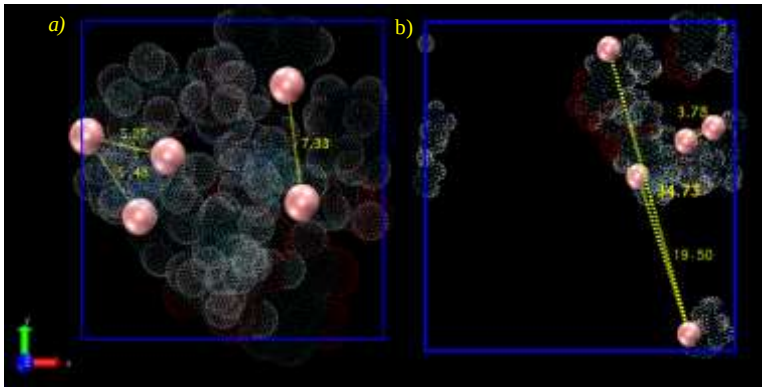

Figure 5. Distance between fluorine atoms in CFX, a) W.CFX system and b) DES.CFX.W system.

Conclusion

The properties of the ANT fluoroquinolone CFX in ChCl.Ma-based NADES in the presence of water have been studied by the MD method. The structural properties of DES.CFX.W and W.CFX systems showed that HBD had a stronger interaction with CFX than HBA, which was attributed to the presence of more functional groups in Ma. Furthermore, HBD…HBD is a strong interaction that plays a decisive role in the degree to which species interact with CFX. The W…CFX interaction in the DES.CFX.W system is associated with a decrease in the number of CFX around W compared to the CXF.W system. This was attributed to the correction of water and CFX interactions in the continuous presence of DES components and also reduced CFX accumulation. This was consistent with the results of RMSD, atomic distance F in CFXs, CFX diffusion coefficient, and HB network. D of CFX in DES.CFX. W has increased compared to W.CFX that is a sign of its improved mobility and transfer from water. The development of the HB network was consistent with the RDF results for water interactions with HBD and HBA. The expansion of the HB network between DES and W reduced the HB interaction between CFX and W and CFX transmission faced fewer restrictions.

Acknowledgements

This research project was financially supported by Ferdowsi University of Mashhad, Iran (grant No. 3/57326). The computations were partly carried out in the High-Performance Computing

(HPC) Center at Ferdowsi University of Mashhad. The authors would like to appreciate Ferdowsi Cloud cooperation.

References

[1] Abo-Hamad, A., Hayyan, M., AlSaadi, M. A., and Hashim, M. A., "Potential applications of deep eutectic solvents in nanotechnology". Chem. Eng. J., 273, 551-567 (2015).
[2] Zhekenov, T., Toksanbayev, N., Kazakbayeva, Z., Shah, D., and Mjalli, F. S., "Formation of type III Deep Eutectic Solvents and effect of water on their intermolecular interactions". Fluid Ph. Equilibria., 441, 43-48 (2017).
[3] Zainal-Abidin, M. H., Hayyan, M., Ngoh, G. C., Wong, W. F., and Looi, C. Y., "Emerging frontiers of deep eutectic solvents in drug discovery and drug delivery systems". J. Controlled Release, 316, 168-195 (2019).
[4] Sailau, Z., Almas, N., Aldongarov, A., and Toshtay, K., "Studying the Formation of Choline Chloride-and Glucose-Based Natural Deep Eutectic Solvent at the Molecular Level". J. Mol. Model., 28, 235 (2022).
[5] Torregrosa-Crespo, J., Marset, X., Guillena, G., Ramon, D. J., and Martínez-Espinosa, R. M., "New guidelines for testing “Deep eutectic solvents” toxicity and their effects on the environment and living beings". Sci. Total Environ., 704, 135382 (2020).
[6] Jahanbakhsh Bonab, P., Rastkar Ebrahimzadeh, A., and Jahanbin Sardroodi, J., "Insights into the interactions and dynamics of a DES formed by phenyl propionic acid and choline chloride". Sci. Rep., 11, 6384 (2021).
[7] Kovács, A., Neyts, E. C., Cornet, I., Wijnants, M., and Billen, P., "Modeling the physicochemical properties of natural deep eutectic solvents". ChemSusChem, 13, 3789-3804 (2020).
[8] Shahbaz, K., Mjalli, F., Hashim, M. A., and AlNashef, I., "Prediction of deep eutectic solvents densities at different temperatures". Thermochimica acta, 515, 67-72 (2011).
[9] Tang, W., An, Y., and Row, K. H., "Fabrication of Au nanoparticles embedded holey g-C3N4 as SERS substrates for sensitive and reliable detection". Chem. Eng. J., 402, 126194 (2020).
[10] Barahona, F., Albero, B., Tadeo, J. L., and Martín-Esteban, A., "Molecularly imprinted polymer-hollow fiber microextraction of hydrophilic fluoroquinolone antibiotics in environmental waters and urine samples". J. Chromatogr. A, 1587, 42-49 (2019).
[11] Florindo, C., Lima, F., Branco, L. C., and Marrucho, I. M., "Hydrophobic deep eutectic solvents: a circular approach to purify water contaminated with ciprofloxacin". ACS Sustain. Chem. Eng., 7, 14739-14746 (2019).
[12] Tang, W., Dai, Y., and Row, K. H., "Evaluation of fatty acid/alcohol-based hydrophobic deep eutectic solvents as media for extracting antibiotics from environmental water". Anal. Bioanal. Chem., 410, 7325-7336 (2018).
[13] Chen, C., Cao, Y., Ali, A., Toufouki, S., and Yao, S., "How to apply terpenoid-based deep eutectic solvents for removal of antibiotics and dyes from water: Theoretical prediction, experimental validation and quantum chemical evaluation". Environ. Res., 231, 116180 (2023).
[14] Smith, W., Yong, C., and Rodger, P., "DL_POLY: Application to molecular simulation". Mol. Simul., 28, 385-471 (2002).
[15] Cornell, W. D., Cieplak, P., Bayly, C. I., Gould, I. R., Merz, K. M., Ferguson, D. M., Spellmeyer, D. C., Fox, T., Caldwell, J. W., and Kollman, P. A., "A second generation force field for the simulation of proteins, nucleic acids, and organic molecules". J. Am. Chem. Soc., 117, 5179-5197 (1995).