

**APPLICATIONS OF NMR SPECTROSCOPY TO EXCHANGING
SYSTEMS, LONG LIVED STATES, AND SOLIDS**

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**APPLICATIONS OF NMR SPECTROSCOPY TO EXCHANGING
SYSTEMS, LONG LIVED STATES, AND SOLIDS**

by

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DEPARTMENT OF CHEMISTRY

Submitted

in fulfillment of the requirements of the degree of Doctor of Philosophy
to the



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Dedicated
to my
Parents and Family

Certificate

I certify that the thesis entitled ***Applications of NMR Spectroscopy to Exchanging Systems, Long Lived States, and Solids*** submitted by **Mr. Balvinder Singh** to **Indian Institute of Technology Delhi** for the award of **Doctor of Philosophy** is a record of bona fide research work done by him. He has worked under my guidance and supervision and has fulfilled the requirements for the submission of this thesis which to my knowledge has reached the requisite standard. The results presented in this thesis have not been submitted in part or full to any other University or Institute for the award of any degree or diploma.

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Balvinder Singh

Abstract

Nuclear magnetic resonance (NMR) spectroscopy is one of the most powerful non-destructive techniques available today for probing the structure of matter. High resolution NMR is an important tool for determining the structure of molecules ranging from small chemical compounds to large macromolecules, is a well-established method for determining the 3-D structures of biomolecules in solution. Similarly, solid state NMR, provides structural information on polymeric powdered crystalline and polycrystalline substances. Relaxation of spins play a decisive role in various applications of NMR spectroscopy and development of new methods in NMR. Earlier it was believed that spin-lattice (T_1) and spin-spin relaxation time (T_2) set the upper limit of relaxation. But creation of long-lived states in a two-spin system confirmed that lifetimes longer than T_1 and T_2 are possible. Since then various studies were conducted to generate, sustain and sense long lived states in a number of systems and to explore the structure and dynamics of molecules.

This thesis entitled “**Applications of NMR Spectroscopy to Exchanging Systems, Long Lived States, and Solids**” showcases applications of NMR spectroscopy to different problems along with creation and sustenance of long-lived states at off-resonance with a number of pulses. The first chapter introduces important concepts of solution state and solid-state NMR starting with brief history and development of NMR spectroscopy. Later, a quantum mechanical description of important concepts is also provided.

Chapter 2 describes in detail about generation of long-lived states (LLS) at on resonance and off resonance by applying several composite pulses, windowed pulses, and continuous wave. Here, a comparative study of LLS lifetime is done to see the effect of different sustaining pulses on the efficiency of off-resonance sustenance. These results are compared with results obtained from

simulations for the same. Important findings in this study are that WALTZ-16 composite pulse is most efficient for sustaining LLS off resonance in a weakly coupled two spin system, and windowed acquisition can be used in place of continuous wave method for sustaining LLS.

Chapter 3 demonstrates application of LLS for measuring numerical value of chemical exchange rate in a sample having restricted rotation about the C-N bond in p-Chloroformanilide which has partial double bond character. Earlier a proof of concept has been demonstrated that the long lifetime of LLS can be used for measuring slow chemical exchange, but a measurement of the exchange rate was not accomplished. In this study we created LLS in an inequivalent two spin system having exchange, by applying 1D LLS pulse sequence, and successfully measured numerical value of exchange rate and the activation energy. We also compared exchange rate value with the value obtained for the same system at variable temperature using conventional methods like 2D NOESY and selective inversion recovery method. We also demonstrated that in acetone, p-Chloroformanilide does not exist in a single conformer as suggested in earlier study.

Chapter 4 is about synthesis and structural study of vanadium based yellow foam using solid state NMR, X-ray diffractograms and other complimentary techniques. The structural study of vanadium oxides, xerogels and foams are important for modifying their properties and their applications at industrial scale. In this study we analysed the structure of yellow foam using solid state NMR, small angle X-ray diffraction, and powder X-ray diffractogram (PXRD), IR, TGA and provided a new model for structure of vanadium yellow foam.

The thesis contains **three appendices** on our attempts to extend applications of LLS and NMR spectroscopy to other systems.

The **first appendix** is ‘Monitoring Aggregation in Solution State Using NMR Spectroscopy’. In this study we focused on studying interaction between an acid 5-hydroxybenzene-1,3-dicarboxylic acid and a base 4,4-bipyridyl using liquid state NMR and PXRD. In CSD database we found no cocrystal or salt between these two and on the basis of ΔpK_a rule these two lays in transition range where salt, cocrystal or proton transfer is possible. We found favorable evidence of proton transfer between acid and base after studying this system.

The **second appendix** discusses about a problem which is ‘Measurement of H/D Exchange Rate in Ionic Liquid - H₂O - D₂O Mixture Using NMR Spectroscopy.’ H/D exchange occurs at faster rate in bulk water or aqueous system, making it difficult to monitor by NMR. In highly viscous medium, like some room temperature ionic liquids, for example, confined water shows different behavior than bulk and the H/D exchange rate becomes slow and can be monitored by NMR. Here, we used selective inversion recovery method to measure exchange rate and obtained a numerical value using nonlinear curve fitting.

The **third appendix** contains study on ‘Measuring Paracetamol Interaction With β -Cyclodextrin Using LLS Method.’ At present, emphasis is given to discover target-based drug delivery systems which could bring about decrease in drug quantity required for treatment of a disease as compared to indirect delivery of the drug to the site of infection. In this study we want to measure maximum amount of paracetamol drug that can be loaded in drug carrier β -Cyclodextrin. We started with simple drug paracetamol and measured its LLS lifetime as it has inequivalent two spin system. When it was mixed with β -Cyclodextrin in different molar ratios then we found maximum decrease in LLS lifetime of 1:1 complex. It provides a new way to measure maximum amount of drug that can be loaded in drug carrier if one of them has inequivalent two spin system.

सारांश

परमाणु चुंबकीय अनुनाद (एनएमआर) स्पेक्ट्रोस्कोपी सबसे शक्तिशाली गैर-विनाशकारी तकनीकों में से एक है जो पदार्थ की संरचना की जांच के लिए आज उपलब्ध है। उच्च रिज़ॉल्यूशन एनएमआर छोटे रासायनिक यौगिकों से बड़े मैक्रोमोलेक्यूल्स तक के अणुओं की संरचना का निर्धारण करने के लिए एक महत्वपूर्ण उपकरण है, समाधान में बायोमोलेक्यूल्स की 3-डी संरचनाओं का निर्धारण करने के लिए एक अच्छी तरह से स्थापित विधि है। इसी तरह, ठोस अवस्था एनएमआर, बहुलक पाउडर क्रिस्टलीय और पॉलीक्रिस्टलाइन पदार्थों पर संरचनात्मक जानकारी प्रदान करता है। एनएमआर स्पेक्ट्रोस्कोपी के विभिन्न अनुप्रयोगों और एनएमआर में नए तरीकों के विकास में स्पिनो का विश्राम एक निर्णायक भूमिका निभाता है। पहले यह माना जाता था कि स्पिन-जालक (T_1) और स्पिन-स्पिन विश्राम समय (T_2) विश्राम की ऊपरी सीमा निर्धारित करते हैं। लेकिन लंबे समय तक रहने वाली अवस्थाओं (एलएलएस) के निर्माण ने एक दो-स्पिन प्रणाली की पुष्टि की कि टी 1 और टी 2 की तुलना में लंबे जीवनकाल संभव हैं। तब से कई प्रणालियों को उत्पन्न करने, बनाए रखने और लंबे समय तक जीवित रहने के लिए और अणुओं की संरचना और गतिशीलता का पता लगाने के लिए विभिन्न अध्ययन किए गए थे।

यह थीसिस "एनएमआर स्पेक्ट्रोस्कोपी के अनुप्रयोग को एक्सचेंजिंग सिस्टम, लॉन्ग लिवेड स्टेट्स और सॉलिड्स के लिए" नामांकित करता है, जो एनएमआर स्पेक्ट्रोस्कोपी के विभिन्न अनुप्रयोगों के साथ-साथ कई प्रकार की तरंगों के साथ ऑफ-रेजोनेंस पर लंबे समय तक रहने वाली अवस्थाओं (एलएलएस) के निर्माण और दीर्घायु जीवन के अनुप्रयोगों को प्रदर्शित करता है। पहला अध्याय एनएमआर स्पेक्ट्रोस्कोपी के संक्षिप्त इतिहास और इसके विकास के साथ-साथ द्रव तथा ठोस अवस्था एनएमआर की महत्वपूर्ण अवधारणाओं का परिचय देता है। अध्याय के अंत में एनएमआर की महत्वपूर्ण अवधारणाओं का एक क्रांतिमय यांत्रिक विवरण भी प्रदान किया गया है।

अध्याय 2 कई समग्र तरंगों, खिड़की (विंडो) वाली तरंगों, और निरंतर तरंगों को उपयोग करके अनुनाद और बंद अनुनाद पर लंबे समय तक रहने वाली अवस्थाओं (एलएलएस) के निर्माण के बारे में विस्तार से वर्णन करता है। यहां एलएसएस आजीवन का एक तुलनात्मक अध्ययन ऑफ-रेजोनेंस जीविका की दक्षता पर विभिन्न तरंगों के प्रभाव को देखने के लिए किया जाता है। इन परिणामों की तुलना उसी के लिए सिमुलेशन से प्राप्त परिणामों से की जाती है। इस अध्ययन में महत्वपूर्ण निष्कर्ष यह है कि कमजोर पड़ने वाले दो स्पिन सिस्टम में एलएलएस बंद अनुनाद बनाए रखने के लिए वाल्ट्ज -16 समग्र पल्स सबसे अधिक कुशल है, और एलएलएस को बनाए रखने के लिए निरंतर तरंग विधि के स्थान पर विंडो अधिग्रहण का उपयोग किया जा सकता है।

अध्याय 3 पेरा-क्लोरोफोरमैनालाइड में सी-एन(C-N)बांड के बारे में प्रतिबंधित रोटेशन वाले नमूने में रासायनिक विनिमय दर के संख्यात्मक मूल्य को मापने के लिए एलएलएस के अनुप्रयोग को प्रदर्शित करता है जिसमें आंशिक डबल बांड चरित्र होता है। इससे पहले अवधारणा के एक प्रमाण का प्रदर्शन किया गया है कि धीमी रासायनिक विनिमय को मापने के लिए एलएलएस के लंबे जीवनकाल का उपयोग किया जा सकता है, लेकिन विनिमय दर का एक माप पूरा नहीं किया गया था। इस अध्ययन में हमने 1 डी एलएलएस पल्स अनुक्रम को लागू करके एक असमान दो स्पिन प्रणाली में एलएलएस बनाया, और विनिमय दर और सक्रियण ऊर्जा के संख्यात्मक मूल्य को सफलतापूर्वक मापा। हमने पारंपरिक तरीकों जैसे 2D NOESY और चयनात्मक उलटा पुनर्प्राप्ति विधि का उपयोग करके परिवर्तनीय तापमान पर समान प्रणाली के लिए प्राप्त मूल्य के साथ विनिमय दर मूल्य की तुलना की। हमने यह भी दिखाया कि एसीटोन में, पेरा-क्लोरोफोरमैनालाइड एक कंफर्मर में मौजूद नहीं है जैसा कि पहले के अध्ययन में बताया गया है।

अध्याय 4 ठोस अवस्था एनएमआर, एक्स-रे डिफ्रेक्टोग्राम और अन्य तकनीकों का उपयोग करके वैनेडियम आधारित पीले फोम के संश्लेषण और संरचनात्मक अध्ययन के बारे में है। वैनेडियम ऑक्साइड, जीरोजेल्स

और फोम के संरचनात्मक अध्ययन औद्योगिक पैमाने पर उनके गुणों और उनके अनुप्रयोगों को संशोधित करने के लिए महत्वपूर्ण हैं। इस अध्ययन में हमने ठोस अवस्था एनएमआर, छोटे कोण एक्स-रे विवर्तन, और पाउडर एक्स-रे विवर्तनोग्राम (पीएक्सआरडी), आईआर, टीजीए का उपयोग करके पीले फोम की संरचना का विश्लेषण किया और वैनेडियम पीले फोम की संरचना के लिए एक नया मॉडल प्रदान किया।

थीसिस में एलएलएस और एनएमआर स्पेक्ट्रोस्कोपी के अनुप्रयोगों को अन्य प्रणालियों में विस्तारित करने के हमारे प्रयासों पर तीन परिशिष्ट शामिल हैं।

पहला परिशिष्ट एनएमआर स्पेक्ट्रोस्कोपी का उपयोग कर द्रव अवस्था में अणुओं के एकत्रीकरण अथवा संग्रहण का अध्ययन या निगरानी से संबंधित है। इस अध्ययन में हमने द्रव अवस्था एनएमआर और पीएक्सआरडी का उपयोग करके एक एसिड 5-हाइड्रॉक्सीबेंज़ीन-1,3-डाइकारबोक्सिकलिक एसिड और एक क्षार 4,4-बाइपिरिडिल के बीच अन्तर्क्रिया का अध्ययन करने पर ध्यान केंद्रित किया। सीएसडी डेटाबेस में हमें इन दोनों के बीच कोई कोई क्रिस्टल या लवण नहीं मिला और डेल्टा पिके (ΔpK_a) नियम के आधार पर इन दोनों के लिये अन्तर संक्रमण सीमा में दिया जाता है जहां लवण, सह-क्रिस्टल या प्रोटॉन स्थानांतरण संभव है। हमें इस प्रणाली का अध्ययन करने के बाद एसिड और बेस के बीच प्रोटॉन हस्तांतरण के अनुकूल सबूत मिले।

दूसरे परिशिष्ट में एक समस्या के बारे में चर्चा की गई है, जो है 'मापन / एच / डी विनिमय दर की आयनिक तरल में - एच 2 ओ - डी 2 ओ मिश्रण का उपयोग एनएमआर स्पेक्ट्रोस्कोपी।' एच / डी एक्सचेंज सामान्य पानी या जलीय प्रणाली में तेज दर से होता है, जिससे एनएमआर द्वारा इसकी निगरानी करना मुश्किल हो जाता है। । अत्यधिक सघन माध्यम में, जैसे कुछ कमरे के तापमान वाले आयनिक तरल पदार्थ, उदाहरण के लिए, सीमित पानी सामान्य से अलग व्यवहार दिखाता है और एच / डी विनिमय दर धीमी हो जाती है और एनएमआर

द्वारा इसकी निगरानी की जा सकती है। यहां, हमने विनिमय दर को मापने के लिए चयनात्मक उलटा पुनर्प्राप्ति विधि का इस्तेमाल किया और नॉनलाइन कर्व फिटिंग का उपयोग करके संख्यात्मक मान प्राप्त किया।

तीसरे परिशिष्ट में एलएसएस विधि का उपयोग करके बीटा-साइक्लोडेक्सट्रिन के साथ पैरासिटामोल इंटरैक्शन को मापने पर अध्ययन शामिल है। वर्तमान में, लक्ष्य-आधारित दवा वितरण प्रणाली की खोज करने पर जोर दिया जाता है, जो अप्रत्यक्ष की तुलना में किसी बीमारी के उपचार के लिए आवश्यक दवा की मात्रा जो की संक्रमण साइट पर आवश्यक है, में कमी ला सकता है। इस अध्ययन में हम पैरासिटामोल दवा की अधिकतम मात्रा को मापना चाहते हैं जिसे ड्रग कैरियर बीटा-साइक्लोडेक्सट्रिन में लोड किया जा सकता है। हमने सरल ड्रग पैरासिटामोल के साथ शुरू किया और इसके एलएसएस जीवनकाल को मापा क्योंकि इसमें असमानता वाली दो स्पिन प्रणाली है। जब इसे अलग-अलग अनुपात में बीटा-साइक्लोडेक्सट्रिन के साथ मिलाया गया तब हमने 1: 1 जटिल के एलएसएस जीवनकाल में अधिकतम कमी पाई। यह दवा की अधिकतम मात्रा को मापने के लिए एक नया तरीका प्रदान करता है जिसे ड्रग कैरियर में लोड किया जा सकता है यदि उनमें से एक में असमान दो स्पिन प्रणाली उपस्थित हो।

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