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SYNTHESIS AND CHARACTERISATION OF TETRABUTYLAMMONIUM BROMIDE BASED DEEP EUTECTIC SOLVENTS FOR DNA SOLVATION

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By

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Thesis Submitted to the School of Graduate Studies, Universiti Putra Malaysia, in Fulfilment of the Requirements for the Degree of Doctor of Philosophy

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SYNTHESIS AND CHARACTERISATION OF TETRABUTYLAMMONIUM BROMIDE BASED DEEP EUTECTIC SOLVENTS FOR DNA SOLVATION

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August 2016

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Faculty: Science

Conventionally, DNA is stored in aqueous solution under refrigeration for short and long-term storage. However, slow hydrolytic can disrupt the DNA helical structure and result for a searching of new medium in which DNA is stable for long periods at room temperature. Twenty of new tetrabutylammonium bromide (TBABr)-based DESs were successfully synthesised using various hydrogen bond donors (HBDs) (ethylene glycol, 1,3-propanediol, 1,5-pentanediol and glycerol) with different ratios. Nuclear magnetic resonance (NMR) and Fourier-transform infrared spectroscopy (FTIR) analyses were carried out to identify the molecular structures of the DESs. The properties of the DESs were affected by the structures and ratio of HBD and temperatures. When the length of the HBD decreased, the DESs became less viscous, more conductive and denser. Upon heating, density and viscosity of the DESs decreased while ionic conductivity increased.

The molecular properties for one of the DESs, tetrabutylammonium bromide: ethylene glycol (TBABr:EG) were studied by molecular dynamic (MD) simulation. A good agreement for the DESs densities from experimental and simulation data with a small difference (less than ±3.91%) have validated the force fields and proved the accuracy of the simulation systems. When the ratio of ethylene glycol (EG) increased, the self-diffusion coefficient of ions also increased, resulting in the TBA^+ cations moving further away from Br^- anions. The attraction of the Br^- anions to the EG molecules led to formation of hydrogen bonds which were confirmed by radial distribution function (RDF) and FTIR analysis.

The calf thymus DNA was analysed biophysically in the DESs that were previously characterised using various spectroscopic methods. The electrostatic attractions and hydrophobic interactions were evidenced between TBA^+ cations and DNA. The DESs groove bound via hydrogen bonding into the DNA minor groove, which confirmed through the ability of DES to displace 4',6-diamidino-2-phenylindole (DAPI) with Stern-Volmer constants (K_{sv}) in range of 91.08 to 100.15 M^{-1}. A combination of electrostatic, polar and hydrophobic interactions

between the DES and DNA has contributed to the DNA stability. The strong binding of the DESs to DNA was obtained as the length of HBD decreased and the ratio and polarity of the HBD increased. Hence, TBABr:EG (ratio 1:5) showed the highest binding constant (K_b) of 5.75 x 10^5 M^{-1} with the lowest Gibbs free energy (ΔG^o) of -32.86 $kJmol^{-1}$.

The DESs maintained the B-DNA conformation at 25°C in concentration of 25% in all the DESs, except 50% for TBABr:1,3-PD. The DESs stabilised the DNA helical by melting at 44 to 50°C, which was 1 to 7°C higher than water. TBABr:EG was able to store DNA for 2 months and TBABr:1,3-PD, TBABr:1,5-PD and TBABr:Gly for up to 6 months. The DESs with HBDs more than 3 carbons exhibited long term-stability, as they were more effective in reducing DNA denaturation. The presence of various interactions between the DESs and DNA were responsible for the long-term stability of the DNA in the DESs. Hence, the results revealed that the DNA was better solvated in DESs rather than aqueous solution.

Abstrak tesis yang dikemukakan kepada Senat Universiti Putra Malaysia
sebagai memenuhi keperluan untuk ijazah Doktor Falsafah

SINTESIS DAN PENCIRIAN TETRABUTILAMMONIUM BROMIDA BERASASKAN PELARUT EUTEKTIK UNTUK SOLVASI DNA

Oleh

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Secara konvensional, DNA disimpan di dalam larutan akues dengan penyejukan untuk simpanan jangka masa pendek dan panjang. Walau bagaimanapun, hidrolisis secara perlahan boleh mengganggu struktur helikal DNA dan menyebabkan pencarian kepada media baru, yang mana DNA stabil untuk jangka masa panjang pada suhu bilik. Dua puluh DES baru berasaskan tetrabutilammonium bromida (TBABr) telah berjaya disintesis menggunakan pelbagai penderma ikatan hidrogen (HBD) (etilena glikol, 1,3-propanadiol, 1,5-pentanadiol and gliserol) dengan nisbah yang berlainan. Resonan magnetik nuklear (NMR) dan Fourier penukaran inframerah (FTIR) telah dijalankan untuk mengenalpasti struktur molekul bagi DES. Sifat DES dipengaruhi oleh struktur dan nisbah HBD serta suhu. Apabila panjang HBD dikurangkan, DES menjadi kurang pekat, lebih konduktif dan lebih tumpat. Melalui pemanasan, ketumpatan dan kepekatan DES telah menurun, sementara konduktiviti ionik meningkat.

Sifat molekul bagi salah satu daripada DES, tetrabutilammonium bromida: etilena glikol (TBABr:EG) telah dikaji dengan menggunakan simulasi dinamik molekul (MD). Persetujuan nilai ketumpatan DES daripada data eksperimen dan simulasi dengan perbezaan yang kecil (kurang daripada ±3.91%) telah mengesahkan medan daya dan membuktikan ketepatan sistem simulasi. Apabila nisbah etilena glikol (EG) ditingkatkan, pekali resapan diri ion juga meningkat, menyebabkan kation TBA^+ bergerak jauh daripada anion Br^-. Tarikan anion Br^- kepada molekul EG telah menyebabkan pembentukan ikatan hidrogen yang disahkan oleh analisis fungsi taburan jejarian (RDF) dan FTIR.

Biofizikal DNA anak lembu timus telah dianalisis didalam DES yang telah dicirikan sebelum ini, menggunakan pelbagai kaedah spektroskopi. Tarikan elektrostatik dan interaksi hidrofobik telah dibuktikan berlaku di antara kation TBA^+ dan DNA. DES juga terikat melalui ikatan hidrogen pada alur kecil DNA yang disahkan melalui kebolehan DES untuk menggantikan 4',6-diamidino-2-

fenilindol (DAPI) dengan pemalar Stern-Volmer (K_{sv}) di dalam skala 91.08 hingga 100.15 M^{-1}. Gabungan interaksi elektrostatik, polar dan hidrofobik di antara DES dan DNA menyumbang kepada kestabilan DNA. Kekuatan ikatan DES pada DNA diperolehi apabila panjang HBD dikurangkan serta nisbah dan kepolaran HBD ditingkatkan. Oleh itu, TBABr:EG (nisbah 1:5) telah menunjukkan nilai pemalar ikatan (K_b) tertinggi iatu 5.75 x 10^5 M^{-1} dengan tenaga bebas Gibbs (ΔG^o) terendah iaitu -32.86 kJ mol^{-1}.

DES mengekalkan konformasi B-DNA pada 25°C dengan kepekatan 25% untuk semua DES, kecuali 50% untuk TBABr:1,3-PD. DES menstabilkan struktur helikal DNA dengan melebur pada 44 hingga 50°C, iaitu 1 hingga 7°C lebih tinggi berbanding air. TBABr:EG berupaya menyimpan DNA selama 2 bulan dan TBABr:1,3-PD, TBABr:1,5-PD dan TBABr:Gly sehingga 6 bulan. DES dengan HBD melebihi 3 karbon menunjukkan kestabilan jangka masa panjang kerana lebih berkesan dalam mengurangkan denaturasi pada DNA. Kehadiran pelbagai ikatan diantara DES dan DNA didapati menjadi penyebab kepada kestabilan jangka masa panjang DNA di dalam DES. Oleh itu, keputusan mendedahkan DNA lebih mudah tersolvasi di dalam DES berbanding larutan akues.

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I certify that a Thesis Examination Committee has met on 1 August 2016 to conduct the final examination of Rizana binti Yusof on her thesis entitled "Synthesis and Characterisation of Tetrabutylammonium Bromide based Deep Eutectic Solvents for DNA Solvation" in accordance with the Universities and University Colleges Act 1971 and the Constitution of the Universiti Putra Malaysia [P.U.(A) 106] 15 March 1998. The Committee recommends that the student be awarded the Doctor of Philosophy.

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TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF SCHEMES

LIST OF ABBREVIATIONS

A	Absorbance
A_{260}	Absorbance at 260 nm
A_{280}	Absorbance at 280 nm
ACD	Advanced Chemistry Development
A-T	Adenine-Thymine
ATB	Automated topology builder
AA	All-atom
$BMIM^+$	1-butyl-3-methylimidazolium cation
bp	Base pairs
Br^-	Bromide anion
CD	Circular Dichroism
CMAC	carboxymethanaminium chloride
CMEC	1(R)-1-carboxy-2-mercaptoethanaminium chloride
CH_2	Methylene
CH_3	Methyl
ChCl	Choline Chloride
COM	Centre-of-mass
cP	centipoise
D	Self-diffusion coefficient
d	Dublet
dd	Dublet of dublet
DAPI	4',6-diamidino-2-phenylindole
DMSO	Dimethylsulfoxide
DNA	Deoxyribonucleic Acid

DES	Deep eutectic solvent (singular)
DESs	Deep eutectic solvents (plural)
DSC	Differential Scanning Colometry
D_2O	Deuterium oxide
EAC	Ethylammonium chloride
EB	Ethidium bromide
EG	Ethylene glycol
FDBC	4-formyl-N,N-dimethylbenzenaminium chloride
FTIR	Fourier Transform InfraRed spectroscopy
G-C	Guanine-Cytosine
Gly	Glycerol
HBD	Hydrogen bond donor
iCALB	Immobilized *Candida antartica* lipase B
I_o	intensities of the fluorescence emission spectra in the absence of the quencher
I	intensities of the fluorescence emission spectra in the presence of the quencher
IL	Ionic liquid (singular)
ILs	Ionic liquids (plural)
K_b	binding constant
K_{sv}	Stern-Volmer constant
kbp	Kilo base pairs
LINCS	LINear Constraint Solver
LTTM	Low Transition Temperature Mixture
m	Miscible

m	Multiplet
MD	Molecular Dynamic
MSD	Mean square displacement
mdeg	milidegree
n	Binding numbers
NaCl	Sodium chloride
NMR	Nuclear Magnetic Resonance
nm	Non-miscible
NPT	Isothermal-isobaric ensemble
NVT	Isothermal-canonical ensemble
ns	nanosecond
OH	hydroxyl
OPLS	Optimized Potentials for Liquid Simulations
pm	Partially miscible
PBC	Periodic boundary condition
PDB	Protien Data Bank
PO_4^{3-}	Phosphate anion
PEIL	Protic eutectic ionic liquid
PME	Particle-Mesh Eward
ppm	Parts per million
ps	picosecond
PTC	Peltier temperature controller
R	Gas constant
$R_4N^+x^-$	Quaternary ammonium salt
RDF	Radial distribution function

RNA	Ribonucleioc acid
rpm	Rotation per minute
SCF	Supercritical fluids
SDF	Spatial distribution function
t	Triplet
tt	Triplet of triplet
TBA^+	Tetrabutylammonium bromide cation
TBABr	Tetrabutylammonium bromide
TBAC	Tetrabutylammonium chloride
TEAC	Tetraethylammonium chloride
T_m	Melting temperature
TMAC	Tetramethylammonium chloride
UA	United-atom
UV-Vis	Ultra Violet visible
wt%	Percentage weight
%w/w	Percentage weight over weight
$ZnCl_2$	Zinc chloride
1,3-PD	1,3-propanediol
1,5-PD	1,5-pentanediol
ΔG^o	Gibbs free energy
π	pi
δ	delta
ε	Extinction coefficient constant
c	concentration
l	Light path length

CHAPTER 1

INTRODUCTION

1.1 Background of Research

Organic solvents are a chemical class of compounds that are consumed widely as media in many chemical processes and in separation steps. However, the disposal of organic solvents has caused widespread pollution which poses risks to humans as well as environment. Researchers have applied green chemistry concepts to improve their design of chemical products and processes to minimise or eliminate the formation of toxic organic wastes. Hence, the use of organic solvents have been gradually replaced by new environmental-friendly 'green' media which are non-toxic and biodegradable such as supercritical fluids (SCF) and ionic liquids (ILs) (Francisco *et al.*, 2012, Rub & Konig, 2012). The selection of green solvents as opposed to organic solvents is indeed important to keep our environment green, clean and free from toxic wastes.

In the last few years, the search for new molecular solvents for DNA solvation has been of great interest to many researchers (Mamajanov *et al.*, 2010; Mondal *et al.*, 2013; Mukesh *et al.*, 2013). The high demand in the use of DNA is actually owed to the development of DNA-based materials; such as sensors, logic devices, circuits, drugs and biocatalysts (Marrazza *et al.*, 1999; Cheng *et al.*, 2006; Gianneschi and Ghadiri, 2007; Boersma *et al.*, 2010; Lakin *et al.*, 2012). The sustenance of the DNA helical structure is critically important to ensure that the biological functions of DNA work in their developed applications. Studies have shown that many factors may cause low DNA stability and lead to DNA denaturation, such as pH, concentration, temperature and salt concentration. Other than these factors, the type of solvent also influences the conformation and stability of the DNA. Most of the organic solvents such as dimethylsulfoxide (DMSO), phenol, methanol and chloroform have been reported to disrupt the DNA helical structure (Bonner and Klibanov, 2000). At present, DNA maintains its helical structure in aqueous solutions only when stored under refrigeration either for short or long-term applications. At room temperature, the stability of DNA in aqueous solutions is only for a short period of time, which is usually not more than 1 month (Vijayaraghavan *et al.*, 2010).

In this sense, deep eutectic solvents (DES), a new generation of ILs, have attracted much attention due to their special properties; low-vapor pressure, good thermal stability, wide range of solubility, sustainability and cost effectiveness, i.e being cheaper than earlier generations of ILs (Abbott *et al.*, 2003, Abbott *et al.*, 2004). DESs are regarded as ''designer solvents'' because of their tunable nature, whose properties are adjustable by different structures and functional groups of components in the DESs. Hence, these unique characteristics have allowed DESs to be utilised in many industrial applications such as electrochemistry (Alhaji, 2011), separation (Maugeri *et al.*, 2012; Pang

et al., 2012), organic synthesis (Rub and Konig, 2012) and biocatalysis (Chen *et al.*, 2011; Durand *et al*., 2012).

In 2010, the application of DESs in nucleic acid technology, especially as potential media to stabilise and solubilise DNA was reported (Mamajanov *et al.*, 2010; Mondal *et al.*, 2013, 2014; Mukesh *et al.*, 2013). The stability of DNA in the DESs depended on the ability of DNA to maintain the B-conformation that could change during the interaction of DNA with other molecules. Earlier studies of DNA in DESs demonstrated that changes in DNA conformations were strongly influenced by the environment of the DESs, whether they were hydrating or dehydrating, the concentrations and nucleotide sequences (Mamajanov *et al.*, 2010). Recent studies reported that the ability of the DESs to maintain the structure of DNA for long term storage was related to the interactions between the DESs and DNA. It was suggested that excessive hydrogen bonding and electrostatic interactions between the DESs and DNA were one of the reasons for the stability of the DNA in the DESs (Sharma *et al.*, 2015; Vijayaraghavan *et al.*, 2010). Thus far, some DESs have successfully provided stable media for DNA, such as ChCl:urea (Mamajanov *et al.*, 2010). However, the stability of DNA at high temperature in this DES was much lower compared to the aqueous solution, which resulted in the need to study specifically the properties of the DES and its interactions to the DNA.

The overal aim of this work is to search for a new solvent that is able to keep the DNA structure stable for a longer period and in higher temperatures compared to regular aqueous and organic solvents. In order to achieve the aim, the work focus on using newly synthesised TBABr based DES with four different hydrogen bond donors (HBDs). Interestingly, the MD simulation was used to provide the insight into the physical properties and intermolecular interaction in DESs structure. The study of DNA stability in various conditions of DESs has provided new informations that are very limited and less been reported in previous studies, such as binding interaction between DNA and DES. The details are very helpful to understand the structure-stability relationship in developing new potential DES for DNA technologies.

1.2 Problem Statements

Traditionally, DNA is stored under refrigeration in aqueous solutions for short and long term applications. Although DNA is considered to be stable in aqueous solutions, it is still susceptible to slow hydrolytic reactions, such as depurination and deamination which can cause serious damage to the DNA structure (Lukin and de Los Santos, 2006). After few days to 1 month in aqueous solutions at ambient temperature, the nucleic acid structures can be denatured (Vijayaraghavan *et al.*, 2010). Moreover, the small volume of water that keeps DNA stable is easily vaporised under open-air conditions or high temperatures, which causes a loss or change in the sample concentration.

In various organic solvents such as formamide, methanol and DMSO, DNA loses its native structure due to denaturation (Bonner and Klibanov, 2000). However, ethylene glycol (99%) and glycerol (99%) have been reported to retain the double helical structure of DNA, but with low thermostability that

limited the storage of DNA at high temperatures. External factors such as temperature, pH, salt concentration and ionic strength of solvent have also been reported to affect the helical structures and cause DNA denaturation (Hammouda and Worcester, 2006).

Hence, the search for a new solvent to overcome the problems of solvating DNA in aqueous and organic solvents is an ongoing process. DESs are favored because of their properties (low vapor pressure, high thermal stability and wide range of solubility) that are best suited for DNA solvation purposes.

1.3 Objectives

(i) To design and synthesise new DESs composed of TBABr salt with different hydrogen bond donors.
(ii) To characterise the physico-chemical properties of the newly synthesised DESs.
(iii) To analyze the physical properties and intermolecular interactions in the DESs by molecular dynamic simulation.
(iv) To elucidate the DES-DNA interactions by biophysical analyses.

1.4 Sections in the Thesis

This thesis is divided into five chapters according to the research studies. Chapter 1 presents the background of the research, problem statements and the objectives of the research. Chapter 2 discusses the literature review on the history of DESs, physical properties of DESs, molecular dynamic simulation on DESs, applications of DESs in life sciences, structure and properties of DNA, interaction and binding studies between various DES-DNA as well as the stability of DNA in DESs. Chapter 3 includes the materials and methods used in the research including the preparation of new DESs, experimental and computational methods to characterise DESs and biophysical analyses to characterise DNA in DESs using spectroscopic methods. Chapter 4 presents the results and discussion of the research including the appearance of the newly synthesised DES and the effects of some factors on the physical and chemical properties studied by experimental techniques (density, viscosity, ionic conductivity, water content and miscibility) and MD simulation (radial distribution function (RDF), spatial distribution function (SDF) and self-diffusion coefficient). The results also include the interactions between the DESs-DNA by biophysical analyses. Chapter 5 is the summary and conclusions of the research findings. The ability of the newly synthesised DES to solvate and retain the DNA helical structure is reported. Recommendations for the solution to the problems discovered in the study are also suggested in the context of future research.

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