DEVELOPMENT AND INITIAL
CHARACTERIZATION
OF A NUCLEAR MAGNETIC RESONANCE
DOSIMETRY SYSTEM

by

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A thesis submitted in partial fulfillment
of the requirement for the degree of

Doctor of Philosophy
(Medical Physics)

at the

UNIVERSITY OF WISCONSIN-MADISON

1990

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ACKNOWLEDGEMENTS

I am indebted to several people for the successful completion of this project. First, I greatly acknowledge the support of Bill Perinan who got me started on my road to understanding the potential of NMR as a research tool. It was through work on his sodium imaging projects that I was able to appreciate the theoretical and technical aspects of a complete NMR project. I am also very indebted to Professor Tom Farrar in the Department of Chemistry along with Bruce Adams and the entire group of graduate students. It was through their support that I was able to delve into the world of NMR spectroscopy. All the results from my experiments were obtained using their departmental equipment which had to have been maintained in peak operational performance to accomplish my goals. Finally, none of this project could have been started if it were not for the moral support of Professor Paul DeLuca. In addition to the educational and financial support he provided, his faith in this somewhat bizarre project gave me the confidence to proceed through some trying experimental times.

I acknowledge the support of the U.S. Department of Energy through contract number DE-FG02-86ER60417 and the University of Wisconsin Radiological Sciences Training Program National Research Service Award by the National Cancer Institute 5-T32-CA09206.

Contents

Abstract	viii
1 Introduction	1
1.1 Fundamentals of an MRD System	2
1.2 Previous NMR Studies of Radiation Effects	4
1.2.1 Charlesby: Scission and Crosslinking in Polymers	4
1.2.2 Gore: Paramagnetic induced relaxation	5
1.2.3 Randall: Sequence Distribution and Tacticity	6
1.2.4 Pannin: Aliphatic peptides and amino acids	6
1.3 Research Goals	7
2 Background	8
2.1 General Characteristics of a Dosimeter	9
2.2 Chemical Dosimetry	16
2.2.1 Previous Chemical Dosimeter Systems	17
2.2.2 Radiation Chemistry	18
2.2.3 Radiation Chemistry of Methanol	30
2.3 NMR as an Analytical Tool	34
2.3.1 Basic Physics of NMR	35

2.3.2	Physical Limitations of NMR	37
2.3.3	Technological Limitations of NMR	38
2.3.4	Aspects of Quantitative NMR	41
3	Materials and Methods	48
3.1	Reference Spectra	51
3.2	Qualitative high dose spectrum (50kGy)	56
4	Results	57
4.1	Dose response	57
4.2	Reproducibility	62
4.3	Temporal Stability	68
5	Discussion	75
5.1	Dose Response	76
5.2	Reproducibility	77
5.3	Temporal Stability	78
6	Future Studies	79
6.1	Extended Dosimetry Characterization	80
6.2	Energy and LET Response	81
6.3	Alternative Spectral Estimation	82
6.4	Spectrometer Technology	82
6.5	Alternative Molecular Systems	83
7	Conclusion	85

Bibliography

85

List of Tables

2.1	Common integrating dosimeters with respective dose range. . . .	11
2.2	Mass Spectrum Data for Methanol	47
4.1	Effect of varying pulse power and ability of normalization to com- pensate	66
4.2	Effect of varying receiver gain and ability of normalization to com- pensate	67
4.3	Intra-sample Reproducibility, 10 samples	70
4.4	Inter-sample reproducibility for three different samples.	71
4.5	Improvement in reproducibility by simple averaging	72
4.6	Temporal stability at 1 kGy	73
4.7	Temporal stability at 6 kGy	74

List of Figures

2.1	Ionization probability curve for He^+ from Hickam	20
2.2	Potential-energy curves for a diatomic molecule in its ground state and in an electronically excited state from Spinks.	21
2.3	Effect of electron energy on the mass spectrum of methylal from Kiser.	25
2.4	G Values <i>vs.</i> LET for formaldehyde and ethylene glycol production.	33
3.1	High resolution proton CH_3OD spectrum	52
3.2	High resolution proton CH_3OD with formaldehyde (CH_2O). . .	53
3.3	High resolution proton CH_3OD with formaldehyde (CH_2O) and ethylene glycol $C_2H_6O_2$	54
3.4	Formaldehyde Calibration Curve	55
3.5	CH_3OD Irradiated to 50 kGy	56
4.1	CH_3OD Irradiated to 6 kGy.	58
4.2	Integrated CH_2O peak areas as a function of absorbed dose 10 to 60 kGy.	59
4.3	7ppm spectrum acquired with presaturation.	61
4.4	Integrated CH_2O peak areas as a function of absorbed dose 1 to 10 kGy.	62

4.5	2ppm spectrum acquired with presaturation	63
4.6	Integrated CH_2O peak areas as a function of absorbed dose 0.1 to 1 kGy	64

Abstract

DEVELOPMENT AND INITIAL CHARACTERIZATION OF A NUCLEAR MAGNETIC RESONANCE DOSIMETRY SYSTEM

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A novel high dose radiation dosimeter was developed employing NMR spectroscopic quantitation of the radiolytic products of methanol. Chemical shifts of product resonances relative to the solvent allow quantification using NMR techniques. Due to expected dynamic range limitations of NMR instrumentation, deuterated methanol is used with a presaturation suppression sequence to reduce the solvent proton signals. Methanol's ^{13}C -coupled proton resonance is used as an internal reference to normalize product signals otherwise subject to spectrometer variability. Data on reproducibility, dose response, and temporal stability were acquired. System reproducibility for a sample at 1 kGy is $\approx 10\%$. The dose response is linear in the range between 200 Gy and 50 kGy. No significant signal degradation was observed during a six month period. Advantages of this type dosimeter system include ease of use, large dynamic range, and temporal stability. An additional characteristic of a methanol based system is the LET dependent response in the chemical yields of formaldehyde and ethylene glycol.

Chapter 1

Introduction

Radiation dosimetry is important in health and medical physics as a means of regulating an individual's exposure to ionizing radiations and to quantify absorbed dose for radiotherapy prescriptions. There have been numerous methods of dosimetry proposed and developed since the first discovery of radiation. Each of these methods has been developed to address specific applications such as low dose, high dose, interaction specificity, tissue mimicking, or differentiation of mixed field radiation sources. The purpose of this research is to investigate a dosimetry system that may simultaneously accomplish several of these goals. This research project is based on radiation induced interactions which have been used in various chemical dosimetry systems since the 1920s [8]. Chemical dosimetry has advantages over thermoluminescent dosimetry (TLD), or electronic-based dosimeter systems either in being more tissue like or having a higher dose range. The primary disadvantage of chemical dosimetry has been the difficulty involved in the analytical techniques used to measure the radiolytic products. Advances in NMR technology have reached the point where it is now useful as a sensitive analytical technique. The specificity of NMR methods also makes this technique worthwhile to pursue for related radiation research applications.

1.1 Fundamentals of an MRD System

All methods currently in practice which measure absorbed dose share a common basic concept. Quantifying the absorption of radiant energy can be separated into three basic steps. The first step is to alter a given system from an equilibrium state by the absorption of energy. The second step involves the fixing of the altered equilibrium state so that it remains in that state for a sufficient period of time to quantify the change. The third step is to measure the magnitude or other properties of change in the altered system. An ionization chamber is a simple example of this process. The passage of charged particles through a gas alters an equilibrium state by the ionization and excitation of the gas molecules. The fixing process is accomplished by collecting the charge created using an electric field to sweep the charge onto a storage capacitor. The quantification process is performed by measuring the charge produced using an electrometer.

A magnetic resonance based dosimetry (MRD) system also consists of the same three-step process. First, altering of an initial state is achieved by radiation-induced formation of impurity molecules in an otherwise pure target solvent. Impurity molecules are formed by radiolytic processes such as simple dissociation of molecules into free radicals or molecular fragments and recombination of these species through free radical and/or ion-molecule reactions producing rearrangement molecules. The fixing process in this chemical system is inherent for the production of stable molecules. Fixing may, however, be artificially established by introducing a competitive reactive ion that would create stable impurities, as in a free radical scavenging mechanism. Quantification of the molecules formed

is accomplished using spectroscopic NMR methods. A spectrum of the target molecules acquired before exposure to ionizing radiation would consist of a resonance peak or peaks corresponding to the initial system target molecules. The spectrum obtained after irradiation would consist of peaks corresponding to the original molecule and the newly formed impurity molecules. By integrating the area under these impurity peaks a quantitative measure of the absorbed radiation is obtained.

The radiation response of methanol makes this molecule particularly appropriate for a dosimeter system. Formation of the products formaldehyde and ethylene glycol have been shown to increase linearly with dose in the range between 729 Gy to 2.9 kGy at a dose rate of 48.6 Gy/min [52]. The rate of production of these two molecules, however depends on the linear energy transfer (LET) of the incident radiation. Ethylene glycol production decreases with increasing LET while formaldehyde production increases. In addition the LET response for the production of formaldehyde increases in a fashion similar to the relative biological effectiveness (RBE) for radiobiological cell survival curves. This suggests the potential as an inherent quality factor for a dosimeter based on this solvent. A subsequent decrease in the rate of formation of ethylene glycol as a function of LET may allow for the first order separation of dose contribution in a mixed (high/low) LET radiation field.

Previous chemical-based dosimetry systems have used various analytical chemistry techniques to quantify the dosimetric response. Nuclear magnetic resonance as a quantitative spectroscopic tool is preferable over other analytical chemistry

techniques despite its relative insensitivity. Its advantages include being non-destructive, having a large dynamic range, and having good spectroscopic resolution. Without any additional sophisticated hardware one is able to quantify absorbed doses from 200 Gy to 50 kGy using a standard 270MHz spectrometer.

1.2 Previous NMR Studies of Radiation Effects

While not specifically related to dosimetry, several research efforts have used NMR to evaluate the effects of radiation on different chemical systems. A review of this literature provides insight into a wide variety of applications as well as potential limitations of this type of research, such as the expected lower limits of dose response. Several researchers have investigated the change in NMR relaxation properties due to either radiation produced paramagnetics or changes in the molecular motions coincident with dissociation and or polymerization of long chain polymers. Other researchers have observed additional resonances due to molecular breakdown products. The work by Panin [55,56] studying radiolysis products of aliphatic peptides with proton NMR is closely related to the work performed here. The following is a brief synopsis of several research projects using various NMR techniques.

1.2.1 Charlesby: Scission and Crosslinking in Polymers

Charlesby has studied radiation-induced crosslinking and gel formation in polymer materials using NMR [29,3]. The radiation interactions result in main chain scission or crosslinking which affects the molecular motions at sites within the

material. Changes in local molecular motions affect the T_1 and T_2 relaxation properties and consequently the NMR line widths for the irradiated samples. Charlesby found that the line widths varied consistently with absorbed dose up to 100 MGy. This technique depends on accurate measurements of the relaxation parameters T_1 and T_2 by evaluating linewidths for the respective resonance peaks. The resolution between dose points will be limited by the accuracy with which one is able to determine changes in linewidth which are also subject to inhomogeneous magnetic field line broadening. Relaxation parameters may also be measured using spin-echo pulse trains but these too suffer instrumental variations which may limit the dose resolution.

1.2.2 Gore: Paramagnetic induced relaxation

Another system of monitoring radiation dose based on a slightly different mechanism for altering relaxation properties has been presented by Gore [33]. The proposed system not only quantifies the amount of absorbed dose but also spatially maps the dose distribution using NMR imaging techniques. In this system the relaxation is enhanced due to the production of paramagnetic Fe^{2+} and Fe^{3+} in a Fricke dosimeter fashion. The increased concentration of paramagnetic molecules changed the proton relaxation rate linearly with dose. This technique too suffers due to relaxation properties being subject to factors other than paramagnetic concentration such as temperature and solvent effects.

1.2.3 Randall: Sequence Distribution and Tacticity

NMR research by polymer chemists quantified the sequence distributions and tacticity in polymers irradiated with kGy doses of ^{60}Co [60]. No attempt was made to evaluate their results with respect to absorbed dose although they did observe the amount of change was proportional to exposure. Their research was performed to simply observe structural changes produced by radiation interactions. High density polyethylene in the fluff form was used in these experiments. After irradiation, ^{13}C spectroscopy was used to identify the various structural units.

1.2.4 Pannin: Aliphatic peptides and amino acids

Several researchers have studied the effects of radiation on biologically significant molecules using various analytical techniques [48,23,11,12]. Recently Panin [55,56] reproduced earlier work by Barron but observed the changes using proton NMR. Using doses on the order of 1 to 10 MGy, he was able to record peaks corresponding to the presence of newly formed radiation induced molecules. He also reported a linear relationship between the amount of products formed and the absorbed dose. The purpose of this research however, was to simply identify the radiolytic products for this system of molecules. His work was performed on a 60 MHz continuous wave spectrometer consequently the characterization could have been significantly improved if more modern equipment was available.

1.3 Research Goals

The goal of this research project was to develop and characterize a dosimetry system which takes advantage of the specificity and quantitative ability of nuclear magnetic resonance (NMR) spectroscopy. This project relies on previously researched radiation chemical results to provide the initial framework on which to characterize a basic photon dosimetry system. We quantify the radiolytically produced formaldehyde in the irradiation of methyl alcohol and investigate the potential to quantify the ethylene glycol resonance. The methanol dosimetry system was characterized by standard dosimetric parameters including dose response, reproducibility, and temporal stability. Implementation of solvent suppression techniques was necessary to solve expected dynamic range problems and subsequently maximize the sensitivity of NMR in measuring low radiation doses. The results of this research project include an initial framework for an NMR based dosimetry system as well as the characterization of the initial system within the limitations of current technology. Research results also point to areas which limit this approach to high range dosimetry. Understanding the theoretical and technical limitations will suggest further research areas which may lead to improvement of this system.

Chapter 2

Background

This research project combines three distinct fields of science, radiation dosimetry, radiation chemistry, and NMR spectroscopy, to develop a novel method of quantifying the absorption of radiant energy. Radiation dosimetry as a science includes the fundamental principles of measuring a radiation effect as well as the basic requirements of a dose measuring system such as dose response, reproducibility, and temporal stability, and cavity theory. Since dosimetry systems are based on fundamental radiation interaction mechanisms, an understanding of these mechanisms is necessary in the interpretation of the experimental response of measurement systems. The study of radiation interactions specifically applied to molecular systems is founded in radiation chemistry. Analysis of the radiation induced interactions for this system is achieved by taking advantage of the quantitative ability of NMR spectroscopy. The limitations of this analytical tool must also be considered in the development of a dosimetry system.

A brief review of basic principles in each area should serve to acquaint specialists in a particular area to basics of the other two areas. An overview of fundamental principles also provides a background with which to evaluate the significance and limitations of this project.

2.1 General Characteristics of a Dosimeter

Following Attix [8], a dosimeter is defined as any device that is capable of providing a reading r that is a measure of absorbed dose D_g deposited in its *sensitive volume* V by ionizing radiation. Dosimetry includes energy absorbed in materials as well as personnel. Personnel dosimetry however, generally includes conversion factors that relate the absorbed energy measured using various methods to an equivalent amount of absorbed energy in tissue as well as conversion factors which take into consideration the biological effect of a given amount of deposited energy.

Most current dosimeter systems rely on ionization and excitation of atoms as a means of quantifying absorbed energy. Geiger-Mueller tubes, proportional counters, and ion chambers depend on quantification of ionization events to measure deposited energy. Solid state dosimeters such as thermoluminescent dosimeters (TLDs) and solid scintillators are based on excitation of electrons in the crystal structure. This deposited energy is either stored in metastable states, as in TLDs which can be thermally stimulated to deexcite with the emission of a measurable light signal, or the electrons deexcite immediately (as in NaI scintillators) emitting an amount of light proportional to the deposited energy. Calorimetry is a method of quantifying absorbed energy based on the thermal energy gained from the radiation interactions in the medium. Chemical dosimeters such as Fricke [30,31] systems use oxidation or reduction reactions produced by radiation interactions. Different analytical chemistry techniques have been used in the quantification of radiation induced chemical reactions.

The measurement of a radiation induced effect, such as ionization produced in a cavity, light output from energy stored in a thermoluminescent material, or radiolytic species produced in radiation chemical interactions, is only the first step in determining absorbed dose. Conversion relationships are necessary in all the above measurements to relate the reading r to absorbed dose. A potential advantage of chemical dosimetry systems in general is the simplicity with which its reading r , a measure of the quantity of radiolytically produced stable products, can be related to absorbed dose. An example of this advantage is found by considering cavity theory gaseous ionization chamber measurements, which must additionally include polarization-effect correction for in-phantom measurements [8]. Another advantage of chemical dosimeters using NMR as a measurement method compared to spectrophotometric measurements is the temperature dependent molar extinction coefficients which must be included in the dose expression required in the latter [64]. Although the NMR method has an analogous expression its spectroscopic resolution and temperature independence (at room temperature) provides a less complicated measurement result. It is this type of practical advantage in either experimental design or measurement system which suggest that the proposed system may have some definite advantages over existing systems.

The practical limitation for a radiation chemistry based dosimetry system is the high doses required to observe a given response, therefore the proposed system will be most applicable for high dose applications. Table 2.1 shows some common integrating dosimeters and their respective dose ranges. The proposed

MRD system will most closely apply to the same dose response region as the Fricke based system. We do not however, expect the dose range to be limited to the kGy region by saturation effects observed in the Fricke system.

Dosimeter	Dose Range
Photographic Dosimetry	0.25 mGy to 3 Gy
Chemical Dosimetry "Fricke"	4 Gy to 4 kGy
Thermocouple Calorimetry	> 10 Gy
Thermoluminescent Dosimetry	0.01 mGy to 10 Gy

Table 2.1: Common integrating dosimeters with respective dose range.

There are several factors which must be considered in determining the dose deposited in a given media. First, it is important to consider how the energy is being deposited in the detector volume, *i.e.* "cavity". Ionization chamber detectors can be divided into two groups, Bragg-Gray or Burlin, depending on the relationship between the range of charged particles produced and the detector cavity size. The important concept here is based on whether the walls of the detector produce or perturb the energy deposited in the detector sensitive volume. A full treatment of all the considerations may be found in Attix [8]. A practical solution for chemical dosimetry is to choose a detector cavity size greater than the range of the charged particles produced in order to reduce the effect of the walls. Under these conditions a dosimeter could be characterized in

a Burlin cavity treatment as:

$$\frac{\overline{D_{cavity}}}{D_{wall}} = d \times \overline{S_{wall}^{cavity}} (1 - d) \left(\frac{\overline{\mu_{en}}}{\rho} \right)_{cavity}^{wall}, \quad (2.1)$$

where $\overline{D_{cavity}}$ is the average dose to the cavity material such as a chemical dosimeter solution, D_{wall} is the dose to the cavity wall, $\overline{S_{wall}^{cavity}}$ is the stopping power ratio between the wall and the cavity, $\left(\frac{\overline{\mu_{en}}}{\rho} \right)_{cavity}^{wall}$ is the ratio of energy absorption coefficients, and d is a parameter related to the cavity size. For an infinite cavity size the parameter d goes to zero. A further simplification in these considerations is provided by the use of wall material which mimics the cavity detector characteristics in mass stopping power and energy absorption coefficients. Although these parameters are energy dependent, the parameter values change very slowly for Compton dominant processes found in MeV photon irradiations.

Characterization is then made to equate the measurement obtained in a given detector to the amount of energy that would be deposited if the measurement could be made in a tissue like media. Using a gas filled ionization chamber example, at charged particle equilibrium a straightforward conversion factor is applied,

$$D_{tissue} = D_{gas} \left(\frac{\overline{\mu_{en}}}{\rho} \right)_{gas}^{tissue}. \quad (2.2)$$

Alternatively, some ionization detectors are constructed of tissue equivalent walls and filled with tissue equivalent gases in order to better mimic the physical environment and circumvent this conversion step. Otherwise conversion factors have been established in tables and may be implemented directly for the various detector systems used.

The third step is to relate the absorbed dose deposited to a biologically relevant effect. The application of a conversion factor Q (quality factors) is applied to relate absorbed dose to the overall biological effect. This factor is based on the given type and energy of incident radiation and subsequently yields a dose equivalent parameter H ,

$$H = D\bar{Q}N, \quad (2.3)$$

where H is in units of Joules/kg or Sieverts, Q is the conversion factor, and N encompasses all other dose modifying factors. Q values are based on studies of various radiobiological endpoints such as tumour response, cell survival curves, and chromosomal aberrations as well as accidents involving radiation and atomic bomb survivor studies. Relative values are evaluated from the biological effectiveness of a known absorbed dose of one radiation type and energy (250 KVP x-rays) to the radiation type and energy studied. For photon and electron radiations the dose modifying factor is close to one and is not a significant effect. However, for heavy charged particles and neutrons the relative biological effect (RBE) can be as high as 20. Dose modifying factors Q are related to the spatial deposition of energy described by linear energy transfer (LET). The radiation chemical and radiobiological processes involved are quite complex and the only tractable solution at present is the application of this type of empirical conversion factor.

The purpose of a dosimeter system is to quantify the amount of absorbed energy and in order to perform this task several dosimetric characteristics must be considered. Several of these include:

1. reproducibility and accuracy
2. temporal stability
3. energy dependence (LET)
4. dose response
5. dose range
6. dose rate dependence.

An excellent review of the fundamental characteristics of a dosimetry system may be found in the text by Attix [8]. In developing a new dosimeter system experiments evaluating these fundamental characteristics are necessary to determine the inherent limitations of the proposed system.

Reproducibility and accuracy are two related characteristics of a dosimeter system. Reproducibility is defined as the precision of a dosimeter response given a series of equivalent radiation exposures. Variability in the response may be affected by the physical system such as the radiation chemical processes or by the method of quantification. Accuracy is a measure of how the dosimeter response coincides with the actual experimental exposure. This can be assessed by comparing the dosimeter response to the response of a detector in a known radiation field. It is important that the accuracy and reproducibility of the dose response be well behaved under a variety of environmental conditions.

Temporal stability is the ability of a dosimeter to maintain its response either before or after irradiation. Ideal dosimeter temporal stability requires that the

dosimeter would maintain a constant sensitivity and low background reading prior to radiation exposure. After exposure the response should remain accurate and reproducible independent of the time measured post irradiation. Temporal stability is assessed by monitoring dosimeter response over extended periods of time pre- and post-exposure. Chemical dosimeters based on the production and measurement of free radicals are particularly susceptible to decreased temporal stability due to the reactive nature of unpaired electronic configurations.

Energy dependence relates a dosimeter's response exposed to various types of radiation over a range of energies. Energy dependence is most fundamentally based on the linear energy transfer (LET)-sensitive mechanisms of the dosimeter system. Useful information from a dosimeter's measured response requires its energy dependence transfer characteristic be well known. This is also necessary to apply energy dependent conversion factors.

Dose response is the measured response of the dosimeter system as a function of absorbed energy. Although it is not essential to have a linear dose response, non-linear relationships suggest more complicated physical or instrumental processes which may reduce accuracy or reproducibility. Dose range is the useful upper and lower limits of the detector system's dose response. The upper limit of dose range can be imposed by non-linear response from saturation effects. Two factors that determine the lower limit of dose range are background dosimeter response and the sensitivity or dynamic range of the instrumentation.

Dose rate independence is the ability of a dosimeter to provide equivalent responses for measured absorbed energies acquired at different exposure rates.

A desirable characteristic would have a dose response independent of the rate at which the dose is delivered. Most chemical dosimeter systems will have some dose rate dependence if they also have an LET dependent response. This is due to higher dose rates having a similar characteristic to high spatial rates of energy deposition.

2.2 Chemical Dosimetry

Chemical dosimetry is a method of quantifying absorbed dose based on radiation interactions at the molecular level. Since radiation energies in health and medical physics are usually on the order of keV to MeV, and since bond energies for molecules are typically a few eV, radiation interactions at the molecular level are capable of not only ionization and excitation but complete fractionation of the molecular structure. Consequently, there are several quantifiable radiation interaction processes which may be exploited to measure absorbed energy. The basic equation for calculating the mean absorbed dose $\bar{D}$ in a chemical dosimeter system based on radiation interactions at the molecular level is;

$$\bar{D} = \frac{\Delta M}{\rho G(X)}, \quad (2.4)$$

where $G(X)$ is the radiation chemical yield in moles of product per Joule of energy deposited, ρ is the solution density in *kg/liter*, and ΔM is the change in molar concentration (mole/liter) of the product X . $G(X)$ has historically been represented as "G-value" in units of molecules produced/100eV where $G(X)$ can be obtained by multiplication of the G-value by 1.037×10^{-7} .

There are several practical advantages to solution-type chemical dosimeters which include the ability to be formed into any desired geometry, applicability to high dose ranges, and measurement of relatively non-penetrating radiations [8]. Chemical dosimeters may also be solidified in a gel matrix [33] maintaining a spatial dependence useful for determining dose profiles. Other potential advantages in using chemical dosimeter systems stem from the use of solvents composed of tissue like-materials, and the choice of radiochemical reactions which can mimic the LET response of biological tissues. Several different chemical dosimeters have been used, each of which is based on a different radiation chemistry reaction. The following sections describe some of these systems, principles of basic radiochemistry, and the specific radiochemistry of the methanol molecule chosen for this research.

2.2.1 Previous Chemical Dosimeter Systems

Chemical dosimeters are based on specific radiation induced chemical interactions which determine the basic properties of the system and the analytical methods required to quantify absorbed energy. A natural grouping of these systems is based on their respective radiation interactions

The most common chemical dosimeter is the Fricke aqueous ferrous sulfate dosimeter [31] based on the oxidation reaction of ferrous sulfate. Another oxidation reaction used in dosimetry is based on the production of gluconic and glucuronic acid in the radiolysis of glucose solutions [62]. The high dose limitation of the Fricke oxidation system was imposed by oxygen consumption, so a

similar system based on reduction reactions using ceric sulfate ($Ce^{4+} \rightleftharpoons Ce^{3+}$) was investigated [31]. This system is not dependent on oxygen content and may be used to measure doses on the order of 1 MGy.

The basis of the alanine system [37] is the production and trapping of free radicals. Ordinarily free radicals rapidly undergo further chemical interactions due to the highly reactive nature of unpaired electrons. It is this unpaired electron configuration which gives rise to the signal generated in an ESR spectrometer for the quantification of the absorbed dose.

Fractionation by free radicals' attack on polyacrylamide has also been used as a chemical reaction method for dosimetry [16]. This reaction causes long chain polymers to be reduced in molecular weight with a corresponding decrease in viscosity of the solution form. Other similar fractionation reactions include the radiolysis of sugar solutions using neutron radiations [68] and NO_2 yields from both high and low LET radiation of $NaNO_3$ [69].

2.2.2 Radiation Chemistry

The underlying basic science of all chemical dosimeters is radiation chemistry. Radiation chemistry has been defined by Spinks [64] as the study of the chemical effects produced in a system by the absorption of ionizing radiation. Interactions in radiation chemistry involve mechanisms of imparting energy to molecules in the system and the various modes of deexcitation for the excited molecules. Energy imparted to molecules induce radiolytic reactions which produce excited molecules, ions, and free radicals. These undergo two types of deexcitation pro-

cesses, unimolecular and bimolecular, with considerable overlap in specific de-excitation processes. For example, an excited molecule may deexcite producing ions; these ions may interact with other molecules to form free radicals; the free radicals may recombine to form excited molecules. All products share similar types of unimolecular reactions such as non-radiative energy transfer or dissociation (fragmentation). They also have similar types of bimolecular reactions like recombination or addition reactions.

Energy Deposition Processes

Two aspects of energy absorption in chemical systems are the probability of a specific radiation interaction and the amount of energy transferred in that interaction. The probability of a given ionization or excitation interaction depends not only on the type of reaction but also the amount of available energy. The amount of energy transferred will determine the probability and type of deexcitation process. Deexcitation processes for each species are described in respective sections.

In general molecules, like atoms, exist in ground states and excited states which can be characterized by quantum mechanics. Energy is transferred through charged particle coulombic interactions, direct collision with uncharged particles, or absorption interactions with photon radiation. These initial processes are equivalent to atomic interactions. The difference between atomic and molecular energy transfer processes is the greater number of excited states available for molecular interactions. Molecules have both electronic and vibrational excited

Figure 2.1: Ionization probability curve for He^+ from Hickam

states. A quantum mechanical description has been used for modeling the absorption spectrum for simple diatomic molecules based on the Franck-Condon principle [9]. These mathematical descriptions provide theoretical models which help in the understanding of radiation induced chemical processes.

Experimental research has resulted in models which show how ionization interaction cross sections also depend on the energy of the primary radiation. A simple ionization model is given by Morrison [53] for energies close to the threshold (E_0) of the reaction:

$$Q(E) \sim (E - E_0)^{N-1}. \quad (2.5)$$

This model predicts the cross section dependencies for the ionization of atoms as shown by Hickam [39] where $Q(E)$ is the probability of a reaction with an excess energy of $(E - E_0)$ and N defining the number of electrons removed for the target atom. Figure 2.1 shows the increase in the production of atomic ions as a function of electron impact energy following his model.

The amount of energy transferred to product species such as free radicals,

Figure 2.2: Potential-energy curves for a diatomic molecule in its ground state and in an electronically excited state from Spinks.

ions, and ion molecules also governs respective chemical reaction probabilities. A cross section model was proposed by Maier [49] to predict dissociative ionization produced by ion impact. He demonstrated that the probability of inducing reactions with ions is linear in energy for some systems and supralinear in others. Reaction cross sections are also a function of a threshold energy for the particular reaction. This result may be important when comparing the effects of different LET radiations.

Excited Molecules

An excited molecule is one in which the electrons are displaced to higher energy states due to the absorption of radiant energy. Diagrammatically higher energy states are described by vertically displaced potential energy curves. Figure 2.2 from Spinks [64] shows a representative curve for a diatomic molecule. The

bond dissociation energy is represented by the vertical distance between the excited state potential energy curve and the minimum in the ground state curve. Within the higher energy electronic excited states are vibrational energy levels. Transitions to lower vibrational energy levels are achieved through collisions with other molecules. According to Spinks [64] the Franck-Condon principle states that the most probable transitions between different electronic energy states are those which can be represented as a vertical line on a potential energy diagram. There are several mechanisms by which the excited molecule can return to the ground state. These mechanisms are grouped into unimolecular or bimolecular processes.

Fluorescence and phosphorescence are unimolecular deexcitation mechanisms produced as the result of radiative conversion to the ground state. Fluorescence is the decay of singlet excited states to singlet ground states typically with a lifetime on the order of 10^{-13} sec. Phosphorescence is the decay from excited triplet states. A triplet state differs from a singlet state by having the electron spin parallel to the ground state electron. Consequently conversion is forbidden and the lifetime of the transition is on the order of 10^{-3} sec. Triplet states can be produced by intersystem crossing of singlet states or may be produced directly by low velocity charged particles. Slow fluorescence, 10^{-8} sec, is due to transitions through triplet states by intersystem crossings to singlet states.

Non-radiative energy transfer is the transfer of energy from the excited state of one molecule to the ground state of another molecule. This process excites the second molecule to a higher energy level and can be accomplished through direct

molecular collisions, dipole-dipole resonance energy transfer, or the creation of excitons in an ordered array of molecules. An example of direct collision processes occurs in liquid scintillators.

Dissociation is a common type of unimolecular process whereby the excited molecule is broken into different fragments. The minimum energy for a dissociation process is the energy of the bond involved. Dissociation may produce either radicals, ions or stable fragments. If a covalent bond is broken two free radicals are produced. Irradiation in condensed phase increases the probability that the dissociation products would immediately recombine before the products can escape or diffuse through the medium. The increased probability of immediate recombination as a function of increased mass of target molecules is known as the *cage effect* [64]. This is due to the increased time fragments spent in proximity to each other. Cage effects are less likely to occur for irradiation in the gas phase. Another characteristic of dissociation is that the bond most likely to break is not necessarily the bond at which the absorption occurred; it is usually the bond with the lowest energy.

Much of the information on dissociation or fractionation processes in excited molecules has followed the development of mass spectrometry. This technique is based on the fractionation of molecules by low energy ionizing radiation. Mass spectrometry uses electric and magnetic fields to separate charged molecular fragments into a spectrum depending on the mass of the fragment.

Several models have been proposed to explain the fractionation patterns observed in mass spectrometry. While the Franck-Condon model has been used suc-

cessfully to determine the dissociation patterns for simple diatomic molecules, extension to more complex molecules would be too difficult. Alternative statistical methods have been developed in order to predict these more complex fractionation patterns. The quasi-equilibrium theory (QET) was proposed by Rosenstock [61] to predict patterns for more complex molecules. This model was able to predict a pattern for propane which agrees with experimental data. Although this theory requires a large number of parameters and approximations, it does provide functional dependencies. The QET is a rate equation given by:

$$K(E) = \frac{S W \ddagger (E - \epsilon_0)}{h \rho(E)}. \quad (2.6)$$

Where in the notation of Rosenstock, $K(E)$ is the reaction rate in sec^{-1} , h is Planck's constant, ϵ_0 is the activation energy, $W \ddagger (E - \epsilon_0)$ is the number of states of the activated complex, E is the internal energy, $\rho(E)$ is the number of states with energy between E and $E + dE$, and S is the number of identical reactions. From this expression it is possible to determine the probabilities for a given reaction to occur if the parameters for that state are defined.

Other experimental mass spectrometry research demonstrates that activation energies are related to the bond strengths. Bond strengths have been measured using mass spectrometers capable of different incident particle energies [43]. Figure 2.3 shows experimentally how fractionation probabilities are a function of incident electron energies. It is clear from these graphs that the formation of some dissociation products do not occur until a threshold energy is reached, and that the production increases with increasing radiation energies.

The second group of reactions are classed as bimolecular reactions since they

Figure 2.3: Effect of electron energy on the mass spectrum of methylal from Kiser.

involve reactions between two molecules. These reactions are more likely for irradiations in the condensed phase and are concentration dependent. Bimolecular reactions also depend on the spatial distribution of specific excited molecules and therefore may be responsible for LET effects. The spatial density of ionization and excitation events may be grouped into *spurs*, *blobs*, or *tracks* which represent an amount of expended energy less than 100eV, 100 to 500eV, and 500 to 5000eV, respectively. Densely ionizing radiations are characterized by spurs which overlap; this is referred to as *columnar ionization*.

One kind of bimolecular interaction is simple electron transfer between two molecules. Examples of these interactions are reduction interactions of metal ions such as Fe^{3+} to Fe^{2+} . A second type of reaction, hydrogen abstraction, involves the stripping off of a proton from a molecule by an excited molecule.

This will produce two highly reactive free radicals which will undergo further chemical reactions.

Addition reactions are characterized by an excited molecule which breaks into the structure of another molecule to form a new molecule. An example of this type reaction is the formation of sulfinic acid by excited sulfur dioxide combining with aliphatic hydrocarbons. Stern-Volmer reactions are produced when two excited molecules combine to form two completely different molecules. This occurs more frequently in high LET radiation interactions where there is a higher probability for two excited molecules to be in close proximity. The production of hydrogen peroxide and hydrogen gas from two excited water molecules is an example of a Stern-Volmer reaction.

Ions

An ion is an atom or molecule which through radiation interaction has had one or more of its electrons ejected [64]. Ions may be produced in a ground state or excited state, although the ionization process nearly always imparts excess energy to raise the ionized molecule to a higher vibrational energy or electronic energy state. The molecular ion, like excited molecules, may deexcite by either unimolecular or bimolecular interactions. Ion recombination and dissociation are unimolecular deexcitation mechanisms. Charge transfer, ion-molecule interactions, and electron addition reactions are bimolecular processes.

Ion recombination is the joining of a molecular ion and a free electron to form a neutral molecule. Energetic electrons are produced by radiation interactions

used to create the molecular ion. The electron must lose much of its kinetic energy before it can recombine. The new molecule formed in recombination will likely be in an excited state and subsequently undergo one of the previously described excited molecule deexcitation interactions.

Ions in an excited state may also dissociate in a manner similar to excited molecules. As with the previously described dissociation processes the fractionation pattern will depend on the bond energies involved and the amount of excitation energy available. Unlike its excited molecule counterpart, one of the fragments, usually the larger, will carry a positive charge. The charged fragment will then undergo further deexcitation.

Charge transfer is a bimolecular mechanism characterized by the stripping of an electron from a stable molecule by a molecular ion. This process is energetically possible if the ionization potential of the ion is greater than that of the neutral molecule. The probability of this reaction is greater when the two ionization potentials are similar. In charge transfer reactions the newly formed ion must undergo some other interaction.

An ion-molecule reaction is any reaction between an ion and neutral molecule. There are many potential reactions between these two species. The cross sections for ion-molecule reactions are derived from classical impact parameter formulations and can be described as:

$$\sigma(v) = \frac{\pi}{v_0} \left(\frac{4e^2\alpha}{\mu} \right)^{\frac{1}{2}} \quad (2.7)$$

Where α is the polarizability of the neutral particle, e is the electronic charge, μ is the reduced mass, and v_0 is the velocity. This expression treats particles

as energetic point charges which subsequently induce dipole interactions. The reaction cross section is a function of the kinetic energy of the reactant molecules. As the energy of the molecules is increased the cross section for specific reactions decreases [46].

Electron addition is the process of forming a negative ion by the capture of a thermal electron. Since there is no method of dissipating excess energy, electron capture can only occur at discrete energy levels corresponding to specific excited states of the negative ion.

Free Radicals

A free radical is an atom or molecule with one or more electrons removed. Free radicals differ from ions in that the loss of their electrons results in an unpaired electron configuration. This causes the atom or molecule to be very reactive. A molecule with two unpaired electrons is called a biradical. A free radical may or may not be in a charged state. Free radicals may also be created in dissociation processes of excited molecules, breaking of covalent bonds induced by ultrasonic mechanical stress, electrolysis, photolysis, oxidation-reduction reactions, and by high temperatures. Due to the highly reactive unpaired electrons, free radicals have inherently low temporal stability. Some radicals are more stable than others due to their molecular structure. Stability can also be induced by suspending the radical in a non-diffusible matrix. This decreases the interaction probability with other molecules. Free radicals also undergo unimolecular and bimolecular processes.

There are two types of unimolecular processes for free radicals. The radical can undergo a rearrangement of its molecular structure to form a more stable state. Rearrangement molecules are still radicals with an unpaired electron but the free electron is in a position where it has limited access to other molecular interactions. Dissociation is another unimolecular process that produces a stable molecule and a smaller free radical fragment. The smaller fragment may then undergo one of several deexcitation processes.

Addition is a bimolecular process where a radical simply attaches to an unsaturated compound. This may be a simple halogenation step or a chaining process of free radical species, referred to as polymerization. Abstraction is a process where free radicals attack saturated hydrocarbons. The radical picks up the necessary electron along with one or more atoms to form a stable molecule. This leaves the target molecule as a more stable radical.

Another class of bimolecular interactions is the free-radical destroying interactions. These produce stable molecules with no subsequent product radicals. The simplest form is recombination of two free radicals. These processes occur very fast due to the reactive nature of the unpaired electron configuration. Redissociation is likely if the energy liberated in the process is not quickly dissipated. Recombination in the condensed phase is more likely to dissipate energy quickly through collision processes, and therefore the combined radicals are less likely to redissociate. Electron transfer is another mechanism by which free radicals can be destroyed. An example is the reduction of iron Fe^{2+} to Fe^{3+} by a hydroxyl radical.

2.2.3 Radiation Chemistry of Methanol

Two criteria for selecting a suitable molecular system for this dosimetry research are: (1) how it responds to radiation interactions and (2) how amenable this response is to NMR analysis. Methyl alcohol was chosen for this preliminary research for its LET-dependent radiation response, the simple NMR spectrum of its radiolysis products, and the considerable research available on the formation mechanisms of its radiolysis products [2,13,22,38,52,64].

Preliminary information on the radiation response of different molecules is available in mass spectrum analysis. Mass spectral data for methanol provide an initial indication of the various breakdown products and their respective relative intensities. Published mass spectral data from NBS are shown in Table 2.2.

These cracking patterns, however are not a precise indication of all products formed or their absolute probabilities since mass spectral techniques involve ionization of the solute in the gas phase. The radiation environment for this chemical dosimeter system is in a solution form which will allow for significant chemical recombination reactions to occur.

The radiolysis of methanol has been studied by several groups using different energy photons [38], LETs [52], and added chemical agents [2,13,22]. Their research was undertaken to understand the mechanism of formation of the various radiolytic products. McDonell and Gordon [52] show that four products formed from the γ -ray radiolysis of the pure form are hydrogen, carbon monoxide, ethylene glycol, and formaldehyde. They determined the G values for these radiolysis products and demonstrated that these yields were dependent on the LET of the

incident radiation. G values were also affected by pH and the presence of free radical scavengers [64].

Formaldehyde ($HCHO$ or CH_2O) is produced by three different reactions and is the major dissociation product of photolytically excited methanol molecules in the vapor phase [58] where the reaction is described by:

Formaldehyde is also produced in several different ion-molecule reactions [46], such as:

and

In addition formaldehyde is produced by free radical interactions. First the free radical $\cdot CH_2OH$ is produced by

which undergoes further free radical interactions producing HCHO:

and

Ethylene glycol is produced in the bimolecular free radical interaction:

Consequently any reaction which competes for free radicals will affect the production of ethylene glycol. These production mechanisms are verified by the increase in formaldehyde production and decrease in glycol with the introduction of radical scavengers. Radical scavengers such as oxygen or ferric salts interact with the free radical $\cdot CH_2OH$ to produce formaldehyde at the expense of the otherwise competing bimolecular reactions responsible for glycol production. A scavenger reaction example includes:

The addition of ferric sulfate as a scavenger increases the G value for formaldehyde production from 2.25 to 8.4 and decreases the glycol G value to 0.2 [2].

Oxygen also acts to perturb the relative amounts of formaldehyde and glycol. Oxygen, like Fe^{3+} , acts like a free radical scavenger and therefore increases formaldehyde at the expense of glycol [38]. The radical effect is dependent on the amount of dissolved oxygen in the sample but stabilizes at levels greater than 10^{-3} mole/liter [22]. Its reactions include the scavenging reaction:

and the radical reactions,

The effect of increased pH is to increase the G value for all products by a small fraction. This is due to the scavenging of solvated electrons by hydrogen ions [64].

Figure 2.4: G Values vs. LET in units of $eV/\text{\AA}$ for formaldehyde and ethylene glycol production from Lias and Ausloos (note CH_2O at $10 eV/\text{\AA}$ or 100 keV/micron).

LET Effects

Radiolysis research with methanol indicates that the G value for the production of formaldehyde increases with LET while the production of ethylene glycol decreases. Lias and Ausloos [46] have graphed the LET dependence exhibited in the radiolysis of methanol which is reproduced in Figure 2.4.

According to Spinks [64] the LET dependence of products formed is explained by mechanisms similar to the radiolysis products observed for aqueous solutions. LET dependence is based on an increase in intraspur reactions at the expense of radical escape from the spur. The production of molecules via bimolecular radical reactions such as ethylene glycol in the methanol system will subsequently decrease. Two such intraspur radical interactions which produce formaldehyde are:

These results are consistent with other radical scavenging experiments which also showed a decrease in bimolecular interaction products.

2.3 NMR as an Analytical Tool

A goal of this project is to investigate the use of 1H nuclear magnetic resonance (NMR) as a tool for radiation research. Dosimetry is a specific application where quantitative NMR can play a role. The use of NMR as a means of quantifying the results of radiation induced interactions in molecular systems has several advantages over other analytical methods used in chemical dosimetry such as:

- ease of use;
- non-destructive methodology;
- minimum number of procedural steps;
- spectral resolution with subsequent molecular specificity;

Quantitative NMR techniques are possible due to the linear relationship between the number of magnetically equivalent nuclei resonating at a given frequency in a heterogeneous sample and the integrated area of the resulting resonance line in the frequency spectrum. It is this relationship that allows quantification of the amount of radiant energy absorbed through the determination of the integrated peak area of a radiation induced product resonance. Work by Panin [55] investigating the effects of radiation on molecular structure verified that the

integration of the spectral signals obtained from the different product molecules formed was linearly proportional to absorbed dose in the 1 to 10 MGy dose range. His work suggested the potential for using NMR as a high range dosimeter system. In order to use this relationship however it is important to consider some of the fundamental limitations of NMR as a tool. This section includes topics on the basic physics of NMR, fundamental physical limitations of the system, and technological limitations. The information presented will provide an understanding of the potential and limitations of the NMR methodology.

2.3.1 Basic Physics of NMR

In order to exploit NMR as an effective quantification tool it is necessary to understand some of the underlying physics of NMR. This allows one to interpret the experimental results as well as develop special NMR techniques to enhance the quantitative potential of this tool. NMR signals originate from specific populations of nuclei which possess an intrinsic magnetic moment. Each nuclear species has a characteristic resonant frequency depending on its gyromagnetic ratio, the static magnetic field strength, its local magnetic environment, and through bond coupling interactions with other nuclei. The Larmor equation:

$$\omega_o = \gamma B_o, \quad (2.21)$$

describes the basic resonant frequency dependence on field strength B_o where ω_o is the Larmor frequency in radians/sec, and γ is the gyromagnetic ratio. For example, given a homogeneous 6.34 T static magnetic field the resonant or Larmor frequency for protons 1H which have a $\frac{\gamma}{2\pi}$ of 42.58 MHz/T will be 270

MHz.

The resonant frequencies of individual nuclei are also affected by local magnetic fields produced by the molecular electronic cloud surrounding the atom. This locally generated magnetic field shields the specific nucleus from the imposed magnetic field and therefore causes it to resonate at a different frequency given by,

$$\omega_o = \gamma B_o(1.0 - \sigma), \quad (2.22)$$

where σ is referred to as a shielding constant. It is this shift in the resonant frequency by the specific chemical configuration (chemical shift) which allows the identification and quantification of different molecular species in a heterogeneous sample.

Spectral resonances may also be split by spin-spin coupling of adjacent nuclei in a given molecule. According to Yoder [70] this can be explained by a Fermi contact mechanism whereby the atomic electrons in the molecule act to perturb the energy levels of adjacent nuclei [70]. Coupling of nuclei can extend over multiple bonds causing energy levels to be perturbed by the presence of several different nuclei within a given molecule. This splitting must be considered in the quantification of the resonances since the integration of the resonance must include all peaks in the coupled multiplet.

Another consideration in the interpretation of NMR spectra are dynamic processes [70]. Intra- and intermolecular exchange between nuclei may broaden spectral lines, shift the resonant frequencies or collapse a multiplet structure. The degree of the effect is determined by the rate of exchange and is usually a

function of the temperature of the sample.

2.3.2 Physical Limitations of NMR

The NMR experiment involves two steps: (a) the establishment of a differential spin state population by the immersion of the sample in a uniform magnetic field, and (b) the perturbation and detection of the equilibrium population difference. The perturbation of the NMR system is accomplished by input of magnetic field energy produced by antennae at a specific radiofrequency for the population of interest. Signal is detected due to the relaxation of this coherent population back to equilibrium. Since NMR is essentially a thermodynamic process the fundamental physical relationships which determine detectability involve the Boltzmann distribution for spin populations. The amount of signal depends on the amount of magnetization produced in the sample and can be described after Abragam [1] as:

$$M = \frac{N\gamma^2\hbar^2 I(I+1)}{3kT} H_o \quad (2.23)$$

where N is the number of spins, I is the spin quantum number, T is the temperature, and H_o is the static magnetic field strength. This shows physical limitations of the signal strength based on the sample size, the main field strength, and the γ of the specific nuclei.

Another parameter in the detected signal strength of the NMR experiment is relaxation. A definition of longitudinal or spin lattice relaxation T_1 by Farrar [28] is the average time required for a spin transition from one state to another. Signals from an NMR experiment come from these spin transitions; therefore if

the rate at which transitions occur is low very little signal would be expected in a given time interval. Another signal modifying relaxation process is spin-spin relaxation T_2 . T_2 can be understood as a rate constant for loss of phase coherence in a spin population. The phenomenological Bloch equations [15] includes these relaxation effects in order to model the magnetization in an NMR experiment.

$$\dot{M}_x - \gamma(M_y H_z - M_z H_y) + \frac{1}{T_2} M_x = 0 \quad (2.24)$$

$$\dot{M}_y - \gamma(M_z H_x - M_x H_z) + \frac{1}{T_2} M_y = 0 \quad (2.25)$$

$$\dot{M}_z - \gamma(M_x H_y - M_y H_x) + \frac{1}{T_1} M_z = \frac{1}{T_1} M_0 \quad (2.26)$$

If these relaxation processes occur too fast the net magnetization will average to zero (for transverse relaxation processes) or relax back along the z axis (for longitudinal relaxation) with no magnetization left in the x-y plane. Consequently there would be no signal available for the receiver electronics, or the signal strength detected may be significantly decreased by these relaxation processes.

2.3.3 Technological Limitations of NMR

Using the equations presented above one can anticipate sources of technological limitation in obtaining maximum sample signal. Maximum signal will require high field strengths, good relaxation properties, and efficient coupling of energy from the sample to the rf probe containing the transmit and receiver electronics. In addition the latter must be capable of high signal amplification with a very low noise figure.

Choice of the proper static magnetic field strength B_0 is of main concern in NMR spectroscopy since the field strength determines sensitivity, relative peak positions, and spectral resolution. The work by Panin was performed with a 60 MHz continuous wave spectrometer and required doses on the order of MGy to demonstrate a radiation induced chemical effect. A reduction in the magnitude of this exposure is possible by analyzing samples with a higher static magnetic field to improve sensitivity. Assessing the increased potential of using higher B_0 -field magnets requires a quantitative measure of spectrometer performance. The signal-to-noise ratio (SNR) is one method of quantifying sensitivity. Edelstein [26] derived a simple expression for the signal received as a function of B_0 which shows that signal is proportional to B_0^2 . A more complete description is given by Hoult and Richards [41] as:

$$SNR = \frac{K(B_1)_{xy} V_s N \gamma \hbar^2 I(I+1)}{7.12 k T_s} \left(\frac{p}{F k T_c l \zeta \Delta f} \right)^{1/2} \frac{\omega_0^{7/4}}{[\mu \mu_0 \rho(T_c)]^{1/4}} \quad (2.27)$$

Where $K(B_1)$ is the effective field in the sample from unit current in the receiver coil, p is the perimeter of the conductor, l is the length of the conductor, V_s is the sample volume, N is the number of spins at resonance, γ is the magnetogyric ratio, I is the quantum spin, k is Boltzmann's constant, T_s is the sample temperature, F is the noise figure of the preamp, T_c is the coil temperature, ζ is the *proximity* factor, Δf is the receiver bandwidth, μ_0 is the permeability of free space, μ is the permeability of the wire, $\rho(T_c)$ is the temperature dependent resistivity of the coil material, and ω_0 is the Larmor angular frequency.

Considering the $\omega_0^{7/4}$ functional dependence for the radiolysis experiments

performed by Panin it is possible to estimate a reduction in the required exposure by a factor of approximately 40 if a 500 MHz (11.7 T B_0) spectrometer is used in place of the 60 MHz spectrometer used in his work.

The other advantage using a higher-field spectrometer is increased spectral resolution where there is the potential of overlapping peaks. Since the chemical shift frequency is field-strength dependent, the absolute frequencies between peaks will increase. However, since the splitting of resonances is field-strength independent, the relative positions of these peaks will change as a function of field strength.

Two limitations for quantification of resonance peaks in a NMR experiment are spectrometer dynamic range and receiver gain. Dynamic range has been defined as the ratio of the largest to the smallest signal in a given data set [32]. A large dynamic range is necessary for detecting low concentration byproduct signal resonances in the presence of larger solvent proton resonances. The analog-to-digital converter (ADC) word length is another instrumental parameter which limits the spectrometer's dynamic range. The criterion for acceptable ADC word length is the ability to digitize the inherent system noise in the presence of maximum expected NMR signal. Dynamic range problems arise when the solvent signal is so large that the receiver gain must be set very low to avoid saturating or overflowing the ADC. The technical solution to this problem is to use a larger ADC having more bits and thus dynamic range. However, alternative physical solutions are possible which reduce the amplitude of solvent resonances. If the solvent resonances can be suppressed the next limitation will be imposed by the

receiver gain. In solution spectroscopy the dominant noise source is due to the electronics, therefore receiver electronics with better gain characteristics and low noise figure will improve the detectability of low concentration signals.

2.3.4 Aspects of Quantitative NMR

Methods of quantifying resonances determine the upper and lower limits of detectability as well as reproducibility. Quantification includes detection and processing of the raw data, integration procedures, and correction for spectrometer variability. Simple Fourier transforms are used to convert the measured voltage versus time data to an amplitude versus frequency spectrum. Although there are several methods of pre-processing data for resolution or signal-to-noise enhancement, these methods were not used for this initial work. Integration of the resonance peaks is accomplished by first subtracting out the baseline contribution and then implementing an analytical integration procedure. Correction for spectrometer variability is accomplished using normalization procedures similar to those found in other quantitative NMR works.

According to Linden [47] the data collection parameters for an optimum signal-to-noise ratio for a given resonance depend on the rate at which the free induction signal (FID) decays (T_2^*) and the data acquisition time. The maximum SNR is obtained when the data acquisition period is equal to $3 \times T_2^*$. *Apodisation* of the raw data is a processing technique to improve the signal-to-noise ratio of peaks in a spectrum at the expense of resolution [47]. The method is based on weighting more strongly the earlier portion of the FID data where the predomi-

nant signal is due to the resonating nuclei and then decrease the weighting factor where the predominant signal is due to the noise. This is accomplished using a decaying exponential filter function. This filter increases the line width but preserves the Lorentzian line shape. The optimum exponential decay parameter for the filter function is the experimentally determined decay constant. After the filter function is applied the temporal data are padded with trailing zero values (zero filled) to improve spectral digital resolution and then Fourier transformed to yield the frequency data.

Processing of the raw data may also be performed using some of the recently proposed spectral estimation methods. Several research groups are investigating the use of alternative spectral estimation techniques to improve both the SNR and reproducibility above what can be obtained with the standard Fourier Transform methods. These alternative methods of transforming temporal to frequency data include maximum entropy methods [67] ; autoregressive techniques [50]; and linear prediction [10]; and Bayesian spectral analysis [18]. A limitation with these techniques is the computationally intense nature of the iterative algorithms used.

The number of product molecules formed can be quantified by measuring either the resonance peak height or peak area. A problem with relying on peak height as a reproducible measure is its variation as a function of magnet shimming. Inhomogeneous magnetic fields introduce line broadening which reduces the peak height. However, the peak areas remain constant through different degrees of magnet homogeneity. Consequently, peak integration will produce more

reproducible integrated peak area (IPA) values of the measured products.

Determining the correct fitting parameters for subsequent analytical integration requires correcting for the fluctuating baseline upon which the peaks are superimposed. Non-uniform baselines in a spectrum are produced by large adjacent resonances and/or instrumental parameters, and can be corrected using a post-processing technique. A straightforward method is to digitize the data beyond the peak. From data acquired at the extremes of the data set, correction coefficients corresponding to a constant and trend in the baseline are determined and subtracted from the peak data.

Integration of the peak is accomplished by first fitting the raw data to a Lorentzian line shape to determine the best fit parameters for the function:

$$f(x) = A * \frac{1/t_2^*}{(mean - x)^2 + (1/t_2^*)^2}. \quad (2.28)$$

The fitting routine used is based on the non-linear CURFIT routine by Bevington [14]. This function is then analytically integrated to determine the peak integral value.

In order to reduce the variability of peak integration caused by both sample spectrometer drift and electronic instability, normalization techniques are typically implemented. The technique Panin used to demonstrate the linear dependence of peak integrals upon absorbed dose was based on integration values obtained for the ratio of an individual peak relative to an integration of the total spectrum. Using this method Panin was able to remove machine variations between samples which demonstrate that the amount of product formed is proportional to the total absorbed dose. A more appropriate solution for this type

of measurement is the implementation of an internal standard reference peak which is used to normalize the data. Since spectrometer variability is consistent for all measured peaks, this normalization technique will correct for instrumental drift.

An alternative method of improving the dynamic range of the spectrometer which requires no hardware modification is by suppressing unwanted signals using solvent suppression pulse techniques. There are three classes of solvent suppression, presaturation, tailored excitation, and multiple quantum filtering. Each method has advantages depending on the specific application.

Presaturation solvent suppression techniques are used for spectra containing one large unwanted resonance. This technique is implemented by irradiating the sample with a long low power pulse at the frequency of the resonance one desires to suppress. This equalizes the population of spins at that frequency, therefore subsequent rf pulses produces no coherent magnetization to be detected. This effective method is used by itself or in conjunction with other solvent suppression techniques.

Spectral editing pulse sequences produce a tailored excitation profile designed to excite spins at specific spectral frequencies. The excellent review article by Hore [40] discusses both the theory and application of several of the commonly used solvent-suppression pulse sequences. His work demonstrates the ability of these sequences to yield suppression factors on the order of 1000. The most common of these methods is the $\bar{1}33\bar{1}$ solvent-suppression technique where the relative amplitude of the pulses are designated by 1 and 3 and the bar represents

a 180 degree phase shifted amplitude. This sequence is characterized with a sine cubed excitation profile with the maximum of the excitation determined from the pulse spacing. An extension of this technique is the computer optimized suppression sequence which produces a flatter excitation profile [35]. Another desirable excitation profile is implemented with the $1\bar{3}4\bar{4}3\bar{1}$ pulse sequence which produces two nulls in the excitation profile. The maximum of the excitation for this sequence is located an equal distance from the two nulls. The sequence by Levitt and Roberts [45] is a similar solvent-suppression technique with decreased phase distortion over the spectral frequencies.

Multiple quantum filtering is a technique where a particular nucleus can be selected from the total spectrum based spin-spin coupling. Coupled nuclei have zero and double quantum coherences, and while these coherences cannot be detected by themselves, magnetization can be stored in these populations to be recovered after other single quantum coherences have been dephased. This technique has been used for water suppression in both solution spectra and in imaging [25].

Improving the SNR of a spectroscopy experiment can be accomplished by simply averaging the data obtained in multiple excitations. Signal averaging provides an improvement in SNR proportional the square root of the number of scans. The only precaution to be observed for signal averaging is to ensure that equilibrium magnetization is restored between scans, allowing accurate quantification between peak heights and concentration. This criterion is met as long as the time between successive scans lasts at least $5 T_1$ time constants. If, in

addition to simple averaging, a phase cycling routine (the use of pulses along alternatively the x and y axis of the spectrometer) is also used, it will improve the quality of the scans by reducing quadrature ghost signals.

Mass-Charge Ratio	Type of Peak	Relative Intensity
18.0	r	1.92
19.0	r	0.32
27.0		0.16
27.4	m	0.16
28.0		6.37
29.0		64.66
30.0		0.81
31.0		100.00
32.0	p	66.68
33.0	i	1.01

Table 2.2: Mass Spectrum Data for Methanol where p=parent, r=rearrangement
m=metastable, i=isotope

Chapter 3

Materials and Methods

This research involved both the selection of a promising chemical system and the development of the 1H NMR methods to use for the initial characterization of the dosimeter system. The solvent investigated was chosen based on its radiation chemistry behavior and NMR properties. Development of the basic method includes obtaining some baseline spectra and implementing appropriate high resolution proton (HRP) NMR techniques to improve the dosimeter performance. Baseline reference spectra were acquired for both the solvent samples, and solvent spiked with known quantities of the expected radiolytic product samples. Solvent suppression NMR techniques were then used to improve reaction product detection sensitivity. In addition an analytic technique was developed to directly relate integral peak area (IPA) determined from the NMR spectrum to the number of reaction molecules formed. The overall feasibility of the proposed system is demonstrated through the analysis of the NMR spectrum obtained from a high dose sample included in this section.

A deuterated form of methanol was used for this research to minimize the hydroxyl proton resonance peak. Deuterated methanol, C^1H_3OD (99.5+ atom %

D) was obtained from Aldrich Chemical Company¹. The methanol used was delivered under nitrogen, and for these preliminary experiments no attempt was made to deaerate the methanol. Since nitrogen also acts as a free radical scavenger we anticipated an increased G value for the production of formaldehyde and decreased production of ethylene glycol. According to Choi [22] oxygen saturated methanol will have a G value of 8.7 and the glycol G value will be 0.1. More importantly the G value for formaldehyde remains stable under saturation conditions. Therefore, we expected to obtain consistent results for the formaldehyde data at the expense of the glycol data. A trace amount of tetramethylsilane (TMS) was added to the $C'H_3OD$ stock solution as a reference peak in subsequent NMR spectra presented.

The dosimeter system consisted of 0.5ml aliquots of the stock $C'H_3OD$ solution in Norrell No. 507 high precision thin walled 5mm NMR sample tubes. The wall thickness for these tubes is 0.38mm. Samples were double parafilm capped, sealed, and transferred from the irradiator to the spectrometer without special handling. Samples were analysed on a Bruker 270 MHz high resolution spectrometer, equipped with an Aspect 2000 computer running DISNMR software. Unless otherwise stated the acquisition parameters were:

1. Excitation Pulse width (PW) $0.5 \mu sec$
2. Receiver Gain (RG) 2
3. Spectral Width (SW) 7ppm (parts per million of 270 MHz)

¹Aldrich Chemical Co. Milwaukee, WI

4. Acquisition Time (AQ) 4.325 sec
5. Number of averages (NS) 8
6. Total Data points (SI) 16k

Initial Fourier transform and phasing was performed using standard spectrometer software. Subsequently data were transferred to an IBM PC computer running PCNMR² software for plotting and to a Macintosh PC computer for baseline correction, non-linear curve fitting to a Lorentzian line shape, and analytical integration using software written during this project specifically for this purpose. The fitting routine was based on the Marquardt algorithm [51] as implemented in CURFIT from Bevington [14].

For our initial experiments an absolute dose calibration was not attempted as these experiments were designed primarily to evaluate the dose response, only a cursory calibration of the deposited dose was made. Samples were irradiated with a US Nuclear Corporation GR-4 ¹³⁷Cs irradiator consisting of a 600 Ci source as of 15 July, 1966. The distributed source is constructed of a hexagonal array of Cs line sources placed to deliver a uniform dose in the central volume of the irradiation cell. The irradiator was calibrated using LiF TLDs (TLD-100) placed along the central volume. Measured TLD response along the cylindrical cell volume had a relative standard deviation of 6%, with the average value to all the TLDs used as a measure of the exposure. Roentgen to rad to Gray conversion factors were used to determine the dose in Gy to tissue media. At

²available from UW Dept of Chemistry

this photon energy, 662 keV, interaction with low-z material are principally due to the Compton process which depends only on electron density. Hence the dose to the deuterated methanol and SiO_2 encapsulation are very similar to dose to tissue. Moreover the SiO_2 provides sufficient electronic equilibrium to ensure that kerma and dose are equal. After correcting for source decay, the dose rate was assumed to be 12 Gy/min at the sample position. A well-aligned sample feed tube ensured reproducible sample alignment in the radiation field.

3.1 Reference Spectra

In order to demonstrate the expected NMR response several spectra were acquired with known aliquots of the radiolysis products added to the solvent CH_3OD . A plot of a seven ppm reference HRP NMR spectrum of the CH_3OD stock solution is shown in Figure 3.1. The following assignments have been made on the resonances present in the stock solution: tetramethylsilane (TMS) reference at 0.0ppm, CH_3 methyl proton resonance at 3.35ppm, resonances produced by methyl protons coupled to natural occurring ^{13}C at 3.60 and 3.08ppm, contaminant hydroxyl protons at 4.90ppm, and an unidentified contaminant resonance at 3.17ppm.

The spectrum obtained by adding a 1 μl aliquot of a 37 % (by weight) formaldehyde solution is shown in Figure 3.2. The formaldehyde protons produce a narrow resonance at approximately 4.64ppm relative to TMS at 0.0ppm.

The spectrum obtained by adding a 1 μl aliquot of a 37 % by weight formaldehyde solution and a 1 μl aliquot of ethylene glycol is shown in Figure 3.3. The

Figure 3.1: High resolution proton CH_3OD spectrum. Large resonance at 3.35ppm is due to three equivalent methyl protons, resonance at 4.90ppm is due to contaminant hydroxyl protons. Satellite resonances at 3.60 and 3.08ppm are due to protons coupled to natural abundance ^{13}C

ethylene glycol protons resonate at 3.59ppm and are adjacent to the intense carbon-coupled proton resonances at 3.60ppm when acquired on a 270 MHz spectrometer. A stronger magnetic field would provide better separation between the two resonant frequencies since coupled resonances are independent of field-strength while chemical shift frequencies are field strength dependent.

Spectral quantitation was accomplished by the use of a spectrometer efficiency factor. This factor was determined by relating NMR integrated peak area (IPA)

Figure 3.2: High resolution proton CH_3OD with $1.0 \mu l$ aliquot of Formaldehyde (CH_2O) added to sample. The CH_2O resonance is observed at 4.64ppm. Inset is an expanded region from 4.50 to 5.00ppm

to known solute concentrations. Using this calibration factor it is possible to determine the number of solute molecules in an unknown sample.

The integrated peak area for these and subsequent samples were determined by first subtracting a baseline from the peak data. The baseline is determined by taking four points at the extremes of the data set and evaluating a constant and slope correction factor which is subtracted from all the data points. Next, the data is used in a curve fitting routine to a Lorentzian line shape where the fit parameters are used in an analytical integration calculation.

Figure 3.3: High resolution proton CH_3OD with $1.0 \mu l$ aliquot of formaldehyde (37 % by weight) and $1.0 \mu l$ aliquot of ethylene glycol $C_2H_6O_2$ added to sample. $C_2H_6O_2$ resonance at 3.59ppm.

Data for determination of the calibration factor were acquired using a presaturation solvent suppression pulse sequence which will be described in the next section. Five reference samples of increasing solute concentration were used in the evaluation of the calibration factor. The number of formaldehyde molecules in the sample is calculated and plotted as a function of integrated peak area in Figure 3.4. The calibration factor determined from the least squares fit to the slope of these data and in units of molecules per arbitrary integration area units is 1.205×10^{15} (molecules/unit area) for our spectrometer.

Figure 3.4: Formaldehyde Calibration Curve

The IPA/molecular number calibration factor may then be used to determine G-values when samples are irradiated to known doses. For example, a 1.0 kGy dose (1000 J/kg) deposited in the 0.5ml sample at a density of 0.8127 kg/l is equivalent to 0.406 Joules or $2.536 \times 10^{18} \text{ eV}$ and for a corresponding integrated area of 189.13 units (2.28×10^{17} molecules) results in a G-value of 8.98 molecules/100eV deposited energy. This value is similar to the published data for formaldehyde production of 8.7 in oxygen-saturated methanol [22]. We were unable to find G-value data for nitrogen-saturated methanol in the published literature. The free radical scavenger effects of the nitrogen may explain why the G-value obtained using our technique is different from that of Choi [22].

3.2 Qualitative high dose spectrum (50kGy)

The first experiment was performed at a high dose to demonstrate the feasibility of the overall technique. Figure 3.5 shows a spectrum acquired with a 0.5 ml sample of nitrogen-saturated CH_3OD irradiated in the NMR sample tube to 50kGy. The same acquisition parameters were used as in the previous 7ppm reference spectrum. Both the formaldehyde and ethylene glycol resonances are

Figure 3.5: HRP NMR Spectrum of CH_3OD Irradiated to 50 kGy. Insets are expansions around product peaks.

clearly present.

Chapter 4

Results

The results of this research include optimizing the pulse sequence and acquisition parameters to obtain maximum radiolytic product peak sensitivity (dose response), and assessing system reproducibility and temporal chemical stability. The useful dose range of this system was extended through the implementation of both solvent suppression and restricted acquisition NMR techniques. Studies were also performed to identify potential sources of sample variability, and this knowledge was then used to develop a normalization technique to reduce system variability.

4.1 Dose response

The first set of dose response experiments determined the limitations of dose range using a standard spectroscopy pulse sequence. Since the spectrum contained the large solvent resonance in addition to the much smaller product resonances it was necessary to set the excitation rf pulse width to $0.5 \mu\text{sec}$ and the receiver gain to 2. The NMR spectrum obtained using this technique for a CH_3OD sample irradiated to 6 kGy is shown in Figure 4.1. The small formalde-

Figure 4.1: The HRP NMR spectrum of CH_3OD Irradiated to 6 kGy. The small formaldehyde peak is barely seen at 4.64ppm. The signal-to-noise ratio (SNR) was insufficient to allow IPA determination.

hyde peak was observed, however the signal-to-noise ratio (SNR) of this peak was insufficient to allow IPA determination. The dose was therefore increased and the relationship between absorbed dose and IPA determined by serial irradiations on a single sample irradiated from 13 to 50 kGy. The integrated peak areas are plotted as a function of absorbed dose in Figure 4.2 where we find a linear relationship between the absorbed dose and integrated peak values with a slope equal to 3.42, intercept equal to -5.0, and a correlation coefficient of 0.994. The results of these experiments indicate that it would be necessary to develop

NMR pulse sequence and acquisition parameters optimized for our particular application.

Figure 4.2: Integrated CH_2O peak areas as a function of absorbed dose 10 to 60 kGy.

Increased sensitivity was obtained by the implementation of a presaturation solvent suppression pulse sequence optimized for this application. This sequence consists of a long low power pulse set at the frequency one wishes to suppress and is followed by a standard short duration pulse used to excite the frequencies of interest. The effect of this sequence is to suppress the large resonance due to the methyl protons of the solvent thereby allowing optimization of the rf flip angle and receiver gain settings. The instrumental parameters of rf pulse width and receiver gain were adjusted following implementation of the solvent suppression pulse sequence to achieve maximum dose sensitivity. The rf pulse power (pulse

width) affects the fraction of spins which contribute to the observed NMR signal (flip angle), where the pulse power due to a $0.5 \mu\text{sec}$ long excitation used in the previous experiments only excites approximately 20% of the available signal. This small rf flip angle was necessary to keep the NMR signal within the range of the analog-to-digital converter (ADC) since the spectrometer gain was set to a low value of 2. A low receiver gain value affects the ability of the ADC to digitize low signals superimposed on a larger background. Using this technique a 7ppm spectrum can be obtained with a maximum pulse width of $2.3 \mu\text{sec}$ and a receiver gain of 20 extending the dose range from 6 down to 1 kGy. A spectrum of a CH_3OD sample irradiated to 6 kGy demonstrating the effect of presaturation on the methyl protons is shown in Figure 4.3. The integrated peak areas plotted as a function of absorbed dose for spectra obtained using the presaturation sequence is shown in Figure 4.4 where three samples were measured for each data point. The error bars indicate the standard deviation between the three similarly irradiated samples. Under these conditions the IPA versus absorbed dose slope becomes 5.96, the intercept equals 2.97, and the correlation coefficient is 0.976. Comparison of the slope values between the standard and the presaturation pulse sequences yields an improvement of 1.74 in dose sensitivity.

Following implementation of the presaturation sequence we also determined that further gains would result from reducing the spectral width to 2ppm during acquisition of the NMR signal. This was accomplished by increasing the ADC sampling interval. Additional noise filtering and was provided by the analog filters of the spectrometer which effectively band-limit the NMR signal before

Figure 4.3: NMR spectrum of CH_3OD irradiated to 6 kGy obtained using the presaturation solvent suppression pulse sequence. Acquisition parameters were $SW=7\text{ppm}$, $PW=2.3\ \mu\text{sec}$, $RG=20$.

ADC, removing the unwanted signal and noise from all the upfield and downfield resonances. This allowed an increase in the pulse width to $4.4\ \mu\text{sec}$ corresponding to 100% of the available signal without overranging the spectrometer ADC. A representative spectrum at a dose of 1 kGy obtained using this technique is shown in Figure 4.5. Note the increased visibility of the formaldehyde peak for this spectrum at 1 kGy as compared to that of figure 4.3 (1 kGy) and figure 4.1 (6 kGy). We now find that the pulse sequence and acquisition parameter modifications have substantially increased our dose sensitivity allowing irradiations

Figure 4.4: NMR integrated CH_2O peak area as a function of absorbed dose using the presaturation pulse sequence.

in the range of 200 Gy.

The integrated peak area versus absorbed dose is plotted in Figure 4.6 for this technique with three samples per data point. The error bars represent the standard deviation between the three samples. These results show improved dose sensitivity with a slope of 239 (IPA/kGy), and intercept of 3.88 (IPA), and a correlation coefficient of 0.976.

4.2 Reproducibility

This set of experiments was performed to identify the major sources of sample variability and assesses the reproducibility of the IPA measurements using a normalization procedure developed specifically for this application. Reproducibility

Figure 4.5: NMR spectrum of CH_3OD irradiated to 1.0kGy obtained using solvent suppression together with limited (2ppm) spectral bandwidth. The acquisition parameters were $PW=4.4 \mu sec$ and $RG=20$.

includes both inter- and intra-sample variability. Intra-sample reproducibility is measured using a single sample to determine the inherent electronic stability of the spectrometer. Inter-sample reproducibility assesses sample to sample variability for a constant exposure. Factors contributing to measured sample variability are low signal-to-noise ratio resonance peaks, variation in individual sample geometry, shim, and NMR spectrometer instability.

A normalization method was developed to correct for variation due to sample geometry, shim and spectrometer instability. Although there are NMR sample

Figure 4.6: Integrated CH_2O peak areas as a function of absorbed dose obtained using solvent suppression together with limited (2ppm) spectral bandwidth.

tubes which have removable inner volumes which could be used to store a reference sample, a simpler solution was to use part of the solvent resonance signal. We choose the carbon coupled proton resonance at 3.60ppm as the reference peak since the larger methyl proton signal is presaturated in order to optimize data acquisition and the carbon coupled resonance is smaller than the methyl peak due to the low natural abundance of ^{13}C at approximately 1.1%. Normalization requires a stable resonance in the spectrum that does not change with irradiation and, although the solvent is being depleted by radiochemical processes, its relative change in concentration is negligible in this dose range. Since the reference peak and the desired formaldehyde peak are contained within the same sample they experience the same sample geometry, shim and spectrometer variations.

Therefore, the IPA of the formaldehyde peak can be corrected by normalization to the IPA ^{13}C peak which primarily undergoes changes due to these variations.

Radiolytic product data are normalized in a two step process. First, the product resonance integral is divided by the reference peak integral. This provides a ratio value which would be independent of spectrometer variations. Second, this ratio value is multiplied by an average of the reference peak integral data. This step is appropriate if the average reference IPA is assumed to represent the correct reference concentration. Subsequently, this allows one to use the previously determined formaldehyde calibration curve to obtain the formaldehyde concentration from the measured formaldehyde IPA value.

$$\text{normalized } \text{CH}_2\text{O IPA} = \frac{\text{CH}_2\text{O IPA}}{\text{reference IPA}} \times \text{average reference IPA} \quad (4.1)$$

Since rf pulse width (pulse power) and receiver gain are instrumental factors which significantly affect the amount of signal in a spectrum the normalization technique as described above should be able to compensate for changes in these parameters. Two experiments were performed to validate the implementation of the normalization technique. For these experiments a formaldehyde spiked reference sample is used. Also the reference peak data is scaled down by a factor of 256 therefore reference data shown in all subsequent tables are actually much larger than the scaled values shown in the table. The effect of varying the rf pulse width on the IPA of the reference and formaldehyde peaks is shown in Table 4.1. The standard deviation (STD) of the normalized formaldehyde IPA is 5 times smaller than that of the un-normalized formaldehyde. This result demonstrates the ability of the normalization method to compensate for large changes in NMR

signal due to rf fluctuations.

Pulse Width	Formaldehyde (IPA)	Reference (IPA)	Normalized (IPA)
2.0 μsec	57.51	36.82	182.83
3.0 μsec	117.50	77.84	176.69
4.0 μsec	267.40	156.90	199.49
4.4 μsec	227.90	148.60	179.52
5.0 μsec	311.90	165.10	221.13
Mean	196.44	117.05	191.93
Standard Dev	105.94	56.72	18.57
Std Dev/Mean	53.93%	48.45%	9.67%

Table 4.1: IPA for reference and formaldehyde peaks as a function of rf pulse width. Note that the standard deviation of the formaldehyde IPA decreases a factor of 5 after normalization.

The second experiment varied the receiver gain from 4 to 20 to simulate receiver gain instability. The results are shown in Table 4.2. Again we find that the formaldehyde IPA standard deviation is reduced significantly to the order of the reference peak STD following normalization.

Intra-sample variation was evaluated by performing 10 consecutive NMR IPA determinations on a single sample irradiated to 1.0kGy. This intra-sample experiment evaluates the experimental variation due solely to the spectrometer. The

Receiver Gain	Formaldehyde (IPA)	Reference (IPA)	Normalized (IPA)
20	60.48	27.45	38.81
16	66.69	27.44	42.81
10	56.52	17.76	56.05
4	23.16	9.34	43.66
Mean	51.71	20.50	45.33
Standard Dev	19.49	8.73	7.45
Std Dev/Mean	37.69%	42.57%	16.44%

Table 4.2: IPA for reference and formaldehyde peaks as a function of receiver gain. Note that the standard deviation of the formaldehyde IPA is reduced by factor of two following normalization.

results shown in Table 4.3 indicate that our normalization technique does not decrease the standard deviation of the formaldehyde peak to the level attained by the STD of the reference IPA. This result indicates that the dose sensitivity of our technique is currently limited by the accuracy of our curve fitting and integration methods when applied to low SNR resonances.

The inherent dose determination accuracy of our technique was evaluated by irradiating three samples to the same exposure. Under these conditions the inter-sample variability may be due to variations in sample volume, exposure time, shim, rf probe tuning, and fluctuations in the rf power and receiver gain of the spectrometer. The results shown in Table 4.4 indicate slightly reduced IPA

standard deviation of the formaldehyde peak following normalization.

Since the accuracy of the IPA determinations using a curve fitting and analytical integration technique is a function of signal-to-noise ratio, simple averaging over many pulses should improve sample reproducibility for low dose samples. Since a fitting technique is used one would not expect the $\sqrt{2}$ advantage as predicted by simple peak height variations, however, some improvement can be expected. This result is shown in Table 4.5 where the number of averages is doubled from the normal 32 to 64. The standard deviation in the formaldehyde data at 64 scans is less than the standard deviation acquired with 32 scans. However, the same reduction in standard deviation was not observed in the reference peak data. Since the signal-to-noise ratio for the reference resonance was already very large we did not expect an improvement in these results based on an increased number of scans. However, we did not expect the increase in standard deviation. This was most likely due to spectrometer drift during the increased data acquisition time. There was no improvement in the normalized data due to the increased variability in the reference data.

4.3 Temporal Stability

Temporal stability is the ability of a dosimeter to retain the same reading over extended periods of time. In our dosimeter we are concerned with the stability of both the chemical reaction products, as well as several spectrometer instrumental parameters such as probe position, probe efficiency, and transmit/receive gain. We evaluated temporal stability by irradiating a given sample and pe-

riodically monitoring the IPA results. For this initial study two samples are used, one is irradiated to 6 kGy on Feb 16, 1989 and the second to 1 kGy on Apr 27, 1989. Sample protocols were improved during this time and results obtained were normalized to compare data. The effectiveness of this normalization technique is more significant in the monitoring of temporal stability since several spectrometer instrumental parameters such as probe position, probe efficiency, and transmit/receive gains can change remarkably over extended periods of time. The results for the 1kGy samples are shown in Table 4.6. The first column contains the integrated peak intensities for the formaldehyde peak data, the second shows the carbon coupled proton resonance integrals; and the last column shows the normalized formaldehyde data. The considerable deviation in the early results is due to the use of different sampling protocols since the newer more efficient protocols were implemented as they became available. The normalization however allowed for a coarse comparison of the data which showed no remarkable fading or growth of signal intensity.

Similarly, the evaluation of temporal stability using a 6kGy sample to improve SNR in the NMR formaldehyde resonance is shown in Table 4.7. The percent standard deviation for the 6 kGy data was better than the 1 kGy data due to a better signal-to-noise ratio.

Sample no.	Formaldehyde (IPA)	Reference (IPA)	Normalized (IPA)
1	173.40	85.17	174.31
2	175.10	84.86	176.67
3	211.50	83.46	216.97
4	186.90	82.78	193.31
5	179.10	84.28	181.95
6	220.10	87.37	215.69
7	192.60	87.07	189.39
8	171.60	87.49	167.93
9	190.70	92.78	175.98
10	190.30	80.93	201.33
Mean	189.13	85.62	189.35
Standard Dev	16.10	3.29	17.30
Std Dev/Mean	8.51%	3.84%	9.14%

Table 4.3: Intra-sample IPA Reproducibility, 10 samples

Sample	Formaldehyde (IPA)	Reference (IPA)	Normalized (IPA)
ld1.008	57.84	41.19	47.04
ld2.008	57.57	35.19	54.81
ld3.008	42.23	24.12	58.65
Mean	52.55	33.50	53.50
Standard Dev	8.94	8.66	5.91
Std Dev/Mean	17.00%	25.85%	11.06%

Table 4.4: Inter-sample reproducibility for three different samples. Note that the standard deviation of the formaldehyde IPA is on the order of the reference standard deviation following normalization.

Sample for Avg = 32	Formaldehyde	Reference	Normalized
1	173.40	85.17	174.31
2	175.10	84.86	176.67
3	211.50	83.46	216.97
4	186.90	82.78	193.31
5	179.10	84.28	181.95
Mean	185.20	84.11	188.64
Standard Dev	15.60	0.99	17.45
Std Dev/Mean	8.42%	1.17%	9.25%

Sample for Avg = 64	Formaldehyde	Reference	Normalized
1	187.10	98.15	178.82
2	200.90	95.37	197.61
3	218.30	89.22	229.52
4	192.90	92.78	195.03
5	217.60	93.51	218.29
Mean	203.36	93.81	203.85
Standard Dev	14.19	3.30	20.07
Std Dev/Mean	6.98%	3.51%	9.84%

Table 4.5: Effect of increased averaging on the accuracy of IPA determination. The samples were irradiated to 1kGy and then the IPA were determined after 32 or 64 rf excitations were collected.

Date	Formaldehyde	Reference	Normalized
4/27/89	65.09	38.39	169.38
7/10/89	338.20	230.50	146.58
7/19/89	690.60	285.90	241.31
7/31/89	303.20	165.80	182.69
8/4/89	227.90	148.60	153.21
8/9/89	143.30	77.79	184.03
8/14/89	129.80	88.34	146.79
8/21/89	170.30	81.42	208.95
8/28/89	111.50	58.89	189.15
9/6/89	131.40	52.33	250.85
9/13/89	147.50	58.22	253.10
9/25/89	105.10	48.98	214.36
10/2/89	113.20	53.16	212.73
10/9/89	152.10	59.52	255.29
10/20/89	102.4	50.60	202.17
Mean	195.44	99.90	200.71
Standard Dev	156.25	74.47	37.89
Std Dev/Mean	79.95%	74.54%	18.88%

Table 4.6: Temporal stability at 1 kGy

Date	Formaldehyde	Reference	Normalized
8/17/89	796.30	161.90	821.88
8/21/89	922.20	205.60	749.51
8/28/89	879.30	157.20	934.68
9/6/89	874.60	172.10	849.19
9/13/89	1108.00	211.32	876.14
9/25/89	957.40	169.60	942.29
10/2/89	820.40	151.80	903.09
10/9/89	729.40	134.76	904.44
10/20/89	777.20	139.60	930.30
Mean	873.87	167.10	879.17
Standard Dev	113.61	26.53	63.26
Std Dev/Mean	13.00%	15.88%	7.20%

Table 4.7: Temporal stability at 6 kGy

Chapter 5

Discussion

The goal of this research was to develop and characterize a dosimetry system based upon the production of radiolytic molecules formed by the irradiation of methanol and their subsequent quantitation using high resolution 1H NMR spectroscopy. We studied several dosimetric properties of the system such as dose response, reproducibility, and temporal stability as well as some of the NMR system limitations. These preliminary data demonstrate the feasibility of the proposed system, and, indicate several important areas in which to concentrate future research efforts. Although significant gains in sensitivity were realized during this research the primary disadvantage of the current system for general purpose dosimetry is the relatively high dose (200Gy) necessary to obtain significant measurements. The lower limit of dose response was determined by the NMR spectrometer and pulse sequence used for data acquisition. The dose response of the system for the production of formaldehyde is linear over three decades of absorbed dose with no observed saturation. The reproducibility (standard deviation) of the system using the presaturation pulse sequence with restricted acquisition is approximately 5 to 10% where reproducibility was influenced by the spectrometer electronics and signal-to-noise ratios obtained for

the spectral peaks. The measured temporal stability from the 1 kGy and 6 kGy doses remained within system variability over the last six months. We expect that the results for dose response, reproducibility, and dose specificity can be improved by taking advantage of newer NMR technology, better data acquisition protocols, and data processing techniques.

5.1 Dose Response

The extension of the useful dose range of this dosimetry system to higher and lower doses involves different limitations at the two extremes. The extension to higher doses will be limited by depletion of solvent and radiolysis of the product formed. Since the probability of interaction is low and pure solvents are used in this research the upper dose limit is expected to be in the 10's to 100's of MGy. The work by Panin [55] on dilute solutions of various of aliphatic amino acids required doses in the MGy range in order to observe similar radiation induced chemical results. His work also showed linearity for products in the MGy range. The present research focused on techniques to extend the dose response to lower ranges.

The instrumental factors addressed in lowering the dose response were spectrometer dynamic range and bandwidth. Three different pulse sequence protocols were used to evaluate and improve the dose response based on optimizing the dynamic range. This problem was largely alleviated using a presaturation pulse sequence to significantly reduced the large solvent resonance. This allowed the optimization of the receiver electronics gain adjustments (RG) to observe small

radiolysis product resonances in the presence of the large solvent signal. Implementation of the presaturation solvent suppression pulse sequence increased the dose sensitivity by a factor of 2. Reducing the spectral width also improved the system response by taking advantage of the spectrometer's analog filters in removing both noise and unwanted upfield and downfield resonances. Implementation of the limited spectral width acquisition together with the solvent saturation pulse sequence yielded a significant gain in dose sensitivity. An additional benefit achieved from using this technique was improved reproducibility. This was directly related to the improvement in signal-to-noise ratio of the formaldehyde resonance which improved the IPA determination using the current curve fitting and analytical integration techniques.

5.2 Reproducibility

Reproducible response is essential to any dosimeter system and several experiments were performed to identify the major sources of inter- and intra-sample variation for our chemical dosimetry system. Our investigations demonstrated that significant changes in either rf pulse width (flip angle) or receiver gain could be successfully minimized by implementing a normalization technique which utilized a stable neighboring resonance peak. Some variations were due to low signal-to-noise ratios as demonstrated by the low dose samples. A system with improved dose response would have improved signal-to-noise ratio and consequently a better system reproducibility. The use of alternative spectral estimation techniques has also been shown to produce better quantitative results

[63]. While Fourier transform is the most robust method of relating temporal to frequency data, alternative spectral estimation methods such as LPSVD (linear prediction using single value decomposition), MEM (maximum entropy methods), or Bayesian methods may improve sensitivity in these types of experiments. Their potential lies in the amount of *a priori* information available to fit data models, since approximate amplitudes and frequencies are known in irradiated samples.

5.3 Temporal Stability

The temporal stability of a given irradiation sample is the reproducibility of the integrated peak intensity evaluated over an extended period of time. This reproducibility depends on spectrometer reproducibility and the chemical stability of the radiolytic products induced.

Spectrometer reproducibility was improved by the use of a normalization technique as described above. This normalization was able to reduce a variation of 17% to 8% in the 6 kGy data.

The chemical stability of the products was not expected to change over time and no significant change was observed in these peaks. There was however a change in the hydroxyl peak intensity, most likely due to leakage of oxygen through the parafilm-sealed NMR tubes. Future samples should be vacuum sealed to prevent this effect.

Chapter 6

Future Studies

The next steps in this research project should include five general areas: first, a more extensive initial characterization should be performed to fill in some of the experimental gaps. This would include a finer dose spacing throughout the response range, an extension to higher and lower doses, and a longer period of time over which to assess temporal stability with a consistent technique. The second research area should include the dosimeter response to other types of ionizing radiations such as proton, neutron, or electron beams. As discussed in the original proposal there is some LET dependence in the product yields which may be exploited to discriminate the type of radiation. The third area is to investigate implementation of alternative spectral estimation techniques to improve system signal-to-noise ratios. This is appropriate for this type of NMR research since both the frequency and approximate amplitudes of the resonant peaks are well known. The fourth area is to continue to follow the progress in NMR technology useful to this type of project. This includes new pulse sequences which improve spectrometer response as well as advances in spectrometer hardware. SQUID amplifiers have been shown to improve the sensitivity of NMR techniques significantly. This technology would be important for this type of research project.

A fifth area is continued investigation of other potential radiochemical systems which have improved lower-dose response or better radiation response specificity.

6.1 Extended Dosimetry Characterization

These first experiments were primarily designed to demonstrate feasibility of the technique and evaluate some of the system limitations. A more complete characterization would include :

1. more experimental dose points between 20 Gy and 2 MGy
2. dose rate dependence
3. temporal stability over longer time periods, with constant technique
4. extended characterization of spectrometer protocols
5. implementation under different environmental conditions

Better dose point resolution would better characterize the expected linear-dose response function. It would also ensure no dose point discontinuities, although their presence is highly unlikely. Dose rate studies need to be performed to ensure that the radiochemical yield values are not significantly perturbed by high radiochemical reaction rates. Although a dose rate dependence is likely, it is not expected to be significant in the expected dose rate range for most practical applications. Temporal chemical stability should be an ongoing part of this research project. This study should also be extended to include higher and lower

dose samples. A further characterization of the spectrometer instrumental parameters may provide information on how to improve the dosimetry system's accuracy and reproducibility. Further studies would involve the use of different hardware and software. Hardware studies should include different probes or sample sizes (use of larger 10mm diameter sample tubes). Software studies should involve better pulse sequence parameters for solvent suppression. Another area of characterization would be investigation of environmental factors which could affect results. If the proposed system is implemented in a severe temperature or pressure environment the dosimetric response may be affected. These experiments would be essential for a more complete analysis of this type dosimetry system.

6.2 Energy and LET Response

Extension to other types and energies of radiations is necessary to further determine the systems characteristics. These studies would include using different energy photon irradiations and the use of other charged particle radiations. This would also include studies with neutron radiations. A fundamental premise in the advantages of this type of dosimetry system is its LET dependence. Radiation interactions in methanol are similar to radiation interactions in water, therefore, a dosimeter system based on methanol may be more appropriate than the traditional dosimeter systems based on either film or TLD. The LET dependence of formaldehyde production can be verified using various radiations spanning the LET range from 1 to 100 $\text{keV}/\mu\text{m}$.

6.3 Alternative Spectral Estimation

Research should also be continued on various parameter estimation techniques. Based on the *a priori* information available, these techniques are well suited to analyzing these NMR data. The advantages include better signal-to-noise ratios which should also improve system reproducibility [63]. Current techniques for peak integration require careful post-processing of the peak data which includes removal of baseline artifacts typical in Fourier transform techniques. Baseline artifacts may be introduced by closely lying adjacent peaks or overranging of the ADC hardware. Elimination of such artifacts by substituting other spectral estimation techniques may therefore improve peak integration and subsequently the system reproducibility.

6.4 Spectrometer Technology

The major limitation to the extension of this dosimeter to lower doses is primarily instrumental. As implemented this system is only useful for high range dosimetry applications, but there is no physical reason why the concept cannot be extended to lower dose ranges. Research in NMR spectroscopic techniques are addressing methods of improving sensitivity using techniques of sample cooling [44] and improved receiver gain [27]. There are several ways in which the lower dose limit may be extended with available technology. The simplest of these is to use a higher field strength spectrometer. The problem of spectrometer dynamic range is due to residual solvent or contaminant which contributes significant signal strength. Dynamic range problems may be addressed using better solvent-

suppression techniques, multiple quantum filtering, [25] or higher range A/D converters.

6.5 Alternative Molecular Systems

Another area for continued investigation is in different molecular systems. Other systems may provide either better sensitivity or specificity. Several different systems which may be considered include:

1. dimethyl sulfone
2. Fe spiked methanol
3. B(n,α) reactions using Li NMR
4. $D_2O(n,2n)HOD$ with proton NMR

Radiation interactions in dimethyl sulfone have a G value of 10 for main-chain scission [17,59]. This produces several products with methyl groups which have the additional sensitivity advantages of three equivalent protons leading to an inherent NMR amplification. The radiation induced products also have a significant chemical shift from the DMSO solvent due to the sulfur atom.

An improvement in formaldehyde production sensitivity for a methanol system is also possible by saturating the sample with free-radical scavengers. The G value for the production of formaldehyde can be increased from approximately 3 to 9 by the introduction of free radical scavengers. Scavengers such as oxygen, nitrogen, or iron may be used. An advantage of using Fe includes the potential to simultaneously use standard spectrophotometry techniques to measure

radiation effects based on the Fricke dosimeter technique. The use of oxygen or nitrogen added free radical scavengers may better mimic biological media. The disadvantage of using scavengers is the potential of losing the LET dependence of the formaldehyde produced.

There are several methods which may be used to develop a system with better radiation specificity. A system based on thermal neutron capture of boron to produce lithium may be a useful neutron dosimeter system. In a solution of boron compounds there would be no resonances at the Li NMR frequency. This type system would require no solvent-suppression, and would have the lowest background. A similar concept may be used for very high energy neutrons, based on the (n,2n) reaction on D_2O . Once again there would be a very low background based on the contaminant protons in the D_2O solvent.

Chapter 7

Conclusion

Nuclear magnetic resonance as a quantitative spectroscopic tool is useful for the measurement of absorbed doses in the 100Gy to 10kGy dose range using the radiation chemical production of formaldehyde in methanol. NMR is preferable in some respects over other analytical chemistry techniques despite its relative insensitivity, since it is non-destructive, and has a large dynamic range with good spectroscopic resolution. Without any additional sophisticated hardware one is able to quantify absorbed doses from 200 Gy to 50 kGy with about a 10% standard deviation using a standard 270MHz Bruker spectrometer and product software.

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