Modern Methods of Pharmaceutical Analysis

Volume II

Editor

Roger E. Schirmer

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FOREWORD

The analysis of pharmaceuticals can be subdivided into several distinct classes of analytical problems. The classes are listed in Table 1. Each class of problems imposes a unique set of constraints on the analyst. For example, the determination of the purity of a drug substance usually requires an analysis of high specificity and precision, but does not require high sensitivity or preliminary isolation of the analyte from a sample matrix. Analysis of a potent drug in a low dose formulation on the other hand requires selectivity, precision, high sensitivity, and (usually) a preliminary separation of the drug from excipients. Evaluation of reference standards requires use of absolute methods such as coulometry, differential scanning calorimetry, or NMR that do not need a standard of the test substance for calibration, and so on. As a consequence of the diverse requirements of the different classes of problems, all common organic analytical techniques are routinely used in pharmaceutical analysis. Instrumental methods are particularly important in modern pharmaceutical analysis, but classical procedures are often used in conjunction with them. The classical methods remain very important in routine quality control of pharmaceuticals.

The objective of "Modern Methods of Pharmaceutical Analysis" is to review the major methods in current use in pharmaceutical analysis. The review covers principles, special instrumentation, experimental techniques, and a survey of pharmaceutical applications for each method. The discussion of principles is intended to provide insight into important experimental variables, possible sources of error in applications of the technique, and factors that should be taken into account when adapting the method to solve new analytical problems. Tables of buffer compositions, characteristics of chromatographic column packings, physical properties of solvents, positions of UV, IR, and NMR absorption bands, and other frequently used reference data are also included in the text. The literature surveyed in each section has been selected to demonstrate the range of applications of the technique in pharmaceutical analysis and to provide essential details of specific applications that can serve as a guide in related analytical development efforts. More comprehensive reviews of the applications literature are referenced whenever they are available.

Table 1
Classes of Problems in Pharmaceutical Analysis

- Detection, isolation, and identification of impurities in a drug substance or formulation
- Evaluation of the purity of reference standards of drug substances
- Purity determination of a drug substance for routine quality control
- Identification tests for quality control of a drug substance
- Determination of the potency of a formulation for routine quality control
- Identification of the drug substances in a formulation for routine quality control
- Evaluation of content uniformity for low dose formulations
- Analysis of other materials such as moisture, residual solvents, heavy metals, preservatives, specific impurities, etc. in drug substances and their formulations
- Determination of the chemical and physical stability of drug substances and their formulations
- Measurement of physical properties such as crystalline form, dissolution rate, disintegration times, hardness, pH, color, etc. for drug substances and formulations

INTRODUCTION

During the development of a new drug product, detailed chemical studies must be made of raw materials, synthetic intermediates, the drug substance itself, and the final formulated product. These studies must identify types and levels of impurities, degradation products, degradation rates, and analytical methods suitable for monitoring these factors. The information resulting from these studies is used to identify potential sources of safety problems in the product, to meet the requirements of foreign and domestic regulatory agencies, and as a basis for establishing quality control procedures and specifications for the product. The analytical effort required to provide this information can be divided into a number of tasks as shown in Table 1. The requirements for specificity, precision, accuracy, and the degree of complexity acceptable in the analytical procedure vary considerably from task to task and therefore require a variety of analytical techniques to satisfy them.

For example, the identification of impurities and degradation products requires the extensive use of chemical separations followed by qualitative analysis of the isolated product. Gas chromatography(GC) and high pressure liquid chromatography (HPLC) are frequently used to separate trace impurities, but older techniques such as thin layer chromatography (TLC), fractional crystallization, fractional distillation, and solvent extraction are still very important. However, the classical methods of identification by preparation and characterization of derivatives have been almost completely replaced by modern spectral methods of analysis. Elemental analysis, nuclear magnetic resonance spectroscopy (NMR), infrared spectroscopy (IR), and mass spectroscopy (MS) — especially GC/MS — are used almost exclusively for identification of unknown products.

In addition to identification of degradation products, it is necessary to measure the rates of degradation of the drug and its formulations under a variety of conditions. This information is needed to define conditions for storage and handling that will assure potency and safety throughout the expected shelf life of the product. Stability studies are especially demanding of analytical precision and accuracy because changes of a few percent over a period of 3 to 5 years are significant and must be accurately quantitated. In order to be able to detect such small changes reliably with a limited number of replicate assays at each time point, the analysis must be very precise, free of interference from the degradation products, and free of "drift" due to changes in instruments, standards, operators, etc. over a period of years. Gas chromatography, high pressure liquid chromatography, spectrophotometric, titrimetric, and electrochemical metbods are all capable of adequate precision. Regardless of the method of measurement, the procedure must be carefully designed to avoid chemical interferences and the method precision must be determined experimentally for use in designing the stability study.

The set of analytical procedures developed to control the quality of the final marketed product must include both qualitative and quantitative methods in order to assure the identity and purity of the product. Several categories of tests are usually included in a product specification and these are summarized in Table 2. All the procedures called out in the specification must be amenable to routine use in a quality control laboratory and must therefore be as simple and rapid as possible. The procedures used during product development can often be simplified without loss of essential specificity or accuracy because the real problems associated with the product have been defined by the developmental work. However, control limits on both the purity of the drug substance and the drug content of the finished formulation are usually very tight, thus requiring very precise quantitative procedures for testing compliance. The preferred solution to the problem of quantitative control assays is therefore to use

HPLC or GC methods which afford simplicity, high speed, good specificity, and excellent precision and accuracy. An alternate that may be chosen when suitable GC or HPLC systems cannot be found, or for facilities where these instruments are not readily available (a common problem in some foreign countries), is to combine a precise but nonspecific quantitative assay with a qualitative chromatographic test that shows the absence of interfering impurities. This approach is widely used in the compendia and in control procedures for older products. The quantitative analysis in these cases is often a titrimetric or spectrophotometric method, and the qualitative test a thin layer or paper chromatogram. Regardless of the methods chosen for the final measurement, quantitative analysis of formulated products almost always requires a preliminary separation of the drug from excipients. This separation is frequently accomplished by extraction, solvent partitioning, filtration, or column chromatography, but many other techniques find occasional application. In spite of the multiplicity of methods available, finding a reasonably simple procedure that gives a clean, quantitative separation of the drug from the excipients is often the most difficult step in development of procedures for analyzing formulations.

In many cases, quantitative analysis of drugs also requires the use of an analytical reference standard of well defined purity. A reference standard is required whenever a relative technique such as GC, HPLC, ultraviolet, visible or infrared spectrophotometry, fluorometry, or polarography is used for the analysis. Standards are also required for some qualitative tests such as identification by retention time, retention volume, R_f value. The evaluation of the reference standard is accomplished using a series of tests similar to those listed in Table 2 for analysis of the drug substance. However, relative analytical techniques cannot be used to obtain a purity value because of their requirement for a reference standard (area normalization is used to estimate purity from GC and HPLC traces, but the values obtained must be treated as rough approximations to the time purity). The purity value of the standard must instead be derived from absolute methods, i.e., methods which do not require a standard of the same substance. The available absolute methods are titrations and gravimetric procedures (including methods used for elemental analysis), NMR, coulometry, differential scanning calorimetry, and phase solubility analysis. The requirement for reference standards in analysis with a wide spectrum of applications in pharmaceutical development and control makes the absolute methods especially important in modern pharmaceutical analysis.

The range of problems encountered in pharmaceutical analysis coupled with the importance of achieving the highest specificity, precision, and accuracy possible result in new techniques for organic analysis being adopted quickly in the pharmaceutical industry. The purpose of this book is to review several of the newer methods that now find wide application in pharmaceutical analysis, as well as several older methods (e.g., phase solubility analysis and ultraviolet/visible spectroscopy) of unique importance. The principle of each technique is discussed with emphasis on factors that directly affect its proper application to analytical problems. A thorough understanding of these principles is essential when selecting instruments, operating conditions, and sample preparation procedures to optimize the performance of an analysis, or when trying to identify the cause of a failure encountered in an existing procedure. Tabulations of data useful in method development and applications are also presented, including tables of characteristic ir, nmr, and uv band positions; composition of standard buffer solutions; properties of solvents; and properties of column packings for GC and HPLC. Finally, selected applications of each technique to problems in pharmaceutical analysis are reviewed. It is hoped that the broad coverage given each of the selected techniques will make *Modern Methods of Pharmaceutical Analysis* useful as a source of ideas and guidance in developing practical solutions to problems in pharmaceutical analysis.

Table 1
ANALYTICAL TASKS IN DEVELOPMENT AND MARKETING OF A DRUG

Determination of identity and purity of starting materials and intermediates used in manufacturing the drug substance
Determination of the identity and purity of the drug substance
Isolation and identification of trace impurities in the drug substance
Determination of degradation rates and products for the drug substance
Determination of identity and purity of excipients used in manufacturing formulated products
Determination of degradation rates and products for the formulated drug
Establishment of an analytical reference standard for the drug substance

Table 2
OUTLINE OF QUALITY CONTROL TESTS FOR DRUG PRODUCTS

Identification Tests

Purpose: to confirm the identity of the principal component of a lot of raw material or formulation
Types of tests: color tests, melting points of the drug or derivative of the drug, formation of precipitates, ir or nmr spectrum, mass spectrum, X-ray powder pattern, chromatographic mobility, optical rotation, refractive index, density

Quantitative Analysis of the Drug Substance

Purpose: to determine the percent purity of the drug substance or the content of the active ingredient(s) in a formulation
Types of tests: *Absolute methods* — titrations, gravimetric procedures, differential scanning calorimetry, coulometry, nuclear magnetic resonance spectrometry, phase solubility analysis
Relative methods — gas chromatography, high pressure liquid chromatography, spectrometry (ultraviolet, visible, or infrared), fluorometry, polarography, microbiological assays

Tests for Specific Impurities

Purpose: to control the quantity of a specific impurity or group of inpurities in the drug product, such as water, solvents, metals, and trace organic impurities
Types of Tests: any test listed in Quantitative Analysis of the Drug Substance, atomic absorption, atomic emission, or semiquantitative limit tests using relative size of spots on thin layer chromatograms, spot tests with visual color comparison, etc.

Chromatographic Screen

Purpose: qualitative examination of the product for impurities, including contaminants not previously encountered
Types of tests: paper, thin layer, gas or high pressure liquid chromatography; electrophoresis; bioautography

Miscellaneous

Purpose: control of specific properties known to affect product performance or required by regulatory agencies
Types of tests: crystal form (X-ray or infrared spectroscopy), sterility, pyrogens, particle size, foreign matter, density, color, odor, etc.

THE EDITOR

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Dr. Schirmer is a member of the American Association for the Advancement of Science, American Chemical Society, Society for Applied Spectroscopy, American Physical Society, and the Academy of Pharmaceutical Sciences of the American Pharmaceutical Association. He has a number of publications in the areas of pharmaceutical analysis and applications of nmr to problems in chemical kinetics and structure, including a book, *The Nuclear Overhauser Effect* co-authored with Dr. Joseph Noggle.

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TABLE OF CONTENTS

Chapter 1

NUCLEAR MAGNETIC RESONANCE SPECTROSCOPY

Roger E. Schirmer

Table of Contents

I. INTRODUCTION

Nuclear magnetic resonance (NMR) spectroscopy is the branch of spectroscopy dealing with the absorption of radio frequency radiation by substances held in a magnetic field. Absorption results from interaction of the radiation with the magnetic moment of nuclei in the sample, and it occurs at different frequencies for nuclei in chemically different environments within a molecule (Figure 1). Because the dependence of frequency on chemical environment is relatively simple, NMR has become an extremely important tool for elucidation of molecular structure, including stereochemistry and conformation. The sensitivity of the NMR spectrum to molecular structure makes it an excellent choice for identification testing in pharmaceutical analysis.

NMR also offers several unique advantages as a quantitative analytical technique. First, it is an absolute quantitative technique, in the sense that a reference standard of the substance being analyzed is not required. Proper choice of the absorption band used in an analysis will often yield a very specific assay which requires very little sample preparation prior to measurement. Finally, NMR is applicable to a very wide range of organic and inorganic compounds.

The principle disadvantages of NMR are the high cost of the instrument and its lack of sensitivity. Under typical operating conditions, a minimum 10 mg sample is required for NMR analysis. Use of signal averaging, high magnetic field strengths, and other special techniques can reduce the quantity of sample to as low as 10 μg in favorable cases, but only with a considerable loss of convenience. Nonetheless, many quantitative applications of NMR in pharmaceutical analysis have been reported in the literature, and the number of applications can be expected to increase rapidly in the future.

II. THEORY OF NMR

The theory of NMR is treated in numerous reference books at the elementary,[1-7] intermediate,[8,9] and advanced levels.[10] The theory will be reviewed here only to the extent necessary to provide a basis for discussing the applications of NMR in pharmaceutical analysis.

A. Nuclear Magnetic Moments

One of the physical properties characterizing a nucleus is its angular momentum. The maximum observable value of the angular momentum is $\hbar I$, where $h = h/2\pi$ where h is Planck's constant and I is the spin quantum number of the nucleus. I is restricted to integral and half integral values. A nucleus with spin I has $2I + 1$ states with corresponding observable components of the angular momentum of $\hbar I$, $\hbar(I - 1)$, $\hbar(I - 2)$,..., $\hbar(-I)$.

Nuclei for which I is not zero also have a magnetic moment which is parallel to the angular momentum vector. The magnitudes of the observable components of the angular momentum and magnetic moment are related by $\mu = \gamma(\hbar I)$ where γ is the gyromagnetic ratio of the nucleus. If the magnetic moment of the nucleus is μ, the maximum observable components of μ are given by $m\mu/I$ where m is the magnetic quantum number and may assume values I, $I - 1$, $I - 2$,..., $-I$. The $2I + 1$ values of the observable component of the magnetic moment correspond to the $2I + 1$ angular momentum states of the nucleus. In the absence of electromagnetic fields, all $2I + 1$ states will have the same energy.

When the spin quantum number of a nucleus is greater than ½, the nucleus will have an electric quadrupole moment in addition to its magnetic moment. This is of considerable importance in NMR spectroscopy because the electric quadrupole moment allows the nucleus to interact with electric as well as magnetic fields, and the electric field interactions are often much stronger than the magnetic interactions. As will be seen a little later, this has an important effect on the width and fine structure in an NMR band. Table 1 lists nuclei with nonzero values of I along with their quadrupole moments and natural abundances. All the elements listed in the table can be studied using NMR techniques. A useful relation between the atomic number (Z), isotopic mass (A) and nuclear spin I is displayed in the following:[1]

1. I is half-integral if A is odd
2. I is zero if both A and Z are even
3. I is integral if A is even but Z is odd

As indicated above, only nuclei with nonzero values of I will have NMR spectra.

B. Nuclear Energy Levels for an Isolated Nucleus in a Magnetic Field

If a magnetic nucleus ($I = 0$) is placed in a magnetic field of strength H, the $2I + 1$ nuclear energy levels will no longer be degenerate, but will have energies given by

$$E_m = m\gamma\hbar H \qquad (1)$$

where m is the magnetic quantum number. The spacing between levels is therefore $\gamma\hbar H$, and is quite small. An example is given in Figure 2. The small spacing between levels limits the absorption of electromagnetic radiation to rather long wavelengths. In particular, NMR spectrometers normally operate at wavelengths between 1 and 300m in the radiofrequency region. The corresponding frequency range is approximately 1 to 350 MHz. The small difference in energy also leads to almost equal populations for the energy levels. The populations of the upper and lower magnetic states will differ only by a few parts per million at room temperature.

The very small population differences have important implications for practical NMR spectroscopy. Net absorption of energy from a radiofrequency field is the result of transitions of nuclei from lower to higher nuclear energy levels, and will only occur when the lower level has a greater population than the upper. As the excess is only one in a million at room temperature, a maximum of one out of every million nuclei is able to participate in energy absorption at a given instant, which is a major cause of the low sensitivity of NMR compared to other spectroscopic techniques. Once excited to an upper level, nuclei are often very slow to return to the lower level: half lives of excited states for a number of frequently studied nuclei including ^1H and ^{13}C are on the order of seconds. A radiofrequency field of moderate intensity can cause upward transitions more rapidly than the nuclei can relax back to the lower states.

A

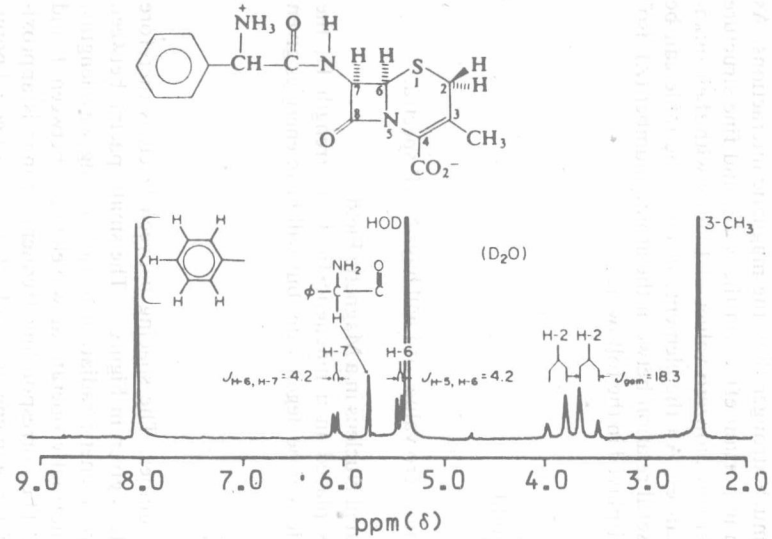

FIGURE 1(A). 60 MHz ^1H NMR Spectrum of cephalexin in D_2O. (From Ryan, C. W., Simon, R. L., and van Heyningen, E. M., *J. Med. Chem.*, 12, 310, 1969, With permission.)

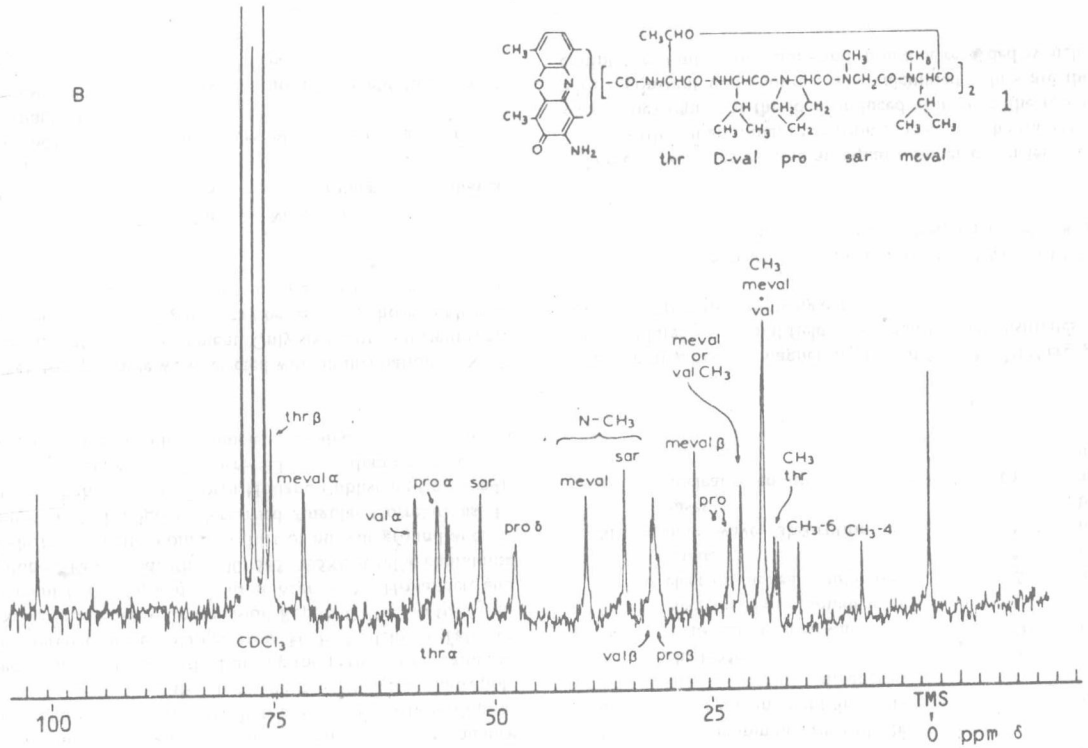

FIGURE 1(B). 25.15 MHz noise decoupled ^{13}C NMR spectrum of actinomycin D in $CDCl_3$. Only the high field portion of the spectrum (0 to 120 ppm with respect to TMS) is shown. (From Booth, H., Mauger, A. B., and Rzeszotarski, W. J., *Org. Magn. Reson.*, 8, 219, 1976. With permission.)

Table 1
NUCLEAR SPINS, MOMENTS, AND MAGNETIC RESONANCE FREQUENCIES

Kenneth Lee and Weston A. Anderson

1967

This table contains the published values for the nuclear spins, magnetic moments, and quadrupole moments, and the calculated values for the nuclear magnetic resonance (NMR) frequency and for the relative sensitivities. Only those isotopes with both published spin and magnetic moment values are tabulated. The magnetic and quadrupole moment values were selected from results published during the period from January, 1955 to June, 1967. Earlier references were obtained from H. E. Walchi, A Table of Nuclear Moment Data, U.S. Atomic Energy Commission Report ORNL—1469, Supplement I (1953) and Supplement II (1955), and D. Streminger, J. M. Hollander, and G. T. Seaborg, Table of Isotopes, Rev. Mod. Phys. 30, 585 (1958). A table containing the known (1963) spin and electromagnetic moment values of nuclear ground and excited states has been compiled by I. Lindgren, Perturbed Angular Correlations; E. Karlsson, E. Mathias, and K. Siegbahn, editors; North-Holland Publishing Co. (1964). The magnetic moments given in this latter table are corrected for the diamagnetic effect. A more complete list of spin and moment results for nuclei in excited states are included in Lindgren's table.

In general, the results chosen for this table were selected with an inclination to NMR measurements and to the precision of the measurement. Only six significant figures are used in this table. Therefore, the number of figures may be less than those published. The experimental methods employed in determing the moments are indicated by the following symbols:

- Ab = atomic beam magnetic resonance (hyperfine structure, double or triple resonance or other method)
- Mb = molecular (or diamagnetic) beam magnetic resonance
- Mc = miscellaneous
- Mo = Mossbauer effect
- N = nuclear magnetic resonance

Other symbols used in the table are:

- A = atomic weight (mass number)
- El = element
- I = nuclear spin in units of $h/2\pi$
- μ = magnetic moment in units of the nuclear magneton $eh/4\pi Mc$
- m = metastable excited state
- E = electron spin resonance or electron-nuclear double resonance
- M = microwave absorption in gases
- No = nuclear orientation
- O = optical spectroscopy (hyperfine structure, band structure, double resonance, or optical pumping)
- Qr = quadrupole resonance
- Q = quadrupole moment in units of barns (10^{-24} cm^2)
- Z = atomic number
- * = radioactive isotope
- * = magnetic moment observed by NMR
- ( ) = assumed or estimated values

Assuming a nuclear magneton value of 5.0505×10^{-24} erg/gauss, the NMR frequency was calculated for a total field of 10^4 gauss. The sensitivites, relative to the proton, are calculated from the following expressions:

$$\text{Sensitivity at constant field} = 7.652 \times 10^{-3} \mu^2 (I+1)/I^2$$
$$\text{Sensitivity at constant frequency} = 0.2387\, \mu(I+1).$$

These expressions assume an equal number of nuclei, a constant temperature, and $T_1 = T_2$ (the longitudinal relaxation time equals the transverse relaxation time). These sensitivities represent the ideal induced voltage in the receiver coil at saturation and with a constant noise source. The calculated values are therefore determined under complete optimum conditions and should be regarded as such.

Isotope			Spin I	NMR Frequency in MHz for a 10 kilogauss field	Natural Abundance %	Relative Sensitivity for Equal Number of Nuclei		Magnetic Moment μ			Electric Quadrupole Moment Q		
Z	El	A				At constant field	At constant frequency	In multiples of the nuclear magneton (eh/4πMc)	Reference	Method	In multiples of barns (10^{-24}cm^2)	Reference	Method
0	n	1*	1/2	29.167	—	0.322	0.685	−1.91315	1	Ab	—		
1	*H	1	1/2	42.5759	99.985	1.00	1.00	2.79268	2	N	—		
1	*H	2	1	6.53566	1.5×10^{-2}	9.65×10^{-3}	0.409	0.857387	3	N	2.73×10^{-3}	4	Ab
1	*H	3*	1/2	45.4129	—	1.21	1.07	2.97877	5	N	—		
2	*He	3	1/2	32.433	1.3×10^{-4}	0.442	0.762	−2.1274	6 7	N	—		
3	*Li	6	1	6.2653	7.42	8.50×10^{-3}	0.392	0.82192	8	N	6.9×10^{-4}	9	N
3	*Li	7	3/2	16.546	92.58	0.293	1.94	3.2560	8	N	-3×10^{-2}	10	O
3	Li	8*	2	6.300	—	2.59×10^{-2}	1.184	1.653	11	Ab			
4	*Be	9	3/2	5.9834	100	1.39×10^{-2}	0.703	−1.1774	12 13	N	5.2×10^{-2}	14	Ab
5	*B	10	3	4.5754	19.58	1.99×10^{-2}	1.72	1.8007	15	N	7.4×10^{-2}	16	Ab
5	*B	11	3/2	13.660	80.42	0.165	1.60	2.6880	17	N	3.55×10^{-2}	16	Ab
6	*C	13	1/2	10.7054	1.108	1.59×10^{-2}	0.251	0.702199	18	N	—		
7	N	13*	1/2	4.91	—	1.53×10^{-3}	0.115	(−)0.322	19	Ab	—		
7	*N	14	1	3.0756	99.63	1.01×10^{-3}	0.193	0.40347	20 21	N	1.6×10^{-2}		Mc
7	*N	15	1/2	4.3142	0.37	1.04×10^{-3}	0.101	−0.28298	20 21	N	—		
8	O	15*	1/2	11.0	—	1.70×10^{-2}	0.257	0.719	23	Ab	—		
8	*O	17	5/2	5.772	3.7×10^{-2}	2.91×10^{-2}	1.58	−1.8930	24	N	-2.6×10^{-2}	25	M
9	*F	17*	5/2	14.40	—	0.451	3.94	4.720	26	N			
9	*F	19	1/2	40.0541	100	0.833	0.941	2.62727	17 21	N	—		
9	*F	20*	2	7.977	—	5.26×10^{-2}	1.50	2.093	27	N			
10	Ne	19*	(1/2)	28.75	—	0.308	0.675	−1.886	28	Ab			
10	Ne	21	3/2	3.3611	0.257	2.50×10^{-3}	0.395	−0.66140	29	Ab			
11	Na	21*	3/2	12.126	—	0.116	1.42	2.3861	30	Ab			
11	Na	22*	3	4.436	—	1.81×10^{-3}	1.67	1.746	31	Ab			
11	*Na	23	3/2	11.262	100	9.25×10^{-2}	1.32	2.2161	17	N	0.14-0.15	32 33	O
11	Na	24*	4	3.221	—	1.15×10^{-2}	2.02	1.690	34	Ab			
12	*Mg	25	5/2	2.6054	10.13	2.67×10^{-3}	0.714	−0.85449	13	N			
13	*Al	27	5/2	11.094	100	0.206	3.04	3.6385	35	N	0.149	36	Ab
14	*Si	29	1/2	8.4578	4.70	7.84×10^{-3}	0.199	−0.55477	37	N	—		
15	*P	31	1/2	17.235	100	6.63×10^{-2}	0.405	1.1305	38	N	—		
15	P	32*	1	1.923	—	2.46×10^{-4}	0.120	−0.2523	39	E			
16	*S	33	3/2	3.2654	0.76	2.26×10^{-3}	0.383	0.64257	37	N	-6.4×10^{-2}	40	M
16	S	35*	3/2	5.08	—	8.50×10^{-3}	0.597	1.00	41	M	4.5×10^{-2}	40	M
17	*Cl	35	3/2	4.1717	75.53	4.70×10^{-3}	0.490	0.82091	8	N	-7.89×10^{-2}	42	Ab
17	*Cl	36*	2	4.8931	—	1.21×10^{-3}	0.919	1.2838	43	N	-1.72×10^{-2}	44	M
17	*Cl	37	3/2	3.472	24.47	2.71×10^{-3}	0.408	0.6833	45	N	-6.21×10^{-2}	42	Ab
18	Ar	37*	3/2	5.08	—	8.50×10^{-3}	0.597	1.0	240	O			
19	K	38*	3	3.491	—	8.82×10^{-3}	1.31	1.374	46	Ab			
19	*K	39	3/2	1.9868	93.10	5.08×10^{-4}	0.233	0.39097	47 48	N	0.11	49 50	O
19	K	40*	4	2.470	1.18×10^{-2}	5.21×10^{-3}	1.55	−1.296	51	Mb			
19	*K	41	3/2	1.0905	6.88	8.40×10^{-5}	0.128	0.21459	48	N			
19	K	42*	2	4.345	—	8.50×10^{-3}	0.816	−1.140	52	Ab			
19	K	43*	3/2	0.828	—	3.68×10^{-5}	9.73×10^{-2}	0.163	53	Ab			

Isotope			Spin I	NMR Frequency in MHz for a 10 kilogauss field	Natural Abundance %	Relative Sensitivity for Equal Number of Nuclei		Magnetic Moment μ			Electric Quadrupole Moment Q		
Z	El	A				At constant field	At constant frequency	In multiples of the nuclear magneton (eh/4πMc)	Reference	Method	In multiples of barns (10^{-24}cm^2)	Reference	Method
20	*Ca	41*	7/2	3.4681	—	1.14×10^{-3}	1.71	−1.5924	54	N			
20	*Ca	43	7/2	2.8646	0.145	6.40×10^{-3}	1.41	−1.3153	55	N			
21	Sc	43*	7/2	10.04	—	0.275	4.95	4.61	56	Ab	−0.26	56	Ab
21	Sc	44*	2	9.76	—	9.63×10^{-2}	1.83	2.56	57	Ab	0.14	57	Ab
21	Sc	44^*_m	6	5.03	—	9.24×10^{-2}	6.62	3.96	57	Ab	0.37	57	Ab
21	*Sc	45	7/2	10.343	100	0.301	5.10	4.7492	58	N	−0.22	59	Ab
21	Sc	46*	4	5.77	—	6.65×10^{-2}	3.62	3.03	60	Ab	0.12	60	Ab
21	Sc	47*	7/2	11.6	—	0.426	5.73	5.33	56	Ab	−0.22	56	Ab
22	Ti	45*	7/2	2.207	—	2.40×10^{-6}	0.102	0.095	61	Ab	1.5×10^{-2}	61	Ab
22	*Ti	47	5/2	2.4000	7.28	2.09×10^{-3}	0.658	−0.78710	62	N			
22	*Ti	49	7/2	2.4005	5.51	3.76×10^{-3}	1.18	−1.1022	62	N			
23	V	49*	7/2	9.71	—	0.249	4.79	4.46	63	E			
23	*V	50	6	4.2450	0.24	5.55×10^{-2}	5.58	3.3413	8	N			
23	*V	51	7/2	11.19	99.76	0.382	5.52	5.139	64	N	-4×10^{-2}	65	O
24	*Cr	53	3/2	2.4065	9.55	9.03×10^{-4}	0.283	−0.47354	66	N			
25	Mn	52*	6	3.907	—	4.33×10^{-2}	5.14	3.075	67	Ab			
25	Mn	52^*_m	2	0.030	—	2.9×10^{-9}	5.73×10^{-2}	0.008	68	Ab			
25	Mn	53*	7/2	11.0	—	0.362	5.42	5.05	69	E			
25	Mn	54*	(2) (3)	8.4 6.6	—	6.11×10^{-2} 5.98×10^{-2}	1.58 2.48	(2.2) (2.6)	70	No			
25	*Mn	55	5/2	10.501	100	0.175	2.88	3.444	71	E	0.55	72	M
25	Mn	56*	3	8.233	—	0.116	3.09	3.240	73	Ab			
26	*Fe	57	1/2	1.3758	2.19	3.37×10^{-5}	3.23×10^{-2}	0.09024	74	E	—		
27	Co	55*	7/2	10.0	—	0.274	4.94	4.6	75	No			
27	Co	56*	4	7.34	—	0.136	4.60	3.85	76	E			
27	Co	57*	7/2	10.1	—	0.283	4.99	4.65	76	E			
27	Co	58*	2	15.4	—	0.381	2.90	4.05	77	E			
27	*Co	59	7/2	10.054	100	0.277	4.96	4.6163	241 242	N	0.40	78	Ab
27	Co	60*	5	5.793	—	0.101	5.44	3.800	79	E			
28	*Ni	61	3/2	3.8047	1.19	3.57×10^{-3}	0.447	−0.74868	80	N			
29	Cu	61*	3/2	10.8	—	8.22×10^{-2}	1.27	2.13	81	Ab			
29	*Cu	63	3/2	11.285	69.09	9.31×10^{-2}	1.33	2.2206	8	N	−0.16	82	E
29	Cu	64*	1	3.1	—	9.79×10^{-4}	0.191	0.40	83	Ab			
29	*Cu	65	3/2	12.089	30.91	0.114	1.42	2.3789	8	N	−0.15	82	E
29	Cu	66*	1	1.65	—	1.54×10^{-4}	0.103	−0.216	81	Ab			
30	Zn	65*	5/2	2.345	—	1.95×10^{-3}	0.643	0.7692	83	O	-2.4×10^{-2}	83	O
30	*Zn	67	5/2	2.663	4.11	2.85×10^{-3}	0.730	0.8733	37	N	0.15	83	O
31	Ga	68*	1	0.0892	—	2.45×10^{-6}	5.59×10^{-3}	0.0117	84	Ab	3.1×10^{-2}	84	Ab
31	Ga	69	3/2	10.22	60.4	6.91×10^{-2}	1.20	2.011	8	N	0.178	85	Ab
31	Ga	71	3/2	12.984	39.6	0.142	1.52	2.5549	8	N	0.112	85	Ab
31	Ga	72*	3	0.33591	—	7.80×10^{-6}	0.126	−0.13220	86	Ab	0.72	86	Ab
32	Ge	71*	1/2	8.4	—	7.64×10^{-3}	0.197	0.55	87	Ab	—		
32	*Ge	73	9/2	1.4852	7.76	1.40×10^{-2}	1.15	−0.87679	62	N	−0.2	88	M
33	*As	75	3/2	7.2919	100	2.51×10^{-2}	0.856	1.4349	15	N	0.3	89	M
33	As	76*	2	3.45	—	4.27×10^{-3}	0.649	−0.906	90	No			
34	*Se	77	1/2	8.118	7.58	6.93×10^{-3}	0.191	0.5325	8	N	—		
34	Se	79	7/2	2.22	—	2.98×10^{-3}	1.10	−1.02	91	M	0.9	40	M
35	Br	76*	1	4.18	—	2.52×10^{-3}	0.262	(−)0.548	92	Ab	0.27	92	Ab

NUCLEAR SPINS, MOMENTS, AND MAGNETIC RESONANCE FREQUENCIES (Continued)

Isotope Z	El	A	Spin I	NMR Frequency in MHz for a 10 kilogauss field	Natural Abundance %	Relative Sensitivity for Equal Number of Nuclei: At constant field	At constant frequency	Magnetic Moment μ: In multiples of the nuclear magneton (eh/4πMc)	Reference	Method	Electric Quadrupole Moment Q: In multiples of barns (10^{-24}cm²)	Reference	Method
35	*Br	79	3/2	10.667	50.54	7.96x10⁻²	1.25	2.0990	8	N	0.33	93	Ab
35	Br	80*	1	3.92	—	2.08x10⁻³	0.245	0.514	94	Ab	0.20	94	Ab
35	Br	80^*_m	5	2.008	—	4.20x10⁻³	1.89	1.317	94	Ab	0.76	94	Ab
35	*Br	81	3/2	11.498	49.46	9.85x10⁻²	1.35	2.2626	8	N	0.28	93	Ab
35	Br	82*	5	2.479	—	7.90x10⁻³	2.33	(+)1.626	95	Ab	(+)0.76	95	Ab
36	*Kr	83	9/2	1.638	11.55	1.88x10⁻³	1.27	−0.9671	96	N	0.15	97	O
36	Kr	85*	9/2	1.6956	—	2.08x10⁻³	1.31	−1.001	98	O	0.25	98	O
37	Rb	81*	3/2	10.4	—	7.32x10⁻²	1.22	2.05	99	Ab			
37	Rb	82^*_m	5	2.29	—	6.20x10⁻³	2.15	1.50	99	Ab			
37	Rb	83*	5/2	4.33	—	1.23x10⁻²	1.19	1.42	99	Ab			
37	Rb	84*	2	5.03	—	1.32x10⁻²	0.945	−1.32	99	Ab			
37	*Rb	85	5/2	4.1108	72.15	1.05x10⁻²	1.13	1.3482	100	N	0.27	101	Ab
37	Rb	86*	2	6.44	—	2.77x10⁻²	1.21	−1.69	102	Ab			
37	*Rb	87	3/2	13.931	27.85	0.175	1.64	2.7414	103	N	0.13	101	Ab
38	*Sr	87	9/2	1.8452	7.02	2.69x10⁻³	1.43	−1.0893	66	N	0.2	104	E
39	*Y	89	1/2	2.0859	100	1.18x10⁻⁴	4.90x10⁻²	−0.13682	47	N	—		
39	Y	90*	2	6.17	—	2.44x10⁻²	1.16	−1.62	105	Ab	−0.16	105	Ab
39	Y	91*	1/2	2.49	—	1.99x10⁻⁴	5.84x10⁻²	0.163	60	Ab	—		
40	*Zr	91	5/2	3.97249	11.23	9.48x10⁻³	1.09	−1.30284	106	N			
41	*Nb	93	9/2	10.407	100	0.482	8.07	6.1435	107	N	−0.2	108	O
42	*Mo	95	5/2	2.774	15.72	3.23x10⁻³	0.760	0.9097	45	N	0.12	109	N
42	*Mo	97	5/2	2.832	9.46	3.43x10⁻³	0.776	−0.9289	45	N	1.1	109	N
43	*Tc	99*	9/2	9.5830	—	0.376	7.43	5.6572	110	N	0.3	111	O
44	Ru	99	3/2	1.44	12.72	1.95x10⁻⁴	0.169	−0.284	112	Mo			
44	Ru	101	5/2	2.1	17.07	1.41x10⁻³	0.576	−0.69	113	O			
45	*Rh	103	1/2	1.3401	100	3.11x10⁻⁵	3.15x10⁻²	−0.08790	43 114	N	—		
46	*Pd	105	5/2	1.95	22.23	1.12x10⁻³	0.534	−0.639	115	N			
47	Ag	104*	5	6.1	—	0.118	5.73	4.0	116	Ab			
47	Ag	104^*_m	2	14.0	—	0.291	2.65	3.7	116	Ab			
47	Ag	105*	1/2	1.54	—	4.73x10⁻⁵	3.62x10⁻²	0.101	117	Ab	—		
47	*Ag	107	1/2	1.7229	51.82	6.62x10⁻⁵	4.05x10⁻²	−0.11301	47 118	N	—		
47	Ag	108*	1	32.0	—	1.13	2.01	4.2	119	Ab			
47	*Ag	109	1/2	1.9807	48.18	1.01x10⁻⁴	4.65x10⁻²	−0.12992	47 118	N	—		
47	Ag	110^*_m	6	4.557	—	6.87x10⁻³	5.99	3.587	120	Ab			
47	Ag	111*	1/2	2.21	—	1.40x10⁻⁴	5.19x10⁻²	−0.145	121	Ab	—		
47	Ag	112*	2	0.2077	—	9.00x10⁻⁷	3.90x10⁻²	0.0545	122	Ab			
47	Ag	113*	1/2	2.41	—	1.81x10⁻⁴	5.66x10⁻²	0.158	122	Ab	—		
48	Cd	107*	5/2	1.879	—	1.00x10⁻³	0.515	−0.6162	123	O	0.8	123	O
48	Cd	109*	5/2	2.529	—	2.44x10⁻³	0.693	−0.8293	124	O	0.8	124	O
48	*Cd	111	1/2	9.028	12.75	9.54x10⁻³	0.212	−0.5922	125 126	N	—		
48	*Cd	113	1/2	9.445	12.26	1.09x10⁻²	0.222	−0.6195	125 126	N	—		
48	Cd	113^*_m	11/2	1.51	—	2.13x10⁻³	1.69	−1.09	239	O	−0.79	239	O
48	Cd	115*	1/2	9.862	—	1.24x10⁻²	0.232	−0.6469	127	O	—		
48	Cd	115^*_m	11/2	1.447	—	1.87x10⁻³	1.62	−1.044	127	O	−0.61	127	O
49	*In	113	9/2	9.3099	4.28	0.345	7.22	5.4960	45	N	1.14	97	Ab
49	In	113^*_m	1/2	3.209	—	4.28x10⁻⁴	7.54x10⁻²	−0.2105	128	Ab	—		
49	In	114^*_m	5	7.2	—	0.191	6.73	4.7	129	Ab			
49	*In	115*	9/2	9.3301	95.72	0.347	7.23	5.5079	130	N	1.16	97	Ab
49	In	115^*_m	1/2	3.715	—	6.64x10⁻⁴	8.73x10⁻²	−0.2437	131	Ab	—		
49	In	116*	5	6.42	—	0.137	6.03	4.21	132	Ab			
49	In	116^*_m	5	6.7	—	0.156	6.30	4.4	129	Ab			
50	*Sn	115	1/2	13.922	0.35	3.50x10⁻²	0.327	−0.91320	125	N	—		
50	*Sn	117	1/2	15.168	7.61	4.52x10⁻²	0.356	−0.99490	125	N	—		
50	*Sn	119	1/2	15.869	8.58	5.18x10⁻²	0.373	−1.0409	125	N	—		
51	*Sb	121	5/2	10.189	57.25	0.160	2.79	3.3415	133	N	−0.5	134	O
51	Sb	122*	2	7.24	—	3.94x10⁻²	1.36	−1.90	135 136	No			
51	*Sb	123	7/2	5.5176	42.75	4.57x10⁻²	2.72	2.5334	45	N	−0.7	134	O
52	Te	119*	1/2	4.12	—	9.04x10⁻⁴	9.67x10⁻²	0.27	137	Ab	—		
52	*Te	123	1/2	11.16	0.87	1.8x10⁻²	0.262	−0.7319	37	N	—		
52	*Te	125	1/2	13.45	6.99	3.15x10⁻²	0.316	−0.8824	37	N	—		
53	I	125*	5/2	9.0	—	0.116	2.51	3	138	M	−0.66	138	M
53	*I	127	5/2	8.5183	100	9.34x10⁻²	2.33	2.7937	139	N	−0.69	134	O
53	*I	129*	7/2	5.6694	—	4.96x10⁻²	2.80	2.6031	139	N	−0.48	140	Qr
53	I	131*	7/2	5.963	—	5.77x10⁻²	2.94	2.738	141	Ab	−0.41	141	Ab
54	*Xe	129	1/2	11.777	26.44	2.12x10⁻²	0.277	−0.77247	142	N	—		
54	*Xe	131	3/2	3.4911	21.18	2.76x10⁻³	0.410	0.68697	142	N	−0.12	143	O
55	Cs	127*	1/2	21.8	—	0.134	0.512	1.43	144	Ab	—		
55	Cs	129*	1/2	22.4	—	0.146	0.526	1.47	144	Ab	—		
55	Cs	130*	1	10.7	—	4.20x10⁻²	0.668	1.4	144	Ab			
55	Cs	131*	5/2	10.72	—	0.186	2.94	3.517	145	Ab			
55	Cs	132*	2	8.46	—	6.28x10⁻²	1.59	2.22	144	Ab			
55	*Cs	133	7/2	5.58469	100	4.74x10⁻²	2.75	2.56422	8	N	−3x10⁻³	146 147	Ab
55	Cs	134*	4	5.666	—	6.28x10⁻²	3.55	2.973	148	Ab	0.43	149	O
55	Cs	134^*_m	8	1.0447	—	1.42x10⁻²	2.36	1.0964	150	Ab			
55	Cs	135*	7/2	5.9096	—	5.62x10⁻²	2.91	2.7134	148	Ab			
55	Cs	137*	7/2	6.1459	—	6.32x10⁻²	3.03	2.8219	148	Ab			
56	*Ba	135	3/2	4.2296	6.59	4.90x10⁻³	0.497	0.83229	151 152	N	0.25	153	O
56	*Ba	137	3/2	4.7315	11.32	6.86x10⁻³	0.556	0.93107	151 152	N	0.2	153	O
57	*La	138	5*	5.6171	0.089	9.19x10⁻²	5.28	3.6844	154	N	2.7	154	N
57	*La	139	7/2	6.0144	99.911	5.92x10⁻²	2.97	2.7615	107	N	0.21	155	Ab
58	Ce	137*	3/2	4.6	—	6.20x10⁻³	0.537	0.9	156	No			
58	Ce	137^*_m	11/2	0.96	—	5.40x10⁻⁴	1.07	0.69	157	No			
58	Ce	139*	3/2	5.1	—	8.50x10⁻³	0.597	1.0	156	No			
58	Ce	141*	7/2	2.1	—	2.57x10⁻³	1.04	0.97	158	E			