Journal of Magnetic Resonance **142,** 369–371 (2000)
doi:10.1006/jmre.1999.1957, available online at http://www.idealibrary.com on IDEAL®

Broadband Heteronuclear Hartmann–Hahn Sequences with Short Cycle Times

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Received July 30, 1999; revised October 5, 1999

For some applications, broadband heteronuclear Hartmann–Hahn sequences with very short cycle times are required. A quality factor is presented that makes it possible to assess the relative sizes of cycle time, bandwidth, and maximum RF amplitude for any given multiple-pulse sequence. This quality factor is determined for multiple-pulse sequences that are commonly used in HEHAHA experiments and for some favorable sequences that were so far only discussed in the context of heteronuclear decoupling. © 2000 Academic Press

Key Words: **short mixing sequence; Hartmann–Hahn transfer; HEHAHA.**

Heteronuclear Hartmann–Hahn (HEHAHA) transfer has become an important technique for the transfer of polarization and coherence in high-resolution NMR spectroscopy (*1–5*). The first practical broadband HEHAHA experiments (*6–9*) were derived from heteronuclear decoupling sequences. However, the effective bandwidths can be markedly different if a given multiple-pulse sequence is used as a heteronuclear decoupling sequence (irradiation of one-spin species only, e.g., S) or as a heteronuclear planar mixing sequence (irradiating spins I and S simultaneously) (*4–9*). Even larger bandwidths can be covered by pulse sequences developed specifically for broadband heteronuclear Hartmann–Hahn experiments in liquids (*10, 11*) and it was demonstrated that it is even possible to design HEHAHA sequences with different bandwidths for the I and S spins (*12*). A minimum scaling of the heteronuclear coupling constants J_{ij} is achieved by planar mixing sequences that create an effective heteronuclear coupling term of the form

$$\mathcal{H}_{\mathrm{P}} = 2\pi \sum_i \sum_j J_{ij}^{\mathrm{eff}} \{I_{iy}S_{jy} + I_{iz}S_{jz}\} \qquad [1]$$

with effective coupling constants $J_{ij}^{\mathrm{eff}} \leq J_{ij}/2$ (*4, 5*).

Recently, a new class of heteronuclear coherence-order selective transfer experiments was introduced (*13*) that achieves theoretically predicted upper limits for the transfer amplitude in I_2S and I_3S spin systems (*14*). These sequences consist of short planar mixing periods that are separated by pulses and delays. This poses the problem of finding broadband heteronuclear planar mixing sequences with sufficiently short cycle times τ_c. In principle, the cycle time of any multiple-pulse sequence can be reduced by increasing the RF amplitude ν_{RF} because τ_c is proportional to ν_{RF}^{-1}. However, in practice the maximum RF amplitude is limited by the available RF amplifiers and limitations imposed by the available probes. For example, a planar mixing period of $0.21\ J^{-1}$ (*13*) has a duration of only 1.2 ms for a ^{1}H–^{13}C coupling constant of $J = 170$ Hz and no well-characterized broadband HEHAHA sequence could be found with a sufficiently short cycle time for the maximum available RF amplitude of the ^{13}C channel of the available spectrometer.

For any HEHAHA sequence, the duration of the cycle time τ_c relative to the covered bandwidth $\Delta\nu$ can be expressed in terms of the dimensionless parameter

$$\kappa = \frac{\tau_{\mathrm{red}}}{\Delta\nu_{\mathrm{red}}} = \frac{\tau_c \nu_{\mathrm{RF,max}}^2}{\Delta\nu}, \qquad [2]$$

where $\tau_{\mathrm{red}} = \tau_c\ \nu_{\mathrm{RF,max}}$ is the reduced cycle time, $\Delta\nu_{\mathrm{red}} = \Delta\nu/\nu_{\mathrm{RF,max}}$ is the reduced bandwidth, and $\nu_{\mathrm{RF,max}}$ is the maximum RF amplitude of the pulse sequence. In the following, $\Delta\nu$ is defined as the bandwidth in which the transfer amplitude at $\tau = 1/J$ is larger than 80% of the ideal transfer amplitude. This transfer amplitude reflects the degree to which planar mixing conditions are created by the sequence and can easily be determined both theoretically and experimentally. In Table 1 the durations τ_{red}, the bandwidths $\Delta\nu_{\mathrm{red}}$ (determined using numerical simulations, for details see caption of Fig. 1), and the quality factors κ are given for selected HEHAHA sequences. Of the known and well-characterized HEHAHA sequences, WALTZ-8 (*7, 8, 15*) has the best quality factor with $\kappa = 16$, whereas for most known HEHAHA mixing sequences κ is considerably larger. The DIPSI-2 sequence (*18*) with $\kappa = 28.8$ is based on the composite 180° pulse $Q = 320_x 410_{-x} 290_x 285_{-x} 30_x 245_{-x} 375_x 265_{-x} 370_x$ that is expanded in an MLEV-4 cycle ($Q\bar{Q}\bar{Q}Q$). Surprisingly, the trun-

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1090-7807/00 $35.00

TABLE 1

Comparison of the Reduced Cycle Time τ_{red}, the Reduced Bandwidth $\Delta\nu_{red}$, and the Quality Factor κ (Eq. [2]) for Selected Multiple-Pulse Sequences

Pulse sequence	τ_{red}	$\Delta\nu_{red}$	κ
DIPSI-3 (*9*, *18*)	54.3	1.05	**51.7**
WALTZ-16 (*6*, *9*, *15*)	24	0.8	**30**
DIPSI-2 (*4*, *9*, *18*)	28.8	1.0	**28.8**
SHR-1 (*10*)	26.1	0.95	**27.5**
WALTZ-8 (*7*, *8*, *15*)	12	0.75	**16**
R_2 = 180°(MLEV-4) (*16*, *17*)	2	0.13	**15.4**
DIPSI-2/2	14.4	1.0	**14.4**
180°(MLEV-16) (*16*, *17*)	8	0.72	**11.1**
R_4 (*16*)	8	0.9	**8.9**
180°(MLEV-8) (*16*, *17*)	4	0.5	**8.0**
R_3 (*16*)	4	0.5	**8.0**

cated sequence DIPSI-2/2 with the simple cycle ($Q\bar{Q}$) has a similar bandwidth as DIPSI-2 with only half the cycle time (see Table 1).

Even smaller values of κ were found for relatively simple multiple-pulse sequences that were so far only discussed and analyzed for applications in heteronuclear decoupling. Figure 1 shows the simulated transfer efficiency as a function of the offset of spins I and S for the sequences denoted 180°(MLEV-8) and 180°(MLEV-16) (*16*, *17*) which consist of a single rectangular Q = 180° pulse expanded in an MLEV-8 ($\bar{Q}\bar{Q}QQ\ \bar{Q}QQ\bar{Q}$) or MLEV-16 supercycle ($\bar{Q}\bar{Q}QQ\ \bar{Q}QQ\bar{Q}\ QQ\bar{Q}\bar{Q}\ Q\bar{Q}\bar{Q}Q$) (*17*). Both sequences create an effective

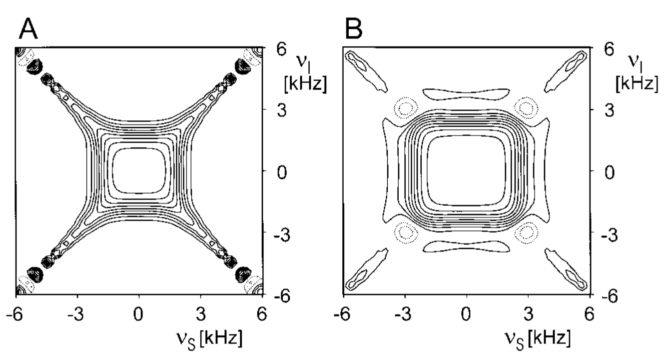

FIG. 1. Simulated offset profiles for the efficiency of the heteronuclear Hartmann–Hahn transfer of the 180°(MLEV-8) (A) and 180°(MLEV-16) (B) sequences. The polarization transfer amplitude is shown at a mixing time τ_{mix} = $1/J$ as a function of the offsets ν_I and ν_S in the range of ±6 kHz. Simulations were performed using the program SIMONE (*19*), assuming an RF amplitude of 5.55 kHz and an uncorrelated Gaussian RF field distribution with a full width at half-height of 10% for both RF channels. The mixing time τ_{mix} = $1/J$ was chosen to yield optimum transfer if both spins I and S are on resonance. In order to realize τ_{mix} with an integer multiple of the cycle time τ_c, slightly different coupling constants J of 92.6 and 96.5 Hz were assumed in the simulations for 180°(MLEV-8) and 180°(MLEV-16), respectively. Positive and negative contour levels are shown by solid and dotted lines, respectively. The level increment is 0.1 and the highest contour level is 0.9.

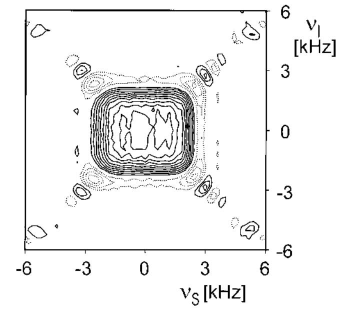

FIG. 2. Experimental offset profile for the efficiency of the heteronuclear Hartmann–Hahn transfer of the 180°(MLEV-16) sequence. HEHAHA transfer was monitored between the ^{15}N and the amide proton of labeled *N*-Boc-alanine in DMSO. The mixing time was 10.1 ms (corresponding to seven complete 180°(MLEV-16) cycles for an RF amplitude of 5.55 kHz), which is slightly shorter than the optimum mixing time τ = $1/J_{HN}$ = 11.1 ms.

planar mixing Hamiltonian (Eq. [1]). For a given RF amplitude ν_{RF}, the reduced bandwidths $\Delta\nu_{red}$ correspond to 50 and 72% of the bandwidth of DIPSI-2 (*4*, *9*, *18*). However, the durations τ_{red} = 4 and τ_{red} = 8 of these sequences are only 13.9 and 27.8% of DIPSI-2 cycle time, resulting in improved quality factors κ = 8.0 and κ = 11.1 for 180°(MLEV-8) and 180°(MLEV-16), respectively. The sequence R_4 = $360_x 270_{-x} 90_x 360_{-x} 270_x 450_{-x} 270_x 90_{-x} 360_x 270_{-x} 90_x$ (*16*) has the same duration τ_{red} as 180°(MLEV-16) with bandwidth $\Delta\nu_{red}$ = 0.9 and a quality factor κ = 8.9 (note that there was a printing error in the definition of R_4 in (*16*)). The sequence R_3 = $90_{-x} 360_x 270_{-x} 90_x 360_{-x} 270_x$ (*16*) has identical duration τ_{red} as 180°(MLEV-8) and a reduced bandwidth $\Delta\nu_{red}$ of 0.5, matching its κ value of 8.0, which is the best quality factor that was found so far. The simpler sequence R_2 = 180°(MLEV-4) (*16*, *17*) was investigated but has a relatively unfavorable quality factor κ = 15.4 (see Table 1).

As an example of an experimentally determined offset profile, Fig. 2 shows the results for the 180°(MLEV-16) sequence. The HEHAHA transfer between the ^{15}N and the amide ^{1}H spins of ^{15}N-labeled *N*-Boc-alanine in DMSO was monitored for a mixing time of 10.1 ms (corresponding to seven complete 180°(MLEV-16) cycles with an RF amplitude of 5.55 kHz) which is slightly shorter than the optimum mixing time τ = $1/J_{HN}$ = 11.1 ms. The transfer amplitudes were extracted from a series of 1-D experiments (*12*) in which the offset of the I and S spins was independently varied in the range of ±6 kHz. A reasonable match between simulations (Fig. 1B) and experiment is found.

The quality factor κ can form the basis for numerical optimizations of new multiple pulse sequences with short cycle times and favorable bandwidths. It is conceivable that sequences with even smaller values of κ can be found, e.g., based on optimized composite pulses with simpler expansion schemes. The definition of the quality factor κ (Eq. [2]) for short HEHAHA sequences is reasonable, but it is by no means unique. Depending on the application, alternative definitions can be useful. For example, the weight of the bandwidth covered by a HEHAHA sequence can be increased relative to the duration of the sequence, if in Eq. [2] $\Delta\nu_{red}$ is replaced by $(\Delta\nu_{red})^2$. In cases where the RF irradiation is limited by the average RF power, rather than by the maximum RF amplitude, this can be taken into account in the definition of τ_{red} and $\Delta\nu_{red}$ where the maximum RF amplitude $\nu_{RF,max}$ is replaced by $\bar{\nu}_{rms}$ (*5*), the root mean square of the RF amplitude.

ACKNOWLEDGMENTS

We thank one of the referees for pointing out the heteronuclear decoupling sequences R_3 and R_4 as promising candidates for HEHAHA sequences with small values of the quality factor κ. This work was supported by the DFG under Grant G1 203/1-6. B.L. acknowledges a scholarship of the Fonds der Chemischen Industrie. S.J.G. thanks the DFG for a Heisenberg Stipendium (G1 203/2-2). The experiments were performed at the "Large Scale Facility for Biomolecular NMR" (ERB CT 950034).

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