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COSMO – RS Based Prediction and Screening of Antimicrobial Activities of Deep Eutectic Solvents

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ABSTRACT

In this study, 18 various types of DESs were screened using COSMO–RS analysis, those DESs consisted of urea, thymol, menthol, and six different fatty acids. To be able to achieve the objective of this study which is to investigate the antimicrobial activity of the various DESs screened, the COSMO–RS analysis was conducted using 4 bacterial cell wall components (2,6-diaminopimelic-acid, N-Acetyl-a-neuraminic-acid, N_Acetyl_Muramic_acid, N_Acetyl_D_Glucosamine), to observe the interaction of the DESs with the bacterial cell. As a result, the σ-profiling and the σ-potential showed that the most interactive DESs against microbial cells were Decanoic acid based. The importance of this study is due to its time-resource saving in the screening of biochemical materials.

Keywords: Deep eutectic solvents; Active pharmaceutical ingredients, COSMO–RS, Antimicrobial activity

1 Introduction

The current advocate for sustainable development balances industry development and environmental protection, a major global concern [1]. Thus, green solvents like DESs have become a research focus for sustainable development. Due to their simplicity, 100% atom economy, low cost, probable biodegradability, and low toxicity, deep eutectic solvents (DESs) can replace organic solvents and ionic liquids. Due to hydrogen bonding interactions between molecules, one of which is a hydrogen bond donor and the other a hydrogen bond acceptor, DESs produce a liquid with a much lower melting point than its components. [2]. Compared to isolated fatty acids, saturated fatty acid-based DESs may be effective antimicrobial agents and components of novel biocompatible biomedical devices for antibacterial purposes [3]. Researchers are becoming interested in DESs as antibacterial agents due to their physicochemical features combining components that customise these solvents. Thus, a sustainable screening method is needed to determine the optimal effective combination of hydrogen bond acceptor (HBA) and hydrogen bond donor (HBD) to formulate. The conductor-like screening model for realistic solvation (COSMO-RS) is an innovative method for predicting thermo-physical data for liquid systems and a convenient alternative to force field-based molecular simulation [4]. Trial and error is still the most common technique to pick the optimal solvent for extracting natural compounds from eutectic mixtures, especially

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for innovative, limit-investigated solvents like deep eutectic solvents (DES). This can produce an extensive or weak solvent list. Thus, COSMO-RS achieves its goal [4].

2 Materials and Methods

This study predicted the thermophysical properties of DES combinations against specified bacterial cell components using COSMO-RS. COSMO calculates DESs as equimolar cation-anion combinations. Thus, the TURBOMOLE program package [5] generated COSMO files of fatty acids, HBDs, bacterial cell components (GlcNAc, DAP, NANA, and MurNAc), APIs (Paracetamol, Ampicillin, penicillin, and ascorbic acid) as cations and anions using Becke and Perdew (BP) functional with triple zeta valence polarised (TZVP) basis set [6]. COSMOthermX used those files to construct the sigma surface and sigma profile graphs to screen charge density. Table 1 shows the DESs combinations.

Table 1: *List of DESs used in the screening*

HBA	HBD	DES
Butanoic Acid	Menthol	DES 1
Decanoic Acid	Menthol	DES 2
Hexanoic Acid	Menthol	DES 3
Levulinic Acid	Menthol	DES 4
Octanoic Acid	Menthol	DES 5
Propanoic Acid	Menthol	DES 6
Butanoic Acid	Thymol	DES 7
Decanoic Acid	Thymol	DES 8
Hexanoic Acid	Thymol	DES 9
Levulinic Acid	Thymol	DES 10
Octanoic Acid	Thymol	DES 11
Propanoic Acid	Thymol	DES 12
Butanoic Acid	Urea	DES 13
Decanoic Acid	Urea	DES 14
Hexanoic Acid	Urea	DES 15
Levulinic Acid	Urea	DES 16
Octanoic Acid	Urea	DES 17
Propanoic Acid	Urea	DES 18

3 Results

3.1 Sigma Surface

To study the interaction of those fatty acids and HBDs, the sigma surface was studied first using COSMOthermX to understand the surface nature of the bacterial cell components. The results revealed that GlcNAc, DAP, NANA, and MurNAc possess both negative and positive groups on their σ-surfaces (Fig 1). The blue colour on σ - surfaces indicates an NH group that will lose electrons and become positively charged. Red spots have a high charge density, indicating O-, which will accept electrons and become negatively charged. Carbon makes the green and blue colours neutral [7].

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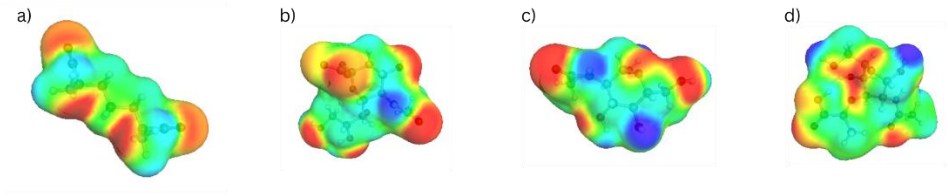

Figure 1: *Sigma profiles of a) DAP b) NANA c) GlcNAc d) MurNAc*

3.2 Sigma profiles

To investigate the interaction of the screened DESs with the bacterial cell components, to confirm the antimicrobial activity, and to be able to choose the best interactive combination of HBA and HBD, sigma profiles were generated using COSMOthermX. Figure 2.a shows the sigma profile of several DESs that consists of Menthol as the HBD, and it showed the highest peak of (53.98) with decanoic acid as the HBA. Fig 2.b shows the sigma profile of DESs that consists of Thymol as the HBD, which showed it highest peak at (43.73) with decanoic acid as the HBA. Lastly, Fig 2.c shows the sigma profile where urea was used as the HBD and demonstrated a peak at (30.5) when using decanoic acid as the HBA. All simulated DESs exhibit interaction peaks with all bacterial cell components, whereas decanoic acid produced the best results with all three HBD among the other fatty acids evaluated.

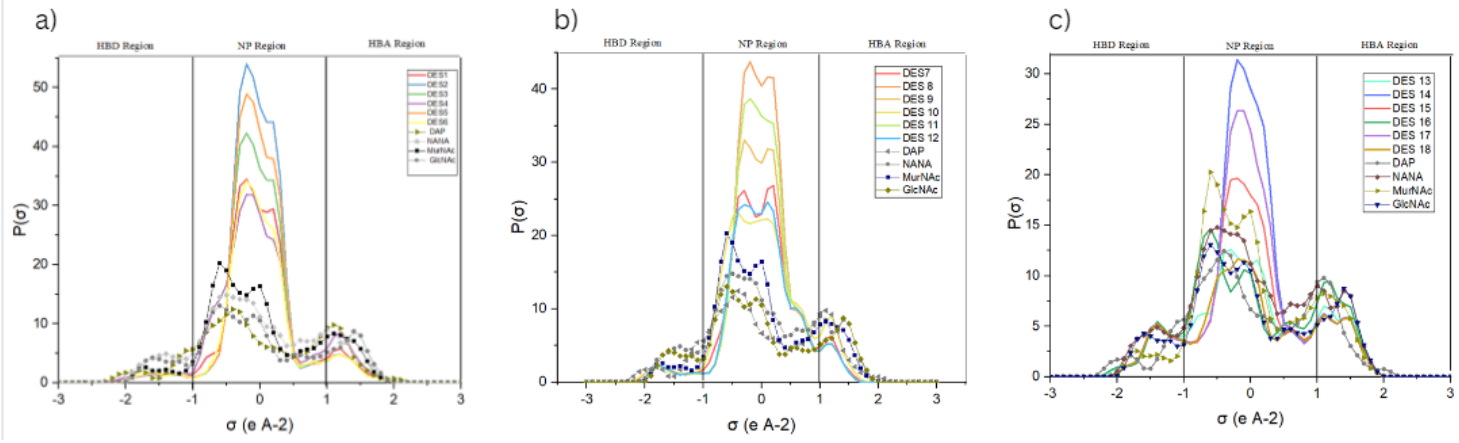

Figure 2: *a) Sigma profiles of selected DESS using Menthol as an HBD. b) Sigma profiles of selected DESs using Thymol as a HBD. c) Sigma profiles of selected DESs using Urea as an HBD.*

4 Discussion

Typically, DESs comprise three components—salt cation, anion (HBA) and HBD, and the results obtained from the sigma surface and sigma profiles assist to understand how the fatty acids behave as a HBD and HBA in the DESs. The series of peaks obtained from the sigma profiles analysis is divided into three regions, HBA, HBD, and nonpolar region. However, the 18 screened DESs in the study possess both HBD and HBA, but there were more notable peaks in the HBA region. DES2 and DES8 also have higher peaks that overlap all four bacterial cell membrane components. Since the peaks overlap, DESs interact with membranes to increase

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permeability and antibacterial action. In general, any peak within the range of $0 < \sigma < 0.01$ e/nm2 which is the right-hand side of the profile, will interact with the left peak of the membranes (-0.006 eA2 that interact with GlcNAc, DAP, NANA, and MurNAc) The Figure shows that all DESs have peaks between the ranges. However, DES2 has the highest peak among all selected DESs at positive and negative - values, which may be due to the hypothesis that fatty acids with longer Alkyl chains enhance antimicrobial activity [8]. In this study, decanoic acid, which has the most carbon atoms, was combined with menthol to create a DES with a longer carbon chain than the other HBA and HBD.

5 Conclusions

This study proposed the production of DESs with fatty acids as HBA and menthol, thymol, or urea as HBD. Fatty acids have antibacterial characteristics. COSMO-RS analysis shows how those DESs fight four types of bacterial membrane components. The sigma pro-files analysis showed that DES2 (Menthol: Decanoic acid) and DES8 (Thymol: Decanoic acid) had the highest peak overlapping the bacterial membrane component peaks, indicating an interaction with all four types of bacterial membrane components. The two promising DESs contained decanoic acid, the longest carbon chain HBA in this analysis. The wide range of screening done in a short time and without wasting resources is a convenient way to analyze equimolar mixes of cations and anions, including DESs and ILs.

6 Declarations

6.1 Acknowledgements

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