Journal of Magnetic Resonance 218 (2012) 147–152

Contents lists available at SciVerse ScienceDirect

Journal of Magnetic Resonance

journal homepage: www.elsevier.com/locate/jmr

Communication

Origin and correction of magnetic field inhomogeneity at the interface in biphasic NMR samples

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ARTICLE INFO

Article history:
Received 15 December 2011
Revised 19 February 2012
Available online 9 March 2012

Keywords:
NMR
MAS
Magic angle spinning
Susceptibility
Biphasic
Shimming
Demagnetization field
Octanol
Bulk magnetism
Chemical shift

ABSTRACT

The use of susceptibility matching to minimize spectral distortion of biphasic samples layered in a standard 5 mm NMR tube is described. The approach uses magic angle spinning (MAS) to first extract chemical shift differences by suppressing bulk magnetization. Then, using biphasic coaxial samples, magnetic susceptibilities are matched by titration with a paramagnetic salt. The matched phases are then layered in a standard NMR tube where they can be shimmed and examined. Linewidths of two distinct spectral lines, selected to characterize homogeneity in each phase, are simultaneously optimized. Two-dimensional distortion-free, slice-resolved spectra of an octanol/water system illustrate the method. These data are obtained using a 2D stepped-gradient pulse sequence devised for this application. Advantages of this sequence over slice-selective methods are that acquisition efficiency is increased and processing requires only conventional software.

1. Introduction

Biphasic phenomenon have been studied to understand reaction kinetics [1], equilibria [2], partition coefficients [3], surfactant aggregation [4], prediction of reaction mechanism [5], and investigation of biological membrane models [6,7]. Techniques other than NMR used to investigate surface properties of biphasic systems include atomic force microscopy [8], scanning electron microscopy [9], nonlinear optics [10], scanning electrochemical microscopy (SECM) [11], and X-ray [12] and neutron [13] scattering. A number of methods have been proposed for generating slice-resolved spectra of biphasic systems prepared in conventional NMR tubes, and run in high resolution liquid probes equipped with z-gradients [3,14–16]. Here we study consequences of, and remedies for, magnetic field inhomogeneity caused by susceptibility mismatch at the interface.

Placing immiscible phases in an NMR tube to obtain spectra from axial slices at first appears to be an elegantly simple way to study *in situ* spatial properties of reactions and transport. However, a number of complexities are revealed by closer examination.

Kozminsky's first demonstration of frequency-selective slice spectroscopy recognized the inherent conflation of spatial and spectroscopic variables from the outset in his pioneering work [14]. Mantel et al. dealt with this latter issue by offering a program which shears the data sets to cleanly separate spectral and spatial coordinates. They further accounted for axial probe sensitivity variation by weighting intensities of slices according to the experimentally determined probe profile [16]. Lambert et al. [15] showed that 1 μm slice resolution is feasible. They employed slices which were transversely restricted to the central flattest part of the meniscus, additionally improving registration between the curved interface and flat selected slice.

Other issues remain. One is whether slice volumes are large enough to provide adequate signals from lower-concentration surface-active species [17]. A second is that it can be difficult to isolate diffusive transport from unanticipated slow convection [16,18], and slice-selection studies [3] have yet to take this into account. A third problem, which we address here, is lineshape distortion in the vicinity of the interface caused by susceptibility mismatch between phases. Our approach is to use paramagnetic doping to make the interface between the aqueous and the organic phases magnetically invisible. Matching the magnetic susceptibility of the bulk phases by doping, prior to slice-resolved studies, provides clean NMR slice spectra up to and at the interface. Additionally, we present data using a 2D pulse sequence based on stepped-gradients. This approach entirely avoids shearing of the chemical shift/position correlation common to frequency-selective methods [16,14], while offering sensitivity

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http://dx.doi.org/10.1016/j.jmr.2012.02.012

advantages analogous to those of Fourier over slow passage NMR spectroscopy [19].

1.1. Theory

Consider a biphasic system composed of organic and aqueous solvents layered in an NMR tube. The NMR frequency of an analyte present in both phases, such as acetone used in the present example, will vary spatially from one phase to the other. The local frequency is determined by two components. The first is the chemical shift (CS) associated with perturbation of electronic wavefunctions due to differences in the chemical environment unique to each solvent [20]. This shift is uniform within each phase, and changes abruptly from one side of the interface to the other.

The second is the bulk magnetic shift (BMS) of the internal magnetic induction $\vec{B}$ that depends on the solvent's magnetic volume susceptibility κ,[1] The discontinuity in κ in biphasic systems distorts both field and lineshape near the interface.

To a first degree of approximation, the effect of BMS susceptibility is as follows. The NMR magnet wire currents generate a magnetic field intensity $\vec{H}_0$ throughout the sample volume. $\vec{H}_0$ is homogeneous at the ppm level, and induces a correspondingly uniform sample magnetization $\vec{M} = \kappa\vec{H}_0$. Therefore, the internal magnetic induction $\vec{B}$, which determines the NMR frequency, is shifted from the free-space value $\mu_0\vec{H}_0$ (in SI units) to

$$\vec{B} = \mu_0(\vec{H}_0 + \vec{M}) = \mu_0(1+\kappa)\vec{H}_0 \tag{1}$$

For homogeneous samples, the Z_0 field compensation can bring the sample resonance to the magnet's specified γB frequency regardless of κ. However, for biphasic samples, since different susceptibilities are present in each sample section, analogous field compensation would require an $\vec{H}_0$ profile with an abrupt step at the interface.

Second degree corrections, due to a "demagnetization field" [22], modify this picture slightly. This additional field arises from an effective magnetic charge density $\hat{n}\cdot\vec{M}$ residing on material surfaces [23,24].

Microscopically, this implies that molecules in liquids do not experience the entire average field, to which they contribute, but the field inside a Lorenz cavity [25] which excludes the field of the molecule itself. This effectively reduces the influence of susceptibility on the NMR frequency, equivalent to rescaling κ in Eq. 1 to $\frac{\kappa}{3}$ [26].

Macroscopically, this means that the ends of high resolution NMR samples situated coaxially in the magnet will appear to have magnetic surface charge densities $\pm\kappa H_0$ at top and bottom. For homogeneous NMR samples, whose ends lie outside the detection region, the effect of end charges is correctable by shimming. A residual uniform field shift is accounted for by the shape factor α discussed in susceptibility studies [26,21]. For biphasic samples, however, the susceptibility discontinuity at the interface effectively places an extra magnetic charge monolayer $\Delta\kappa H_0$ directly in the middle of the detection window. A plot of the resulting magnetic field, modeled using Maple 5.1, is shown in Fig. 1. Note that the demagnetization field from the charge layer is partly beneficial. The field step predicted by the first order discussion above is softened to a gradual transition that occurs over an axial length on the order of the radius of the NMR tube. However, the axial field gradient steepens with increasing distance from the tube axis, so a radial gradient is also present. Therefore, attempts to circumvent

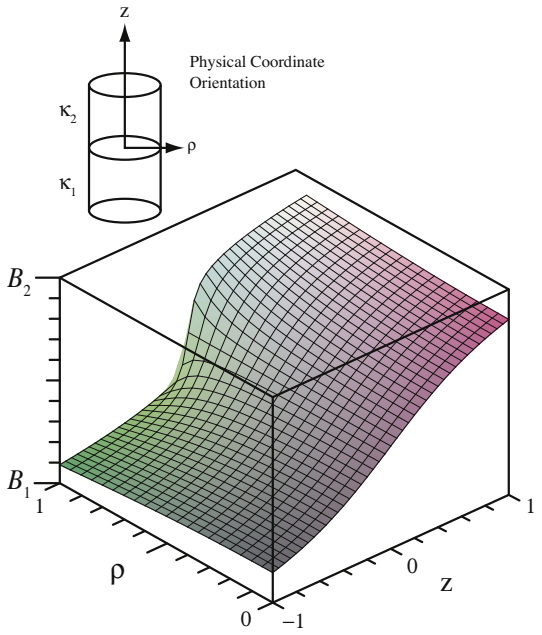

Fig. 1. Simulation of the field transition near the interface between layers of a biphasic system. The phases are layered in an upright NMR tube placed coaxially in a homogeneous vertical magnetic field H_0. Here z represents height from the idealized planar interface, and ρ the distance from the tube axis; lengths are normalized to the tube radius. The field experienced by nuclei in the sample shifts by $\mu_0\Delta\kappa H_0$ as one crosses from one phase to the other. The transition imposes a complex combination of axial and radial gradients. It is assumed that $\kappa \ll 1$, so that only the z component of the B field parallel to H_0 is plotted.

interfacial line broadening due to the axial gradient by decreasing slice thickness will fail, unless slice extent is reduced transversely as well.[2]

For the n-octanol/water system discussed below, we determined the interphase field step due to the BMS alone to be 169 Hz. In a standard NMR tube with 2.5 mm radius, the axial field gradient at the interface will be 169/2.5 ≈ 70 Hz/mm. *Here lies the problem:* spectra from slices near the interface will be significantly broadened, and the strength and short range of the gradient make shim correction impossible.

1.2. Approach

To eliminate lineshape distortion caused by the presence of the interfacial gradient, we propose removing the susceptibility difference between the two solvents entirely. For comparison with H_2O and D_2O, we have converted molar susceptibilities of organic compounds listed in the CRC [27] to their volume susceptibilities, and, for convenience, have supplemented these results with data from other workers [28,29] (see Supplementary materials). Inspection of the table shows that H_2O and D_2O are more diamagnetic than most organic solvents.[3] This suggests the strategy of paramagnetically doping the aqueous phase. Paramagnetic adjustment is common in high-resolution probe design [30,31], and more general matching methods are in use for balancing solvent silica susceptibilities in NMR chromatography [32].

We illustrate this technique for an n-octanol/D_2O biphasic system, using $GdCl_3$ as the dopant. The system was chosen not only because it is a classic system for pharmaceutical partition

[1] Following the NMR susceptibility literature [21], the symbol κ is used throughout to denote volume susceptibility, in contrast to molar susceptibility commonly denoted by χ. Unfortunately, in electromagnetism texts, χ denotes bulk susceptibility [22]; we will avoid this latter usage.

[2] Notably, Lambert et al.'s thin restricted voxel satisfies both these conditions.

[3] Notable exceptions are halogenated and aromatic compounds. In these cases, matching by diluting the organic phase with a very weakly diamagnetic species is appropriate using similar laboratory procedures.