Nuclear Magnetic Resonance

Nuclear magnetic resonance is a phenomenon of absorption and emission of energy in the radiofrequency range of the electromagnetic spectrum by certain atomic nuclei when placed within a magnetic field.

From: Haschek and Rousseaux's Handbook of Toxicologic Pathology (Third Edition), 2013

Related terms:

Peptide, Protein, Carbon 13, Metabolite, RNA, Nuclear Magnetic Resonance Spectroscopy, Proton Nuclear Magnetic Resonance, Proton, Ligand

View all Topics

Nuclear magnetic resonance

Leonardo Vazquez, Gauri Misra, in Data Processing Handbook for Complex Biological Data Sources, 2019

5.1 Introduction

The nuclear magnetic resonance (NMR) technique applied to biological systems is a powerful tool for structural determination and dynamics of both small organic molecules and biopolymers. The dynamic aspects and inherent flexibility play a central role in the facets of biological functionality [1,2]. Regarding natural biopolymers, such as proteins, nucleic acids, and carbohydrates, the structural fluctuations of these molecules can range from nanoseconds to hours, referred to as molecular dynamics [3–5].

The currently available NMR experiments cover a broad spectrum of the observable time-scales phenomena showed by both small molecules and biopolimers (Fig. 5.1). It is possible to monitor structural fluctuations, which may offer information about fast or slow movements. The cellular environment experienced by the molecule includes a wide range of pH, salinity, solutes, and temperature, which exhibits a significant effect on the structure of these molecules [6–10].

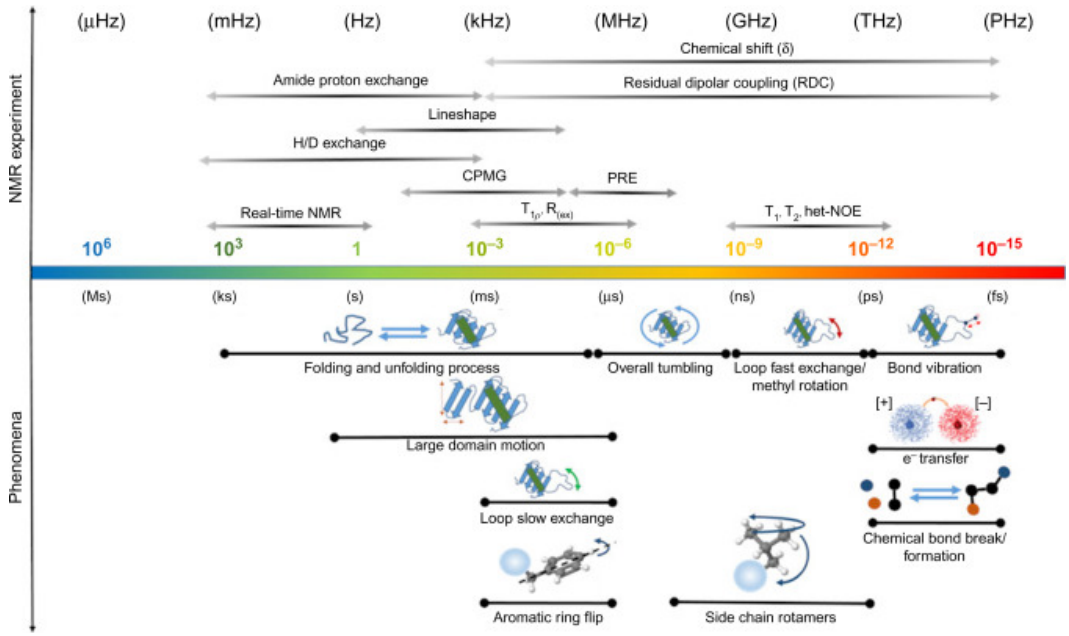

Figure 5.1. General scheme of the NMR techniques and the phenomena associated.

The history of NMR starts in the early 1940s, specifically in 1943, with Dr. Otto Stern at the Carnegie Institute of Technology, United States. He received the Nobel Prize in 1944 for the description of the angular momentum of quantized subatomic particles. He proposed electrons and atoms can act as rotational punctual charges and thus, generate a magnetic field on their surroundings. This work, therefore, opened the doors for further studies of the magnetic properties of nuclei [11].

A few years later, Dr. Isidor I. Rabi, Dr. Felix Bloch, and Dr. Edward M. Purcell, all in the United States, established the first effective approaches to study of NMR and data interpretation expanding the need for a new field of study and deepening the comprehension of the composition of different materials at the atomic level [12,13].

Several years later, Dr. Richard R. Ernst (Nobel Prize, 1991) in Switzerland and Dr. Kurt H. Wüthrich (Nobel Prize, 2002), in the United States and Switzerland, contributed to the development of the high-resolution NMR approach for chemistry and the development of an innovative method for mapping and elucidation of the 3D structure of biological macromolecules in solution [14,15].

With the advent of these methodological advances, today it is possible to extract detailed information related to the structure and dynamics of proteins, molecular complexes, carbohydrates, and nucleic acids in atomic resolution [16–19]. Practical NMR applications include:

1. Measurements and description of the molecular dynamics at the atomic level.
2.

Modeling of protein and carbohydrate structures. However, there are some limitations regarding the molecular weight of these biopolymers. To overcome this problem, new strategies for data acquisition and differential isotopic labeling are possible options [20–22].

3. Intermolecular interactions are widely used for screening of drugs and ligands in the cell, also including biomimetic membranes [16,23].
4. Understanding the mechanisms behind the protein folding is an important application of this technique, as the structural features, dynamic movements, and interaction measurements collaborate for the precise determination of folding mechanisms [24].

Besides the applications on biopolymers, the advances in the organic chemistry brought precise and productive tools for acquisition and analysis of biological fluids like urine, sweat, and saliva. Furthermore, in the metabolomics, it is possible to find specific metabolites in complex mixtures [25–27]. The structural analysis of organic molecules and natural products were, indeed, greatly benefited from these advances [28–30]. The lessons learned from the experience with small molecules have led to significant applications of these techniques in biopolymers with the development of bi- or multidimensional NMR experiments [31,32].

In addition to these applications, the low field NMR, which presents hydrogen frequencies below 100 MHz, has many areas of application, especially relaxometry experiments (transverse relaxation measurements), hyperpolarization, prepolarization, and diffusiometry assays.

This kind of technique is usually economical compared with the measurements using high field magnets. This technique, allows the researcher to obtain direct data interpretation, besides the commercial acquisition of robust and portable spectrometer, which is highly desirable in industrial applications involving food and crude oil industries [33–35].

In diagnostic medicine, the development of magnetic resonance imaging (MRI) has reached a significant qualitative advance, based on hydrogen nuclei, mainly by the study of two researchers: Dr. Paul C. Lauterbur and Dr. Peter Mansfield [36]. This technique became the central tool in noninvasive diagnosis and functional monitoring of in vivo systems, helping in the functional evaluation of physiological disorders.

There are some limitations to the use of high field NMR as an analytical method for the description of biological samples in solution. For instance, a protein with high molecular weight may be a challenge on use of this technique, because the dispersion of the magnetization is too fast, which does not allow several pulse sequences [37]. However, in some cases, this limitation can be partially overcome by modifying the physical conditions of the sample such as increase in temperature

(it increases the tumbling rate, decreasing the viscosity) and buffer solvent. The problem has to be analyzed for each sample, depending on the purpose of the user.

Moreover, changes in the aggregation state (monomer–dimer–oligomer) should be avoided. Homogeneity and stability are necessary conditions for a suitable NMR sample.

Not only may the size and stability be limiting, but also the sample concentration. It is hard to define a minimum or ideal concentration because this parameter is strongly dependent on the experimental objective and the strategy of the researcher. The NMR is a low sensitive technique and diluted samples may provide futile results. In a high magnetic field (>18.8 T, 800 MHz), a collection of meaningful data requires a protein concentration of around 100 μM or even less.

> Read full chapter

Magnetic Resonance, Historical Perspective

J.W. Emsley, J. Feeney, in Encyclopedia of Spectroscopy and Spectrometry, 1999

See also:

Cells Studied By NMR; *In Vivo* NMR, Applications, Other Nuclei; *In Vivo* NMR, Applications, ^{31}P; *In Vivo* NMR, Methods; Labelling Studies in Biochemistry Using NMR; Liquid Crystals and Liquid Crystal Solutions Studied By NMR; Macromolecule–Ligand Interactions Studied By NMR; Membranes Studied By NMR Spectroscopy; MRI Applications, Biological; MRI Applications, Clinical; MRI Instrumentation; MRI Theory; NMR in Anisotropic Systems, Theory; NMR of Solids; NMR Spectrometers; NMR Pulse Sequences; Nuclear Overhauser Effect; Nucleic Acids Studied Using NMR; Perfused Organs Studied Using NMR Spectroscopy; Proteins Studied Using NMR Spectroscopy; Solid State NMR, Methods; Two-Dimensional NMR, Methods

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Quantum Entanglement and Information Processing

J.A. Jones, in Les Houches, 2004

1.1 Introduction

Nuclear Magnetic Resonance (NMR) is the study of the direct transitions between the Zeeman levels of an atomic nucleus in a magnetic field [1, 2, 3, 4, 5, 6, 7]. Put so simply it is hard to see why NMR would be of any interest1
□□□□□□, and the field has been largely neglected by physicists for many years. It has, however, been adopted by chemists, who have turned NMR into one of the most important branches of chemical spectroscopy [8].

Some of the importance of NMR can be traced to the close relationship between the information which can be obtained from NMR spectra and the information about molecular structures which chemists wish to determine, but an equally important factor is the enormous sophistication of modern NMR experiments [3], which go far beyond simple spectroscopy. The techniques developed to implement these modern NMR experiments are essentially the techniques of coherent quantum control, an area in which NMR exhibits unparalleled abilities. It is, of course, this underlying sophistication which has led to the rapid progress of NMR implementations of quantum computing.

The basis of NMR quantum computing will be described in subsequent lectures, but I will begin by outlining the ideas and techniques underlying conventional NMR experiments. This is important, not only to gain an understanding of the key physics behind NMR quantum computing, but also to understand the language used in this field. Throughout these lectures I will use the Product Operator notation, which is almost universally used in conventional NMR [2, 9, 6, 10, 11]. Although ultimately based on traditional treatments of spin physics this notation differs from the usual physics notation in a number of subtle ways.

> Read full chapter

Nuclear Magnetic Resonance of Biological Macromolecules Part A

Jeffrey W. Peng, ... Jonathan M. Moore, in Methods in Enzymology, 2002

Sample Preparation

NMR screening may be carried out in standard 5 mm sample tubes or may be mixed immediately prior to spectroscopic measurement using a liquid handling apparatus such as a Gilson 215, followed by direct injection in a NMR flow probe. Several NMR vendors market these setups. The use of flow techniques is the subject of

another review in this volume and so will not be discussed in detail here. However, since many groups appear to be adopting these method,[52] it is clear that in these settings ease of use outweighs the lower sensitivity of current flow probes versus conventional NMR probes.

Another alternative is to use an automated liquid handler to prepare solutions and inject them into 5 mm NMR tubes, then use a sample changing robot to collect the appropriate NMR experiments for each sample. We currently use this method in our laboratory for preparing samples and screening relatively small libraries of compounds. Turnkey systems for NMR sample tube preparation for biological systems are currently unavailable; however, such systems are straightforward to set up using commercially available programmable liquid handlers with custom racks designed to accommodate NMR tubes.

> Read full chapter

Five-membered Rings with Two Heteroatoms, each with their Fused Carbocyclic Derivatives

M.B. Nielsen, in Comprehensive Heterocyclic Chemistry III, 2008

4.13.3.4 Nuclear Magnetic Resonance Spectroscopy

Nuclear magnetic resonance (NMR) spectra have been used extensively for structure elucidations and for characterization of many of the compounds dealt with in this chapter. In this section, only papers dealing with a more systematic discussion of NMR spectra are mentioned.

The ^{77}Se NMR spectrum of the selenurane **2**· showed two resonances at 535 and 830 ppm, and ^{77}Se satellites in the proton-decoupled ^{77}Se NMR gave a value of 200 Hz for the $^{1}J_{Se–Se}$ coupling constant <1996T10375>. The conformation is fixed as a boat form by transannular bonds between the three selenium atoms.

Variable-temperature NMR studies on hybrid dichalcogena dications **37** (S–Se, S–Te, Se–Te) revealed that the stability among the chalcogenides followed Te >> Se > S <1999CL723>.

Imaging in Biological Research, Part A

A. Heerschap, ... D.W.J. Klomp, in Methods in Enzymology, 2004

Introduction

Nuclear magnetic resonance (NMR) is a very versatile scientific and diagnostic tool. After the discovery of the NMR phenomenon in 1946 by Bloch and Purcell,[1,2] it has proven useful in physics, chemistry, biochemistry, and biomedicine. Nowadays its most widespread application is in medical diagnosis under the name magnetic resonance (MR) imaging, based on conceptions for which Lauterbur and Mansfield received the 2003 Nobel prize in Physiology or Medicine.

After some early attempts, NMR of live intact animals started to be explored more widely in the 1970s.[3–5] Since then the potentials of NMR to study anatomy, physiology, and biochemistry *in vivo* in animals have been utilized in numerous studies. NMR machines designed for animal investigations are found in major biomedical research institutions and are becoming a standard research instrument at most advanced medical faculties. Although NMR has been applied to a wide range of animals, including pinnipeds,[6] birds,[7] sheep,[8] and monkeys,[9] among others, by far the majority of animals undergoing NMR examinations are rats and mice as these serve as the main model systems in biomedical research, mostly for practical reasons. Interest in NMR studies of mice has increased substantially due to the progress in the rapid generation of transgenic mice and mice modified by random mutation, which provide powerful models in studies of *in vivo* protein functions and as models of human disease. By these new approaches, large numbers of specifically modified mice have become available and efficient phenotyping has become a real research bottleneck. Because noninvasive imaging is attractive for mice phenotyping, dedicated mouse imaging centers are currently being established. NMR is a main modality in these centers because of excellent noninvasive imaging possibilities[10] and the potential for parallel mice examinations with relatively high throughput.-[11] These developments, together with continuing progress in diversification and innovation of MR methods and increased sensitivity due to better hardware and higher-field magnets, have given a strong impetus to NMR of small laboratory animals. Although no specific textbooks on animal NMR have been published, some excellent introductions to *in vivo* NMR for scientific purposes, including animal studies, have become available.[12,13]

It is beyond the scope of this Chapter to give a comprehensive overview of all NMR studies in laboratory animals, but rather we focus on more practical aspects

of *in vivo* NMR of animals (i.e., practicalities and optimization of *in vivo* NMR spectroscopy of the mouse with some illustrative examples and anesthesiology and physiological monitoring of animals during NMR experiments). This is preceded by a brief description of the basics and available methods of NMR as far as relevant for animal applications.

> Read full chapter

Cells Studied By NMR

Fátima Cruz, Sebastián Cerdán, in Encyclopedia of Spectroscopy and Spectrometry, 1999

Introduction

Nuclear magnetic resonance (NMR) methods have become available recently to study metabolism and morphology at the cellular level. The NMR methods may be classified as magnetic resonance spectroscopy (MRS), magnetic resonance imaging (MRI) and combinations of both, magnetic resonance spectroscopic imaging (MRSI). MRS provides information on the chemical composition of cells and its changes under specific circumstances, MRI yields X-ray like images of cellular anatomy and physiology and MRSI can study the spatial distribution of some metabolites within large cells or cellular aggregates. Notably, most of the nuclei participating in cellular reactions or some of their isotopes are NMR active. This allows a large variety of cellular functions to be monitored by different NMR methods. Table 1 summarizes the magnetic properties of the nuclei most commonly used in NMR studies of cells as well as the biological information which can be obtained.

Table 1. NMR properties and type of biological information provided by various nuclei

Nuclei	*Frequency (MHz)*	*Spin*	*Natural abundance (%)*	*Relative sensitivity*	*Information*
^{1}H	400	1/2	99.98	1.0	Metabolite concentration. Cell fingerprinting. Flow through some pathways. Intra and extracellular pH. Cellular volume.

					Microscopic imaging. MRI
^{31}P	161.9	1/2	100	6.6×10^{-2}	Concentration of phosphorylated metabolities. Bioenergetic status. Intra- and extracellular pH. Cellular volume. Phospholipid metabolism
^{13}C	100.6	1/2	1.11	1.6×10^{-2}	Quantitative measurements of metabolic flow through specific pathways
^{23}Na	105.8	3/2	100	9.3×10^{-2}	Membrance potential. Cellular volume. Na^+/H exchange
^{19}F	376.3	1/2	100	0.83	Intra- and extracellular pH. Oxygenation state. Divalent metal ion concentration
^{2}H	61.8	1	0.016	9.7×10^{-3}	Lipid structure. Rates of hydration–dehydration reactions. Water flow and perfusion
^{39}K	18.7	3/2	93.1	5.1×10^{-4}	Membrane potential
^{17}O	54.2	5/2	0.037	2.9×10^{-2}	Water transport and metabolism
^{15}N	40.5	1/2	0.37	1.0×10^{-3}	Nitrogen metabolism
^{14}N	28.9	1	99.63	1.0×10^{-3}	Nitrogen metabolism

NMR studies of cells probably started in the mid 1950s analysing the dynamics of water in blood using ^{1}H NMR. However, modern NMR studies of cellular metabolism began later with the introduction of commercially available high-field spectrometers and Fourier transform NMR techniques. Improvements in signal-to-noise ratios allowed, in the early 1970s, a study by ^{13}C NMR of the metabolism of glucose in a suspension of yeast and to determine by ^{31}P NMR the intracellular pH in erythrocyte suspensions. Since then studies of cellular metabolism by NMR methods have been used routinely in many laboratories.

The development of cellular NMR is supported by some inherent advantages of the NMR method with respect to more classical approaches. First, the noninvasive character of NMR allows repetitive, noninvasive measurements of metabolic processes as they occur in their own intracellular environment. Second, the magnetic properties of nuclei like the relaxation times T_1 and T_2 or the homonuclear and heteronuclear spin coupling patterns, contain unique information on the physiological or pathological status of the cells and on the flux through specific metabolic pathways. Third, NMR methods allow the acquisition of images of the spatial distribution of water in sufficiently large single cells or in cellular aggregates, and it seems likely that this approach will be extended to other metabolites in the near future. Despite these advantages, the NMR method is not devoid of drawbacks. In particular, NMR is a relatively insensitive technique with a metabolite detection threshold of around 10^{-1} mM for *in situ* cells and 50 μM in extracts for moderate-field spectrometers. Thus, to be able to obtain useful NMR spectra with an adequate signal-to-noise ratio, the cell cultures need to be grown to densities similar to those found in tissues. Even if cell extracts are used, these must be prepared from a sufficiently large number of cells to generate, in the NMR tube, metabolite concentrations in excess of the lower threshold for detection. These demanding conditions require the use of specialized perifusion systems for *in situ* NMR studies or facilities for large-scale cell culture in work with cell extracts.

In this article, we describe general procedures for cell culture compatible with NMR studies and illustrate the information that NMR methods can provide on cellular metabolism and morphology, with examples involving mainly the use of ^{31}P, ^{13}C and ^{1}H NMR. Several reviews, some of them quoted in the Further reading section, have covered this topic previously.

> Read full chapter

Fragment-Based Drug Design

Roderick E. Hubbard, James B. Murray, in Methods in Enzymology, 2011

3.2 Protein-observed NMR

NMR techniques (such as HSQC) were the first used for fragment screening (Shuker *et al.*, 1996), and NMR can deliver rich information about binding modes and structures for some systems. However, NMR experiments require isotopically labeled protein (difficult if cannot be expressed in bacteria) and there is an effective size limit of about 40 kDa. Nonetheless, NMR experiments such as HSQC are extremely valuable for titrations to determine K_D, as seen later. In our hands, we have found

that as little as 20 μ*M* protein (0.5 mL, 15 min data collection) gives sufficient signal-to-noise ratio to reliably determine the K_D in ^{15}N HSQC titrations.

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Current NMR Strategies for Biomarker Discovery

Que N. Van, in Proteomic and Metabolomic Approaches to Biomarker Discovery, 2013

NMR Metabolite Identification

NMR's biggest advantage compared to other metabolomics platforms is the ability to identify and confirm metabolites in a mixture. Different functional groups have very characteristic NMR frequencies, which can be used to identify components of an unknown metabolite. NMR frequency ranges for numerous functional groups have been tabulated in texts such as Pretsch et al.[176] and Silverstein et al.[177] and the web page of the chemistry department of the University of Wisconsin–Madison at - http://www.chem.wisc.edu/areas/organic/index-chem.htm. Complete structure determination by NMR is based on characteristic NMR chemical shifts, scalar couplings from peak multiplicity patterns, molecular connectivity, and spatial information obtainable from a suite of 1D and 2D experiments. For the interested reader, Berger and Braun contains more than 200 NMR experiments for small molecule NMR spectroscopy.[178] A quick introduction with practical details on how NMR experiments can be used to determine skeletal connectivity, relative stereochemistry, and structure verification can be found in the mini-review by Kwan and Huang.[179] For a more detailed explanation, the reader is referred to two excellent books by Lambert and Mazzola and Crews et al.[180,181]

In recent years, free web-based and commercial databases containing searchable NMR chemical shifts of metabolite standards and natural products have made small molecule NMR identification much easier and faster. Table 1 lists small molecule NMR web-based databases free to the public or to registered users. Several online public spectral tools use these databases for semiautomatic and automatic metabolite identification in 1D and 2D spectral data: (1) MetaboMiner,[182] (2) MetaboHunter,[183] and (3) the Collaborative Computing Project for NMR (CCPN) Metabolomics Project.[184] Metabolite identification is performed by matching ^{1}H and/or ^{13}C chemical shifts of unknown metabolites to those of standards. Brüschweiler's COLMAR Web Server Suite can be used in a semi-automated fashion to identify 1D traces of individual components in 2D TOCSY and HSQC-TOCSY

spectra of a complex mixture which are then searched against the BMRDB, HMDB, and MMCD databases.[185,186] High-resolution NMR spectra can also serve as input for the statistical total correlation spectroscopy (STOCSY) method to help identify peaks belonging to the same metabolite or within the same metabolic pathway, as these may be changing in concert.[187,188]

TABLE 1. Web-Based Small Molecule NMR Databases

Databases	NMR Data	URL
Human Metabolome Database (HMDB)	^{1}H, ^{13}C, HSQC	http://www.hmdb.ca
Biological Magnetic Resonance Data Bank (BMRDB)	^{1}H, ^{13}C	http://www.bmrb.wisc.edu/metabolomics/
Birmingham Metabolite Library (BML)	^{1}H, JRES	http://www.bml-nmr.org
Madison Metabolomic Consortium Database (MMCD)	^{1}H, ^{13}C, TOCSY, HSQC, HMBC	http://mmcd.nmr-fam.wisc.edu
Metabolomics Database of Linkoping (MDL)	^{1}H, ^{13}C, ^{15}N, ^{31}P	http://www.liu.se/hu/mdl/main
NMRShiftDB	^{1}H, ^{13}C, ^{15}N, ^{31}P	http://nmrshift-db.nmr.uni-koeln.de
Spectral Database for Organic Compounds (SDBS)	^{1}H, ^{13}C	http://ri-odb01.ibase.aist.go.jp/sdbs/cgi-bin/cre_index.cgi
Purdue Isotope Enhanced NMR (PIE-NMR) Metabolite Database	^{13}C and ^{15}N tagged metabolites	http://www.chem.purdue.edu/raftery/pie-nmr/pie-nmr.html

 Some databases contain additional information not listed under the “NMR Data” heading.

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Other Techniques of Analysis and the Future of Fire Debris Analysis

Eric Stauffer, ... Reta Newman, in Fire Debris Analysis, 2008

13.10.2 Advantages and Drawbacks

NMR is not a technique of choice for the analysis of fire debris. It does not allow for the observation of the pertinent characteristics necessary to identify ignitable liquids from fire debris samples. NMR does not include a separation technique, nor is it preceded by a separation technique. Thus, potentially hundreds of components are

analyzed simultaneously. This does not provide the means necessary to differentiate which signals come from which components. NMR requires a much greater amount of sample than GC or GC–MS. This sample also has to be either in a pure form or in solution in a particular solvent. In addition, NMR is a very high-cost instrument, rarely found in crime laboratories. Bryce et al. also did not define or demonstrate the criteria that would be used in the identification of ILR from NMR spectra [66]. NMR should not be used in the analysis of fire debris unless further research demonstrates otherwise, which is very unlikely.

NMR can be used for other applications in the petroleum industry, such as the determination of the amount of hydrocarbon types in gasoline, because this does not require a specific identification of each hydrocarbon but, rather, an identification of the amount of one type of hydrocarbon, such as aromatic or olefinic [67].

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