

High Resolution NMR Spectroscopy on Whole-Body Imagers: Optimized Single- and Multi-Pulse Experiments in Vitro

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From 100 ml spherical glass bottles filled with aqueous solutions and suspended in a homogeneous magnetic field, NMR spectra with linewidths of about 0.7 Hz were achieved in single-pulse and multi-pulse spectra. A relatively wide receiver coil as the body coil or the standard head coil of the manufacturer were employed to acquire spectra after different non-localized pulse sequences. Examples of single-pulse spectra and double spin-echo spectra of aqueous solutions with lactate, citrate, or glucose are demonstrated and discussed. The fact that all experiments can be performed using well-defined pulse angles acting on the entire sample at the field strength of the whole-body unit allows to determine the characteristics (e.g. chemical shift differences, coupling constants) of spin systems of biologically important molecules precisely, without need for additional spectrometers. Constant flip angles are advantageous for adequate theoretical analysis of spectra from coupled spin systems. The effects of a defined “misadjustment” of the transmitter on the spectra can be measured directly, whereas localized methods always yield a superposition of signals due to the distribution of flip angles inside the selected volume. In some cases, optimized sequence parameters for localized examinations in vivo can be derived numerically from the analyzed coupling data.

Key words: MR spectroscopy in vitro; signal characterization; *J*-coupling; multi-pulse sequences; set-up for MR spectroscopy.

Introduction

NMR-spectroscopic techniques allow to record signals from nuclei such as ^1H , e.g. [1–4], ^{13}C , e.g. [5, 6], ^{19}F , e.g. [7, 8], and ^{31}P , e.g. [9, 10] of various metabolites in vivo. It is advantageous to determine the location in the body where the recorded signals stem from. Different approaches for volume localization are usually applied: Single-pulse spectra recorded by surface coils mainly show signals from tissue adjacent to the coil. This method does not provide good delimitation of the examined region or selection of a volume inside an internal organ with a distance to the surface coil, since only the receiving characteristics of the coil are used. An arbitrary position of the region to be examined is provided by ISIS (Image-Selected In vivo Spectroscopy) [11]. Signal characteristics in ISIS spectra correspond with those of single-pulse spectra (i.e. spectra from the free induction decay), but the quality of the localization is clearly worsened if movements of the subject under investigation take place during the measurement. For full volume localization by one pulse train, at least three slice selective pulses are necessary. Two different “three pulse methods” are mostly

applied: The stimulated echo method STEAM (STimulated Echo Acquisition Mode) [12] works with a $90^\circ-90^\circ-90^\circ$ sequence, whereas the double spin echo method PRESS (Point RESolved Spectroscopy) [13, 14] uses a pulse train according to $90^\circ-180^\circ-180^\circ$. Using the same echo time, PRESS provides nearly twice the signal intensity from a fixed volume element obtained with STEAM, but STEAM normally allows shorter echo times than PRESS on whole-body imagers [15]. Phase encoding techniques are also applied for volume selection: Further spatial resolution of the signals recorded from a surface coil or from a preselected STEAM or PRESS box can be obtained by this method. Unfortunately, a time period of a few milliseconds is needed for phase encoding in single-pulse sequences, and the quality of the localization is worse than with single voxel methods [16].

Most of the important metabolites examined by physiological or pathophysiological MR studies in vivo have relatively low concentrations of a few mM or less in the organs. The main signals of many substances show signal and phase anomalies after multi-pulse excitation due to homonuclear *J*-coupling: e.g. the ^1H signals of lactate, citrate, many amino acids such as glutamine, glutamate, histamine; methyl and vinyl groups of lipids, as well as e.g. ^{31}P signals of ATP or ADP.

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An adaptation of the sequence parameters to obtain high signal strength and suitable signal shape from the substance of interest is important for sensitive spectroscopy in vivo. Different aspects have to be considered: The signal amplitudes from the substance should be relatively high, but for quantitative measurements in vivo the signal strength should not markedly change due to unavoidable slight misadjustments of the transmitter (especially using surface coils). The adaptation of the sequence parameters is often performed by in-vitro studies using the sequence which is intended for the in-vivo examinations. In this way signal characteristics of metabolites with complex coupled spin systems and unknown coupling constants J_i and chemical shift differences δ_i were investigated [17]. Unfortunately, many spectra recorded with different sequence parameters have to be analyzed to get optimum parameters, and the results are only valid for the particular sequence under investigation. In principle, a theoretical treatment of the density matrix of coupled spin systems during volume selective sequences is possible if the coupling data are known. The theoretical treatment might be difficult for complex spin systems but allows to predict the spectral lines for arbitrary sequence parameters. Especially the distribution of flip angles in volume selective measurements worsens the opportunity for corresponding theoretical treatment. Therefore measurements with constant flip angle in all parts of the sample are more appropriate for corresponding theoretical calculations and for the determination of the coupling data. Such calculations of spectra after multi-pulse excitation from given values of J_i and δ_i were already performed for simple spin systems. For example, signal characteristics were reported for lactate (AX_3 -system) [18] and citrate (AB -system) [19].

Highly resolved spectra of solutions containing the substances of interest recorded by whole-body imagers must be usually performed with volume selective techniques due to inhomogeneities of the magnetic field in the sample [20–22]. The signal shape in spectra obtained by such multi-pulse experiments depend on the excitation profile of the slice selective pulses: The nominal flip angles of the pulse-train are only experienced by the spin ensembles in the center of the selected volume, whereas various combinations of flip angles occur in regions near the edges of this volume, according to the frequency spectrum of the pulses irradiated [23, 24]. So, the recorded signal in the spectrum is a superposition produced by various combinations

of flip angles of the multi-pulse train. The uncertainty of the flip angles in volume selective multi-pulse experiments on whole-body imagers is a severe drawback for the characterization of coupled spin systems by the measured spectra. Furthermore, relatively strong gradient field strengths have to be switched for slice selectivity of the pulses, which might result in problems with eddy currents.

Optimization of the Set-Up

The lineshapes and linewidths (defined as full linewidth at half height) in spectra from entire samples of aqueous solutions in vitro depend on the distribution of the static magnetic field inside the sample during the measurement if the time stability is high enough (as reported in [25]). The following circumstances influence the attainable spectral resolution: the shape and the susceptibility of the sample, the homogeneity of the static magnetic field of the imager before positioning the sample in the magnet, and the extent of the sample.

For in vitro measurements of solutions with low concentrations, dedicated coils were developed by a few investigators to improve signal-to-noise using spherical samples with large volumes and high filling factors [26]. Paramagnetic (or even ferromagnetic) compounds of the coils clearly affect the attainable resolution in the spectra. The homogeneity of the static magnetic field in the center of the body coil can be well adjusted if no sample rests inside the tube: A field homogeneity $<10^{-8}$ in a central region of $(10\text{ cm})^3$ can normally be obtained by shimming if no surface coil, paper clips, ballpoint pen, or other objects lie inside the magnetic (as often found after routine examinations of patients on whole-body units).

The development of a set-up for non-localized spectroscopy of solutions is reported in the following. It is based on the principle of having a spherical sample in a homogeneous magnetic field, as used by other groups for different purposes [e.g. 27]. The size of the sphere should not be too small, since the shape is often closer to an ideal sphere for purchasable glass bottles of 100 ml or more than for very small ones. The diameter of the filler pipe should be as small as possible. Diameters of about 2 mm were found to be suitable (Figure 1 a).

For nonspherical samples (and all “real glass bottles” show deviations) the distribution of the magnetic

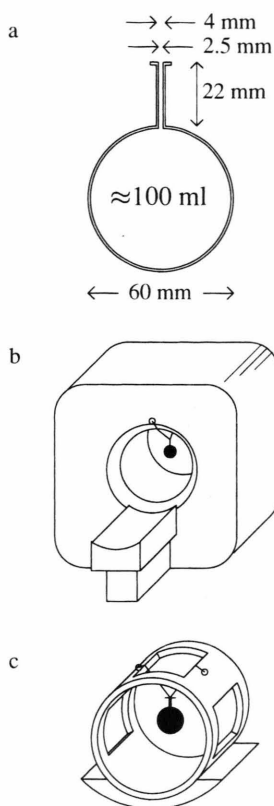


Fig. 1. a) Dimensions of the spherical glass bottles of about 100 ml used for non-localized spectroscopy with high resolution. The entire bottle except the filler pipe should be filled with the solution. b) Position of the spherical sample in the center of a whole-body magnet using a thin fishing line. No materials with a magnetic susceptibility different to air occur near the bottle. c) Position of the bottle in a normal head coil. The dimension of the sample relative to the head coil is demonstrated.

field depends on the homogeneity of the applied static field, on the deviation from the ideal spherical shape and, as an additional factor, on the difference of magnetic susceptibility between the sample and the surroundings. The volume susceptibility of water is $\chi_w = -9.03 \cdot 10^{-6}$ (SI units), whereas the surrounding air has a $\chi_{\text{air}} = 0.35 \cdot 10^{-6}$. The difference between a sample of aqueous solution and the surroundings depends on the amount of diamagnetic and paramagnetic ions.

About 32 acquisitions had to be sampled to obtain acceptable signal-to-noise for ^1H signals from 100 mM solutions by the body coil (Figure 1 b). So the measuring time for solutions with low concentrations became rather long, and problems with the time stability

(1 Hz–10 Hz per hour for normal whole-body imagers) became important.

The measuring time can be reduced by using a smaller coil for signal reception: A circularly polarized head coil recorded signals from the 100 ml sample positioned in the center of the magnet with the sphere simultaneously hanging in the center of the head coil (Figure 1 c). In order to take advantage of the better signal-to-noise provided by the head coil and to optimize the field homogeneity of the outer magnetic field under these conditions, the currents of all 12 shim channels of the imager had to be systematically adjusted. After a shimming procedure of about 3 hours, the linewidth of the water signal in the spectra from the entire sphere of 10 ml was again 0.6 Hz. This value was very similar to that obtained in the case of shimming only the linear channels (and otherwise using the adjusted shim of the manufacturer), but without the head coil inside the magnet. The new optimum shim values were stored and the linewidths were reproducible in a short time of shimming when the set-up was installed similarly in later measuring sessions.

Examples

Spectra from different solutions were recorded by the described set-up using single-pulse and multi-pulse sequences. All spectra shown were obtained by a standard whole-body imager “Siemens Magnetom” (Siemens, Erlangen, Germany) at a field strength of 1.5 T. The standard circularly polarized head coil was used for signal reception. No modification of the implemented materials in the imager or the head coil was performed.

Aqueous solutions of lactate and citrate, each with a concentration of 100 mM, as well as 280 mM solution of glucose (5%) were filled into three different, but very similar, nearly spherical glass bottles of 100 ml.

Lactate Spectra

The 100 mM solution of sodium lactate (with added sodium acetate for simplified phasing of the spectra) was first measured by a single-pulse sequence: A short rectangular pulse of 0.5 ms was used for 90° excitation. 2 K data points were recorded during 4.096 s, resulting in a bandwidth of ± 250 Hz. The delay between the end of the pulse and the beginning of data sampling was 1.0 ms. Water suppression was performed by

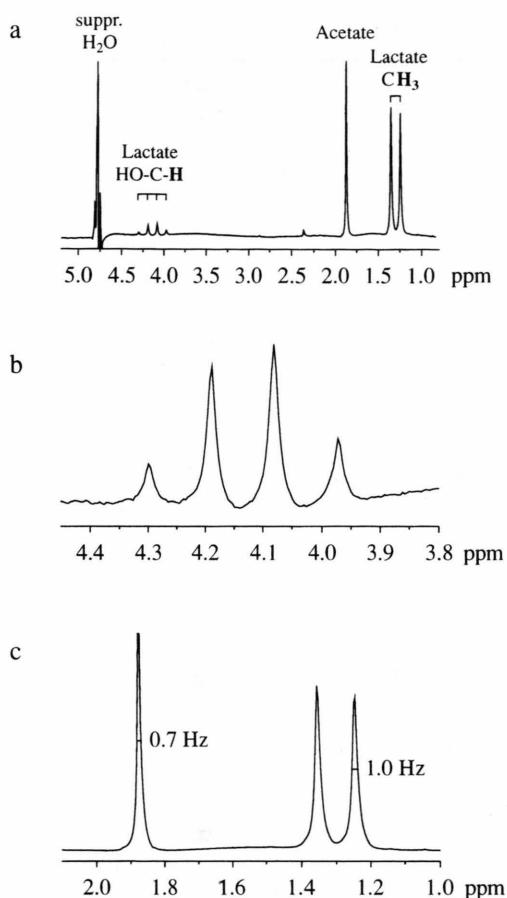


Fig. 2. a) Single-pulse spectrum from aqueous solution with concentrations of 100 mM sodium lactate and 100 mM sodium acetate recorded by the head coil. The signal near 2.3 ppm is due to an impurity. Measuring time: 40 s (4 acq., TR = 10 s). b) Quartet of lactate of the spectrum in a. c) Acetate (CH_3) and doublet of lactate of the spectrum in a.

a 90° Hanning-filtered sinc pulse with a length of 36 ms and a total bandwidth of 60 Hz; the irradiation frequency was adjusted to the resonance frequency of the water protons. A gradient of 0.0003 T/m with a duration of 10 ms spoiled the transverse magnetization of the water protons after the water suppression pulse.

Figure 2a shows a spectrum from 4 acquisitions recorded with a repetition time TR = 10 s. Lactate is a (nearly) weakly coupled AX_3 spin system at the field strength of 1.5 Tesla, so multiplets with binomial signal ratios occur in the spectra. The resolution of the quartet (Fig. 2b) and the doublet (Fig. 2c) of lactate as well as the singlet of acetate (Fig. 2c) are also demon-

strated in an expanded frequency scale. The linewidth amounts to 1.0 Hz for the doublet signals of lactate, but only 0.7 Hz for the signal from acetate. The reason is the difference in the natural linewidths due to transverse relaxation with $T_2 \approx 700$ ms (corresponding to a natural linewidth of $1/\pi \cdot T_2 = 0.45$ Hz) for lactate and $T_2 \approx 2200$ ms (natural linewidth: 0.14 Hz) for acetate. The inhomogeneity of the static field inside the spherical sample has similar influence on the resolution of the signals as the natural linewidth.

Spectra after non-localized 90° – 180° – 180° pulse sequences were recorded as well. Water suppression was performed according to the method described for the single-pulse spectra. The duration of the non-selective rectangular pulses was 0.5 ms. Figure 3a–d shows a series of well-resolved spectra obtained after total echo times TE of 78.5 ms (corresponding to $1/2 J$, where $J \approx 6.9$ Hz [23] is the coupling constant of lactate), 145 ms ($1/J$), 217.5 ms ($3/2 J$), and 290 ms ($2/J$). The first echo time TE₁ of the double spin-echo sequence was fixed to 10 ms for all spectra of this series, whereas the second echo time TE₂ was adjusted to provide the values above.

Localized spectra of coupled spin system as lactate obtained by PRESS (the nominal flip angles correspond to the double spin echo sequence used here) depend on the timing scheme of the localization sequence [23, 24]. The spectra in Fig. 4 were obtained by localized (Fig. 4a–c) and non-localized (Fig. 4d–f) double spin-echo sequences using different combinations of TE₁:TE₂ for a total echo time of 290 ms. The signal intensity and the shape of the doublet of lactate in the localized spectra clearly depend on the timing scheme, whereas the non-localized spectra are very similar. The irregularly shaped localized spectra are produced by the pulse angle distribution of the slice selective Hanning-filtered sinc-pulses, each with a duration of 2.56 ms and a bandwidth of 2.1 kHz. In contrast, the flip angles for the non-localized spectra were precisely 90° – 180° – 180° in all subregions of the sample.

The coupling constant J of lactate can be determined from non-localized double spin-echo spectra with relatively long total echo times TE, which additionally result in pure absorption signals. Double spin-echo spectra with total echo times near $10/J$ were recorded with TE = 1430 ms, ..., 1470 ms. The shape of the spectra showed that pure absorption signals can be obtained for TE = (1447 ± 3) ms, so J of lactate was close to 6.91 Hz in the solution used.

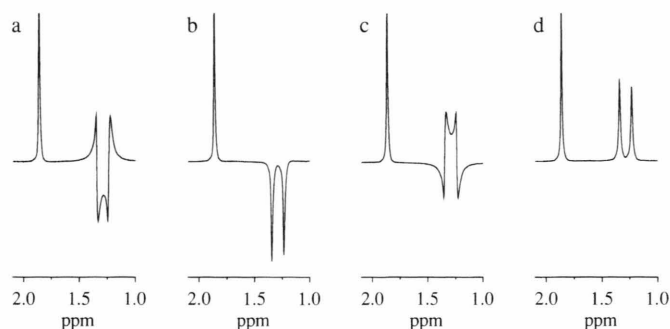


Fig. 3. Non-localized double spin-echo spectra of the solution with 100 mM lactate and 100 mM acetate. The first echo time TE_1 of the sequence $90^\circ - \frac{1}{2}TE_1 - 180^\circ - \frac{1}{2}TE_1 + \frac{1}{2}TE_2 - 180^\circ - \frac{1}{2}TE_2$ acq. was 10 ms for all spectra. Each spectrum was recorded using 4 acq. and $TR = 10$ s. a) $TE_2 = 68.5$ ms, $TE = 78.5$ ms corresponding with $1/2J$ for lactate. b) $TE_2 = 135$ ms, $TE = 145$ ms $\approx 1/J$. c) $TE_2 = 207.5$ ms, $TE = 217.5$ ms $\approx 3/2J$. d) $TE_2 = 280$ ms, $TE = 290$ ms $\approx 2/J$.

Citrate Spectra

The proton signals from citrate stem from strongly coupled AB spin systems. The difference between the chemical shifts δ of the protons A and B is very low. Therefore most low-field spectra reveal only one dominant signal in the spectra, e.g. [28, 29].

A single-pulse spectrum from the sphere in Fig. 5 shows a good separation of four different signals from citrate. Water suppression was performed as described, and 4 acquisitions were recorded with a TR of 10 s.

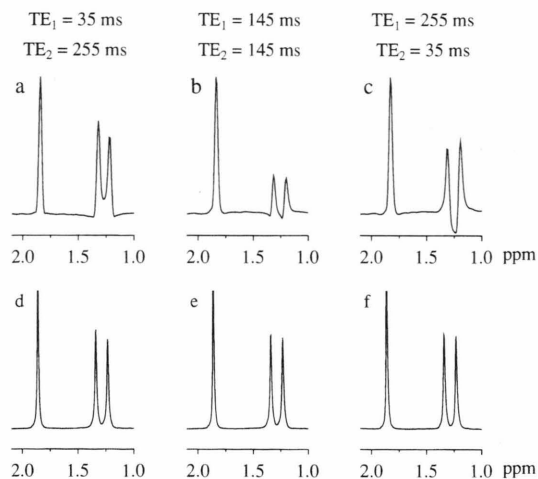


Fig. 4. Spectra of the solution with 100 mM lactate and 100 mM acetate recorded by localized (Fig. 4a–c) and non-localized (Fig. 4d–f) double spin-echo sequences using various combinations of TE_1 and TE_2 for a total echo time $TE = 290$ ms. a)–c) The localized spectra were recorded using a conventional set-up (i.e. a large bottle of 500 ml in the head coil) by a PRESS sequence (8 acq., $TR = 10$ s, volume $(2\text{ cm})^3$). The shape of the doublet of lactate clearly depends on the timing scheme. d)–f) Non-localized spectra from the spherical sample in the head coil obtained with “true flip angle” sequences and corresponding sequence timings (4 acq., $TR = 10$ s). The doublet of the weakly coupled AX_3 spin system does not depend on the timing scheme.

Sodium acetate was added to the citrate solution to simplify phasing of the spectra. The linewidths are again clearly below 1.0 Hz.

Non-localized double spin-echo spectra were also taken from the solution of citrate. In contrast to the weakly coupled AX_3 system of lactate (see Fig. 4d–f), the signal behavior of the strongly coupled AB system depends on the combination of the single echo times TE_1 and TE_2 for a given total echo time TE , even when ideal flip angles are applied. Figure 6 shows an example for $TE = 130$ ms. The shape and signal strength of the four signal components in the spectra differ markedly, although the nominal flip angles of the $90^\circ - 180^\circ - 180^\circ$ pulse sequences are experienced by the whole sample.

Glucose Spectra

Glucose is an important molecule of metabolism with very complex MR signal characteristics of the

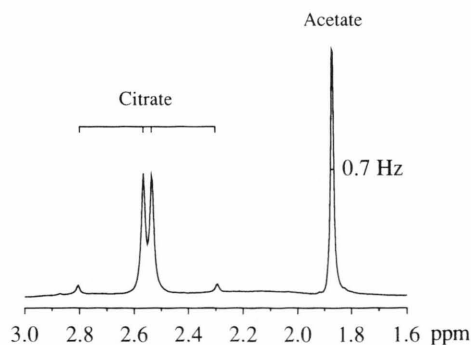


Fig. 5. Single-pulse spectrum from aqueous solution with concentrations of 100 mM sodium citrate and 100 mM sodium acetate recorded by the head coil. The signals from the strongly coupled AB spin system of citrate are well resolved. Measuring time: 40 s (4 acq., $TR = 10$ s).

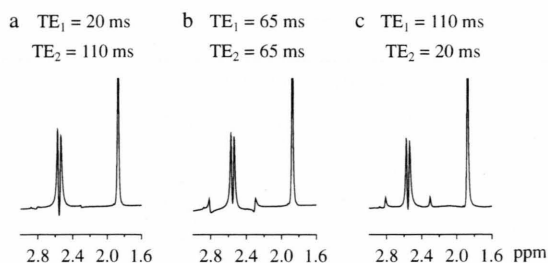


Fig. 6. Double spin-echo spectra of the solution with 100 mM citrate and 100 mM acetate recorded from the spherical sample by "true flip angle" pulse sequences $90^\circ-180^\circ-180^\circ$ (4 acq., TR = 10 s). a)–c) Various combinations of TE_1 and TE_2 for a total echo time $TE = 130$ ms were chosen. The signals of the AB spin system depend on the timing scheme, even under ideal flip angles, in contrast to the doublet of the weakly coupled AX_3 spin system (see Figures 4d–f).

protons: In the natural equilibrium, nearly 100% of the glucose molecules within aqueous solution are cyclic hemiacetals, only <0.5% exist as 6-C-chains with one aldehyde and five hydroxyl groups. The esters between the carbon atoms C_1 and C_5 in the cyclic hemiacetals are built up in two different stereoisomers: there are 38% of α -D-glucose and 62% of β -D-glucose. In aqueous solutions each stereoisomer can be described as a system of seven strongly coupled protons. The signals from the hydroxyl protons are not resolved in the spectra.

The single-pulse spectrum of Fig. 7a was obtained from the whole sphere of 280 mM aqueous solution of glucose without any filtering or other postprocessing. Four acquisitions were recorded with a TR of 10 s by the head coil after water suppression. The effect of the linewidth on the number of resolved signal is marked: Line broadening of the original spectrum in Fig. 7a Gaussian multiplication in the time domain is shown in Figure 7b, c.

Double spin-echo spectra were recorded from the entire sphere of glucose solution using the $90^\circ-180^\circ-180^\circ$ pulse sequence with "true" flip angles for the whole volume inside the bottle. Figure 8 exhibits double spin-echo spectra of glucose for TE of 40 ms (Fig. 8a), 80 ms (Fig. 8b), and 120 ms (Fig. 8c). The first echo time was fixed to $TE_1 = 20$ ms, whereas TE_2 was chosen to 20 ms, 60 ms, and 100 ms, respectively. The signal and phase irregularities due to the coupling of the proton systems are demonstrated in the spectra of the entire spherical sample.

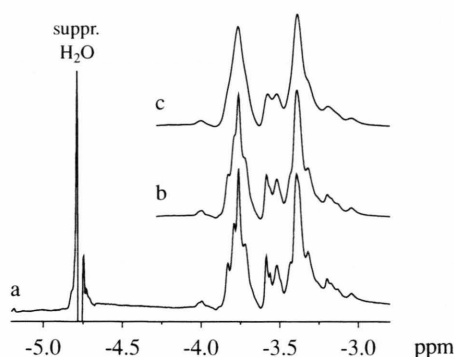


Fig. 7. a) Single-pulse spectrum from aqueous glucose solution with a concentrations of 280 mM recorded by the head coil. High resolution of the signals from the complicated strongly coupled spin systems of α - and β -glucose is demonstrated. Measuring time: 40 s (4 acq., TR = 10 s). b) Effects of line broadening by Gaussian multiplication in the time domain. A Gaussian function centered at the beginning of data acquisition and half height at 500 ms result in a broadening of about 0.3 Hz. c) Multiplication by a Gaussian function centered at the beginning of data acquisition and half height at 200 ms result in line broadening of about 0.89 Hz. The number of resolvable signals is markedly reduced.

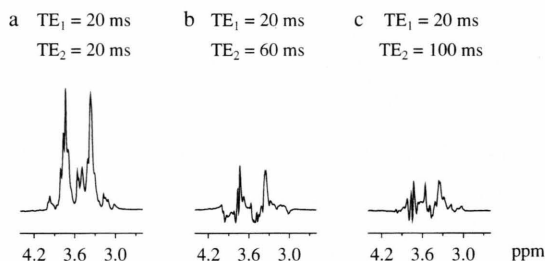


Fig. 8. Non-localized double spin-echo spectra of the 280 mM glucose solution in the spherical sample recorded by the head coil. The first echo time TE_1 of the $90^\circ-180^\circ-180^\circ$ sequence was 20 ms for all spectra of this series. Each spectrum was recorded using 4 acq. and TR = 10 s. a) $TE_2 = 20$ ms, TE = 40 ms. b) $TE_2 = 60$ ms, TE = 80 ms. c) $TE_2 = 100$ ms, TE = 120 ms.

In conclusion, this simple method allows to examine the characteristics of the metabolites of interest with good spectral resolution at the field strength of the whole-body imager, which is used for corresponding examinations in vivo. The relatively good signal-to-noise ratio in the "large volume spectra" is also useful for spectroscopy of body fluids or infusion solutions with low concentrations.

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