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Convection-compensating diffusion experiments with phase-sensitive double-quantum filtering

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Abstract

We present a design scheme for phase-sensitive, convection-compensating diffusion experiments with gradient-selected homonuclear double-quantum filtering. The scheme consists of three blocks: a $1/2J$ evolution period during which antiphase single-quantum coherences are created; a period of double-quantum evolution; and another $1/2J$ period, during which antiphase single-quantum coherences are converted back into an in-phase state. A single coherence transfer pathway is selected using an asymmetric set of gradient pulses, and both diffusion sensitization and convection compensation are built into the gradient coherence transfer pathway selection. Double-quantum filtering can be used either for solvent suppression or spectral editing, and we demonstrate examples of both applications. The new experiment performs well in the absence of a field-frequency lock and does not require magnitude Fourier transformation. The proposed scheme may offer advantages in diffusion measurements of spectrally crowded systems, particularly small molecules solubilized in colloidal solutions or bound to macromolecules.

Keywords: Solvent suppression; Convection-compensating NMR diffusion measurements; Gradient coherence transfer pathway selection; DOSY; Drug binding; Drug delivery

1. Introduction

Pulsed-field gradient (PFG)[1] NMR is a highly versatile method for measuring molecular transport and diffusion [1], which is in large part due to the ability to tailor NMR pulse sequences to specific experimental needs. For example, the measurement of molecular diffusion coefficients at high temperatures and/or in low-viscosity solvents requires the elimination of the effects of thermal convection inevitably present under these conditions; this is usually achieved by using convection-compensating NMR diffusion experiments [1–3]. Solvent suppression is another feature commonly desired of NMR diffusion measurements [4–7]. We recently proposed a diffusion experiment (CONVEX) which contains both convection compensation and built-in solvent suppression [4]. In this work, we present another diffusion experiment which contains both these features; but unlike CONVEX, solvent suppression in the present experiment is based on gradient-selected double-quantum filtering. We refer to the new experiment as "DQDiff," for "double-quantum diffusion."

Multiple-quantum (MQ) filtering has long been a useful element in the toolkit of NMR diffusion measurements. Its applications include elimination of dipolar couplings [8,9] and evaluation of the orientational order in liquid-crystalline systems [10–12]; heteronuclear editing of diffusion spectra [13,14]; and as a general way of

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[1] *Abbreviations used:* CTP, coherence transfer pathway; DDF, dipolar demagnetizing field; DQ(F), double-quantum (filtered); MQ(F), multiple-quantum (filtered); PBS, phosphate-buffered saline; PFG, pulsed-field gradient; (PG)SE, (pulsed-field gradient) spin echo; PGSEcc, convection-compensating double PGSE; RD, radiation damping; SQ, single-quantum.

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amplifying the effective strength of magnetic field gradients [8,9,15]. In designing the DQDiff experiment, we have set out to incorporate MQ-filtered editing into a convection-compensating diffusion measurement. As will become apparent from the following discussion, the main challenge stemmed from the fact that the stability requirements imposed on MQF schemes appear to be stricter in quantitative diffusion measurements than in general NMR spectroscopy.

Multiple-quantum filtering can be achieved by means of either phase cycling or gradient coherence selection [16–19]. The former method is dependent on the successful cancellation of unwanted signal components and is therefore susceptible to temporal instabilities of the spectrometer, which are usually attributed to transient temperature fluctuations or AC interference [20,21]. In gradient-selected MQ filtering, unwanted signal components are suppressed by means of dephasing, and coherence transfer pathway (CTP) selection does not depend on their cancellation between successive transients. Gradient coherence selection is therefore regarded as a "cleaner" way of MQ filtering; it also enables the selection of a single CTP where phase-cycled selection may not afford it.

2. The DQDiff scheme

The proposed experiment, which is shown in Fig. 1, is actually a family of diffusion experiments which provide solvent suppression by means of gradient-selected double-quantum filtering through a single CTP. CTP selection is governed by the condition

$$\sum_{i=1}^{6} p_i g_i = 0, \tag{1}$$

where the meaning of p_i and g_i is evident from Fig. 1, and normally $p_6 = -1$. The gradients used for coherence selection are the same gradients as used for measuring the diffusion displacement. They can (but need not) be chosen so as to allow for compensation of convection, as discussed below. The number of gradient combinations which select a given CTP and at the same time enable convection compensation is probably infinite, but in practice limited by the quantitative efficiency of dephasing of the unwanted components. Some of the possible sets are shown in Table 1.

The proposed experiment contains a double-quantum evolution period sandwiched between two $1/2J$ periods:

$$I_\pm \overset{1/2J}{\rightarrow} I_\pm S_z \mid \overset{\pi/2}{\rightarrow} I_\pm S_\pm \xrightarrow{\text{DQ evolution}} \overset{\pi/2}{\rightarrow} \mid I_\pm S_z \overset{1/2J}{\rightarrow} I_\pm,$$

where I is the observed spin coupled to a like spin S with the coupling constant J. In-phase SQ coherences are converted into antiphase during the first $1/2J$ period, and vice versa during the second. To provide for the refocusing of the chemical shifts, each of the three periods is split in half by a π-pulse, as shown in Fig. 1.

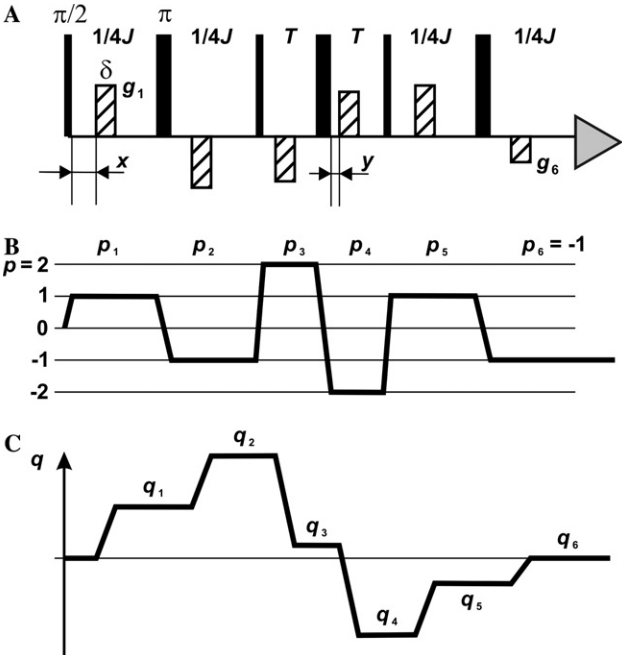

Fig. 1. (A) DQDiff pulse sequence. The gradient values shown here are one of many possible sets which select the CTP $(1, -1, 2, -2, 1, -1)$; examples of other allowed sets are shown in Table 1. (B) Coherence transfer pathway selected by the pulsed-field gradients. No phase cycling is required for CTP selection. (C) Time dependence of the diffusion wave vector $\mathbf{q}$ defined in Eq. (3). Convection compensation is achieved by adjusting the positions of the gradient pulses (x and y) according to Eq. (8); the gradient set used must allow for this.

The structure of DQDiff is similar to a recently proposed uniform-sign cross-peak DQF COSY experiment [22]. Both experiments create an antiphase state, apply a DQ filter, and then convert the antiphase SQ coherence into an in-phase signal at the beginning of acquisition. A key feature of DQDiff is the asymmetric amplitudes of the gradient pulses. This, in turn, is similar to another DQF COSY experiment where asymmetric gradient values are used to filter out longitudinal interference [23,24]. The selection of a single CTP is inherent in the DQDiff experiment and required by its (CTP-specific) convection compensation [4,25].

The diffusion attenuation of the NMR signal arising from a CTP selected in the sense of Eq. (1) can be calculated using the standard approach:

$$S(q) = S(0)\exp\left\{-D\int_0^{t_s} q^2(t)\,\mathrm{d}t\right\}, \tag{2}$$

where

$$q(t) = \int_0^t \gamma p(t')g(t')\,\mathrm{d}t' \tag{3}$$

and D is the diffusion coefficient of the measured species; γ is the magnetogyric ratio; t_s is the duration of the pulse