Solution State ^{19}F Magnetic Resonance (MR) Account of Molecular Interactions in Solutions

A Thesis submitted by

Bhawna Chaubey

in partial fulfillment of the requirements for the award of the degree of

Doctor of Philosophy

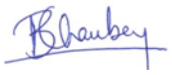
॥ त्वं ज्ञानमयो विज्ञानमयोऽसि ॥

Indian Institute of Technology Jodhpur
Department of Chemistry

March 2021

Declaration

I hereby declare that the work presented in this Thesis titled *Solution State ^{19}F Magnetic Resonance (MR) Account of Molecular Interactions in Solutions* submitted to the Indian Institute of Technology Jodhpur in partial fulfilment of the requirements for the award of the degree of Doctor of Philosophy, is a bonafide record of the research work carried out under the supervision of Dr. Samanwita Pal. The contents of this thesis in full or in parts, have not been submitted to, and will not be submitted by me to, any other Institute or University in India or abroad for the award of any degree or diploma.



Bhawna
P15CY005

Certificate

This is to certify that the thesis titled *Solution State ^{19}F Magnetic Resonance (MR) Account of Molecular Interactions in Solutions*, submitted by *Bhawna Chaubey* (P15CY005) to the Indian Institute of Technology Jodhpur for the award of the degree of *Doctor of Philosophy*, is a bonafide record of the research work done by her under my supervision. To the best of my knowledge, the contents of this report, in full or in parts, have not been submitted to any other Institute or University for the award of any degree or diploma.

Samanwita Pal

Samanwita Pal
Ph.D. Thesis Supervisor

Acknowledgements

I take this opportunity to express my deepest gratitude towards my supervisor and life coach ***Dr. Samanwita Pal*** who extended much of efforts and dedication in the discussion on the chosen research topic, related experimental procedures, and the obtained results. I am thankful to her for introducing me to beautiful world of NMR research and developing a researcher mindset. She guided me in every possible way to become competitive and creative in highly competitive field with limited resources and time at hand. She also guided me to evolve into a better human being by inculcating into me the life & professional skills namely, empathy, confidence, innovative thinking, work-life balance, value system, problem solving, presentation skills and communication etc. I owe the fabulous mentoring by her.

I am thankful to my doctoral committee members, *Dr. Ambesh Dixit, Dr. Manikandan Paranjothy*, and *Dr. Atul Kumar,* for their useful & pin-pointed suggestions, rational critical feedback, insightful cross questioning and scientific discussions. I want to thank *Prof. N Chandrakumar* from bottom of my heart for allowing me to work at MRI-MRS center, IIT Madras and for his valuable guidance and inspiration. I am thankful to the *UGC, India*, *MHRD, India* and *IIT Jodhpur* for taking care of my finances during this journey. I am thankful to my parent department at IITJ, the *Department of Chemistry*, for giving me the memories to cherish forever during this journey. I would like to acknowledge *Head of the Department, Dr. Ritu Gupta* and all the *faculties* of the Department for always being very supportive and hearing the concerns rose by me. I am also grateful to *Ms. Swati Kushwaha*, *Office of Chemistry* for her selfless help and cooperation. I am thankful to technical staff members namely, *Mr. Ganpat, Mr. Subham Mr. Mukesh,* and *Mr. Bharat* for their generous help in making me well acquainted in handling of lab instruments. I am grateful to *Dr. Bhawani Joshi*, *Mr. Anish Nair* and *Mr. Manmohan Vyas* from *Bruker India* for their cooperation & help. I want to express my deepest regards to *Dr. Arnab Dey* and *Dr. Abhishek Banerjee* (MRI-MRS centre, IITM) for introducing me to ODNP technique and brainstorming discussion sessions on NMR experiments. I want to express my sincere gratitude towards *Dr. KirenKumar Hiremath* and *Dr. Meenu Chabbra* for their kind help during MATLAB calculations and extraction of humic acid respectively. I also want to acknowledge *Office of Students, Office of Academics, Office of R&D, Office of Hostel Wardens, Office of Store & Purchase computer centre and Library* at IITJ for their support in formal procedures & documentation work.

I want to thank my lab mates at NMR lab IIT Jodhpur, *Vandana, Deepak, Deepika, Ajeetesh, Sakshi, Pooja, Vinod, Pooja, Vikram*, and *Rajat* for enriching my ideas with deep discussions and maintaining a progressive & competitive lab environment. Special thanks to *Vandana* for her unfailing moral support and fruitful guidance. I want to specially thank *Dr. Arnab Dey* for being my savior during PhD things. I am indebted to you for always listening to all my nonsense related to professional/personal life. I want to thank my friends *Sumitra, Anchal, Shubham, Raghuwanshi, Arpu, Amitap, Gaurav, Erum di, Jaitawat, Megha, Divya, Satya, Anshul, Simran,* and *Poonam* for sharing great memories and laughs. I enjoyed all the moments that we guys shared together during this journey & chit-chat related to personal, campus and academic life. Without these people, it would have been not so interesting & wonderful journey here in IIT Jodhpur. I would specially like to thank *Shubham* for helping me out in things related to coding & fixing technical glitches. I also want to acknowledge my friends *Anamika, Bhavna, Isha, Mohsin, Monika, Nitin* and *Prashant* for their moral & emotional support. I also want to thank all my *seniors, batchmates* and *juniors* from and across the department who taught and supported me, and brought comfort and joy to my soul. They know who they are!!

I would like to thank my lifelines and role model, my mother, Mrs. ***Kavita***, and my father, *Mr.* ***Arbind Chaubey***. They have always got my back. Thank you for always standing for me & believing in me. I am blessed to have their unconditional love and blessing. I also want to

acknowledge my whole maternal and paternal family for their love and affection. A special mention to my brothers *Vivek, Abhishek, Rahul, Alok, Nilesh, Akhilesh, Adarsh and Aaryan*, & my sisters *Shivangi*, *Riya, Goludi, Rakshita, Divya, Lovely and all my niece* for their enduring support, love, care and all the laughters. I specially want to thank a very *special person* in my life who always uplifted me and don't want to appear in this list. I want to thank my *alma-mater IIT Jodhpur* for evolving me into a better, confident & innovative personality. I will miss you my *'Home Away from Home'* and our CS team. Last but not the least, thanks to almighty God who always give hopes to me. I apologize if I somehow missed anyone in this acknowledgment list.

Bhawna Chaubey
Ph.D. Student

List of Figures

List of Tables

List of Symbols

Symbol	*Description*
Å	Angstrom
A	UV absorbance at a particular wavelength
A_F	STD Amplification factor
a	Molecular radius
α	Offset constant
B_0	Zeeman field
°C	Degree Celsius
cP	CentiPoise
dB	Decibel
D	Self-Diffusion Coefficient
ξ	Coupling parameter
δ	Chemical shift/Gradient length
δ_{ppm}	Chemical shift in parts per million
$\Delta\delta$	Chemical shift change
λ	Wavelength
γ_i	Gyromagnetic ratio of the i-th spin
f	Micro-viscosity factor
gm	Gram
$\Delta G°$	Gibbs free energy of transfer
Hz	Hertz
I	Nuclear spin quantum number
h	Planck's constant
K	Kelvin
K_A	Association/Binding constant
K_D	Dissociation constant
K_{ex}	Exchange rate
k_B	Boltzmann constant
k	Photo-degradation Rate constant
k_d	Direct photo-degradation rate constant
k_{id}	Indirect photo-degradation rate constant
kJ/mol	Kilojoules per mole
kcal	Kilocalorie
kDa	Kilo Dalton
L	Litre
M	Molar concentration
mg	Milligrams
MHz	Mega hertz
mM	Millimolar
mL	Milliliter
mW	milliWatt
mins	minutes
n	Number of binding sites
nm	Nanometer
ns	Nanosecond
η_a	Assymetry Parameter
η	Dynamic viscosity

P_b	Ligand bound fraction
ps	picoseconds
r_H	Hyrdodyamic radius
R_1	Spin lattice relaxation rate
R_2	Spin-Spin relaxation rate
r_{ij}	Internuclear distance
s	Second
s	ESR saturation parameter
τ_c	Molecular rotational correlation time
$\tau_{c(F)}$	^{19}F Molecular rotational correlation time
$\tau_{c(D)}$	^{2}H Molecular rotational correlation time
τ_c*	Molecular rotational correlation time from viscosity
τ_{res}	Lifetime of the complex
T	Temperature
T	Tesla
T_1	Spin-Lattice relaxation time
T_2	Spin-Spin relaxation time
t	Time
t_{sat}	Saturation time
$t_{1/2}$	Degradation half-life
μ_0	Permeability of free space
μM	Micromolar
µs	Microsecond
$\nu_{1/2}$	Linewidth at Full Width and Half Maximum (FWHM)
ω_i	Angular frequency/ Larmor frequency of the *i*-th spin
W	Watt

List of Abbreviations

Abbreviation	Full form
ADMET	Absorption Distribution Metabolism Excretion and Toxicity
AFM	Atomic Force Microscopy
AHA	Aldrich Humic acid
AV III	Avance III
BA	Benzoic acid
BBFO	Broadband fluorine observe
B-H	Benesi-Hindelbrand
BPPLED	Bipolar-pair pulse sequence with longitudinal eddy current delay
BSA	Bovine serum albumin
β-CD	β-Cyclodextrin
CA	Carboxyllic acid
CD	Circular Dichroism
CCR	Cross correlation rate
CPMG	Carl Purcell Meiboom Gill
CSA	Chemical Shift Anisotropy
D_2O	Deuterium Oxide
DDNP	Dissolution Dynamic Nuclear Polarization
DD	Dipole-Dipole
DMSO-d_6	Dimethylsulphoxie-d_6
DOM	Dissolved organic matter
DSC	Differential Scanning Calorimetry
d	doublet
dd	doublet of doublet
dt	doublet of triplet
DMSO	Dimethyl Sulfoxide
DPFGSE	Double Pulsed-Field-Gradient Spin Echo
DFBA	2,6 Difluorobezoic acid
DFA	Difluoroacetic acid
DFL	Diflunisal
EHA	Extracted Humic acid
ESR	Electron Spin Resonance
EPR	Electron Paramagnetic Resonance
FABS	Fluorine Atoms for Biochemical Screening
FAXS	Fluorine chemical shift anisotropy and exchange for fluorine
FID	Free Induction Decay
FPD	Flupyradifurone
FTIR	Fourier Transform Infrared spectroscopy
FWHM	Full width at half maximum
GEM	Group Epitope Mapping
GHz	Gigahertz
H_2O	Water
HA	Humic acid
HFM	Hexaflumuron
HTS	High Throughput Screening
HOE	Hetero-nuclear Overhauser Enhancement
HS	Humic substances
HSA	Human Serum albumin
INPHARMA	Inter-ligand NOE for pharmacophore mapping
ITC	Isothermal Titration Calorimetry

KHA	Karwar Humic acid
LED	Longitudinal eddy current
MD	Molecular docking
MLT	Mellitin
MF	Magnetic field
MHz	Megahertz
MRI	Magnetic Resonance Imaging
MT	Magnetization Transfer
MW	Microwave
M. wt.	Molecular Weight
NMR	Nuclear Magnetic Resonance
NOE	Nuclear Overhauser Enhancement
NOESY	Nuclear Overhauser Effect SpectroscopY
NOM	Natural organic matter
ODNP	Overhauser Dynamic Nuclear Polarization
PB	Phosphate Buffer
PFG	Pulse Field Gradient
ppm	Parts per million
RHSTD	Reverse Heteronuclear Saturation Transfer Difference
RF	Radio frequency
SALMON	Solvent accessibility, ligand binding, and mapping of ligand orientation by NMR Spectroscopy
SOM	Soil Organic Matter
SPR	Surface Plasmon Resonance
S/N	Signal-to-noise ratio
STD	Saturation Transfer Difference
SW	Spectral width
STE	Stimulated spin-echo
TFE	Trifluoroethanol
TMS	Trimethylsilane
UV-vis	Ultraviolet-visible spectroscopy
Water-LOGSY	Water ligand observed through gradient spectroscopy
WB	Wide Bore
1D	One-dimensional
^{1}H	Proton
^{2}H	Deuterium
2D	Two-dimensional
5-FU	5-Fluorouracil
^{13}C	13 Carbon
^{19}F	19 Fluorine
^{6,7} Li	6,7 Lithium
^{15}N	15 Nitrogen
^{23}Na	23 Sodium
^{17}O	17 Oxygen
^{31}P	31 Phosphorus
^{29}Si	29 Silicon
^{129}Xe	129 Xenon
^{67}Zn	67 Zinc