JOURNAL OF MAGNETIC RESONANCE 87, 422–428 (1990)

Gradient-Enhanced Spectroscopy

RALPH E. HURD

GE NMR Instruments, 255 Fourier Avenue, Fremont, California 94539

Received December 19, 1989

Although the use of gradients to select specific coherences was introduced several years ago (*1, 2*), widespread application in high-resolution NMR appears to have been impeded by limits in gradient technology. Improvements afforded by the recent introduction of actively shielded gradients (*3*), however, have made it practical to take advantage of gradient-based coherence selection. Our initial efforts were focused on *in vivo* applications in which gradient selection of double-quantum coherence was used to obtain spectra and images of metabolites such as lactate (*4, 5*). It is also possible to devise gradient-enhanced versions of the many useful high-resolution 1D and multidimensional homonuclear and heteronuclear NMR experiments. A major advantage of these methods is that because only the desired coherences are selectively rephased, phase cycling and, in some cases, traditional water suppression methods are not required. The two experiments discussed in this Communication are gradient-enhanced double-quantum COSY (ge-2qcosy) and gradient-enhanced TOCSY (ge-tocsy).

A double-quantum COSY spectrum of 8 mM angiotensin II in H_2O (Fig. 1) was obtained using the gradient-enhanced experiment (ge-2qcosy) shown in Fig. 2. Data were collected on a GE NMR Instruments Omega 400 WB equipped with Microstar gradients (maximum strength ±137 G/cm). The probe used consisted of a 5 mm diameter Helmholtz radiofrequency coil tuned to 400.06 MHz. The potential for eddy current generation within the probe was minimized by use of nonconductive materials where possible. In this experiment, only a single acquisition per evolution time (t_1) increment is required to select the +1/+2 coherence pathway. The large population of water protons remains dephased, thus avoiding loss of signal which can result from misuse of presaturation, selective excitation, and/or attenuation. The receiver never detects this unwanted signal, while desired coherences, even from resonances at the solvent chemical shift, are observed. Water suppression by this method is independent of lineshape or shimming (B_0 homogeneity). Another benefit of this approach is that, because the unwanted signals remain dephased, they contribute very little to coherent t_1 noise as illustrated by the noise floor contour plot shown in Fig. 3. These data were collected nonspin, as a 1K by 1K matrix with a spectral width of 4000 Hz in both ω_1 and ω_2. The average recycle time was 900 ms. Gradients (x, y, and z) were 1 ms half-sinusoid with maximum amplitudes of 10, 10, and 30 G/cm. These gradient strengths were determined empirically to be the minimum required to completely eliminate the water signal in this sample, which had a diameter of 5 mm

0022-2364/90 $3.00

DOI of original item: doi: 10.1016/0022-2364(90)90021-Z

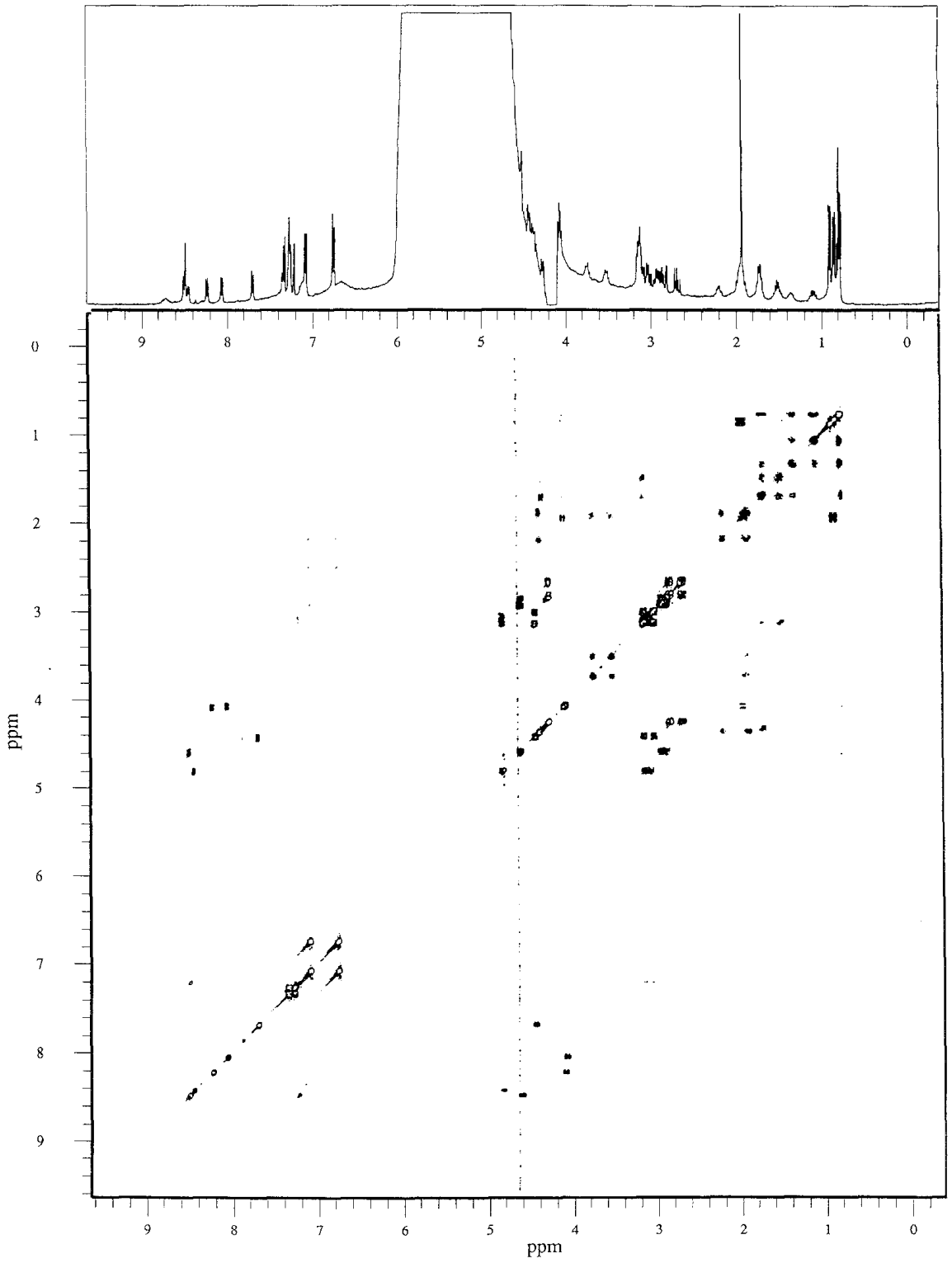

FIG. 1. Contour plot of 400 MHz proton ge-2qcosy spectrum of 8m*M* angiotensin II in H_2O. There were 1024 t_1 increments collected without phase cycling. Acquisition times of 256 ms provided 4 Hz resolution in both ω_1 and ω_2. One millisecond half-sinusoid gradients of 10, 10, and 30 G/cm were used. An 800-fold vertical expansion of the reference one-pulse spectrum is plotted across the top of the contour plot.

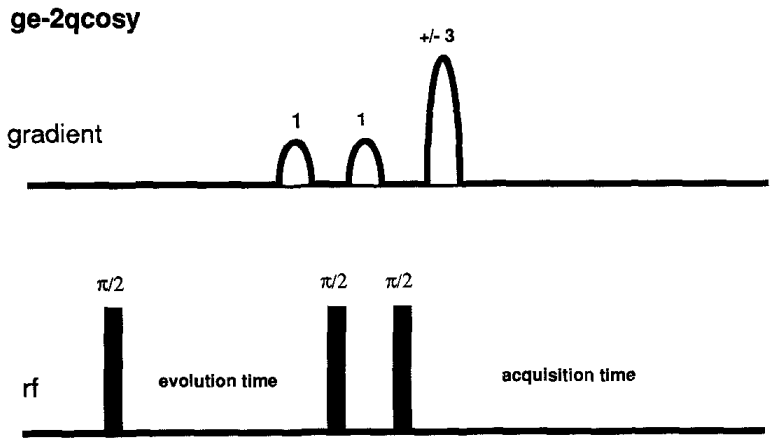

FIG. 2. Gradient-enhanced double-quantum COSY (ge-2qcosy) pulse sequence. Evolution time includes the first gradient pulse and acquisition time starts after the final gradient pulse.

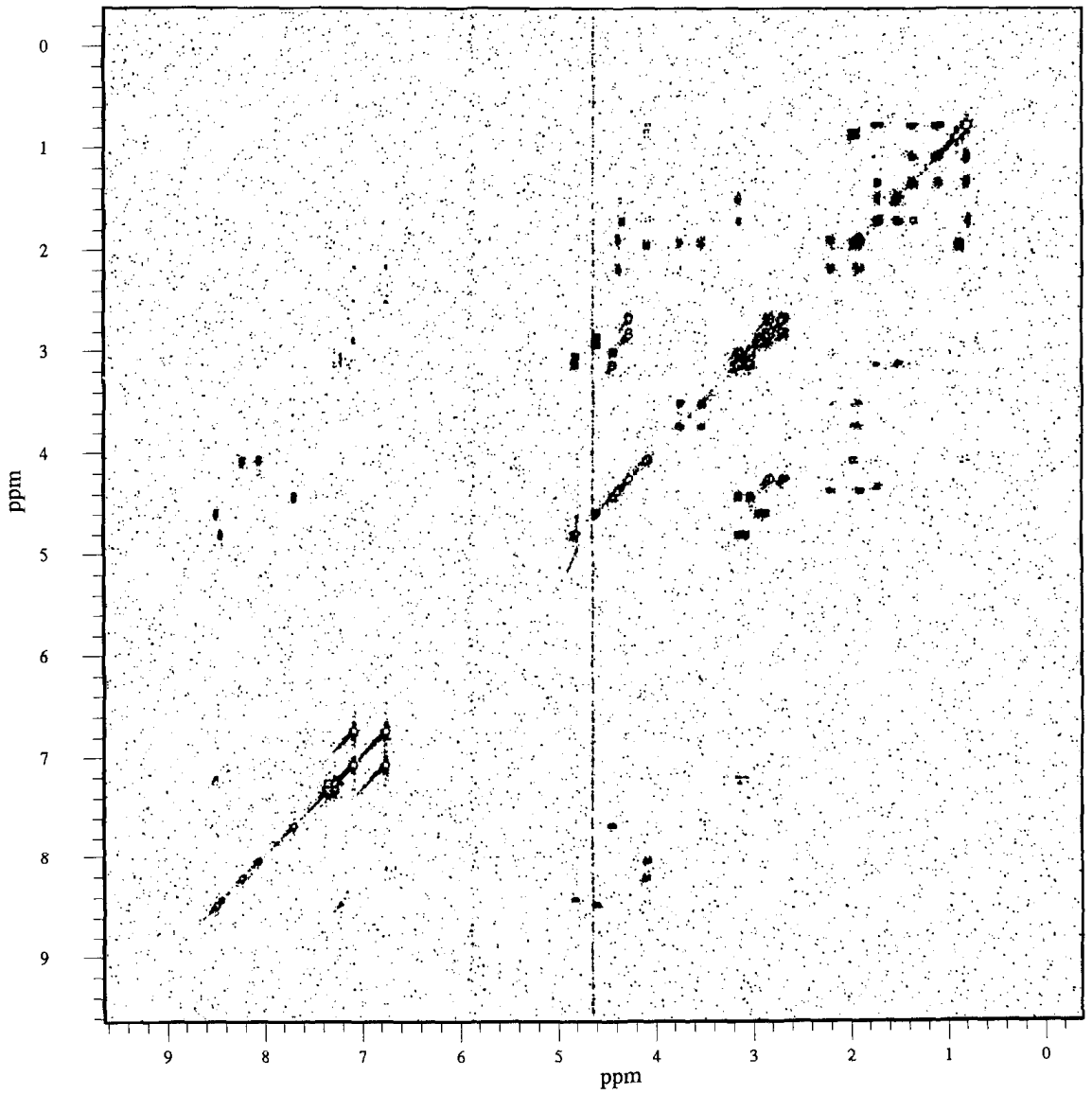

FIG. 3. Noise floor of the contour plot shown in Fig. 1.

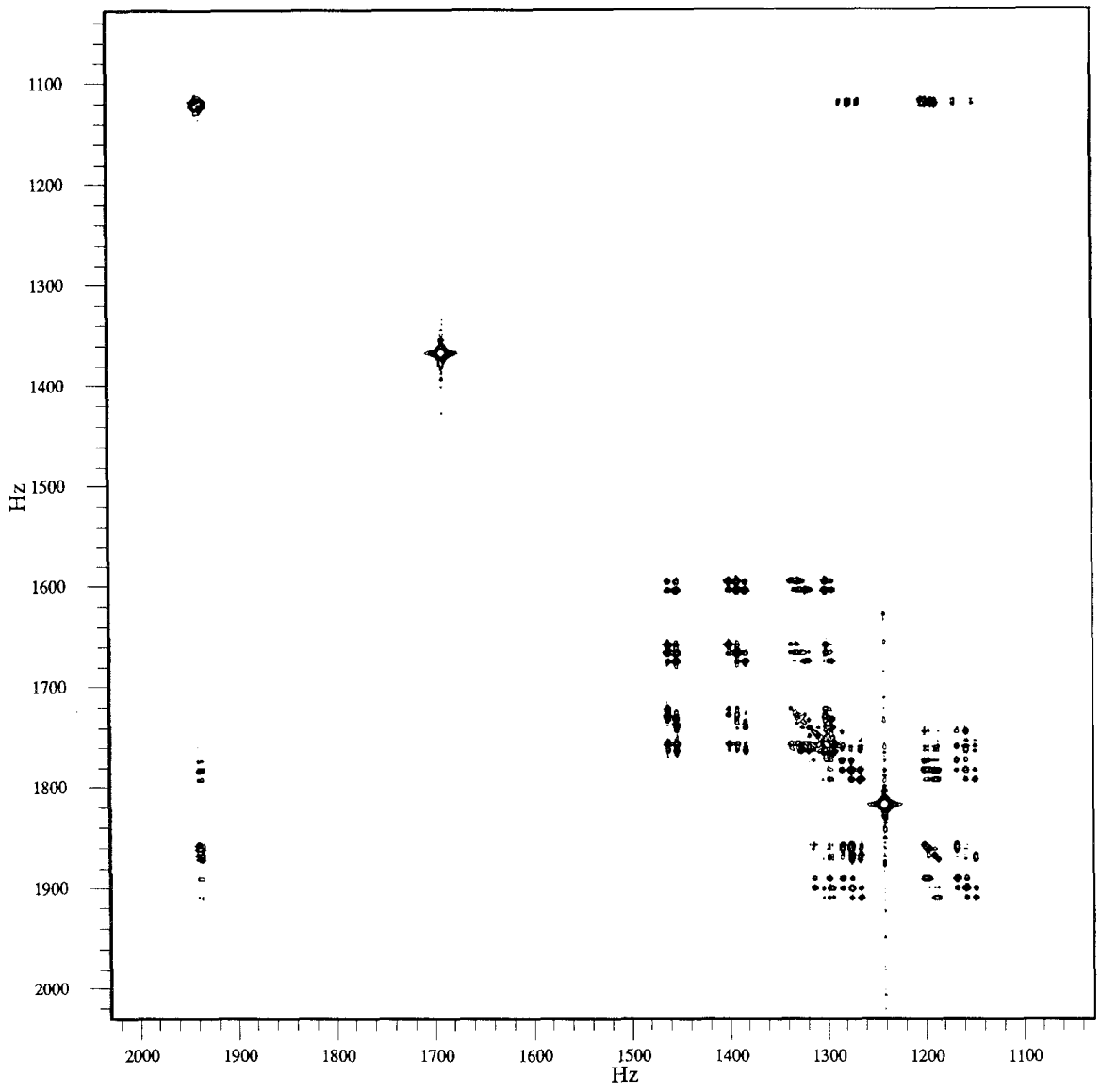

FIG. 4. Contour plot of a 400 MHz proton ge-tocsy spectrum of 10 mM sucrose in D_2O. A single acquisition was collected for each of 512 t_1 increments. Acquisition times of 512 ms provided 2 Hz resolution in both dimensions. A 20 ms MLEV-16 spin-lock pulse with a $\gamma B_1/2\pi$ strength of 4 kHz was bracketed by a 1 ms half-sinusoid gradient pair with maximum amplitudes of +2 and −2 G/cm.

and a length of 35 mm. Signal loss due to self-diffusion (*6*) was calculated to be less than 1% for the observed spins. The elimination of phase cycling resulted in a small zero-frequency artifact at the transmitter setting (4.65 ppm) in ω_2. Minor, yet unexplained, artifacts were observed for the resonances from the tyrosine ring protons at 7.05 and 6.76 ppm. Compromise of quadrature in ω_1 and some peak distortion along the diagonal were noted.

Total scalar correlation spectra (*7*) of 10 mM sucrose in D_2O (Figs. 4 and 5) were obtained to illustrate the gradient-enhanced version of HOHAHA (*8*) using both

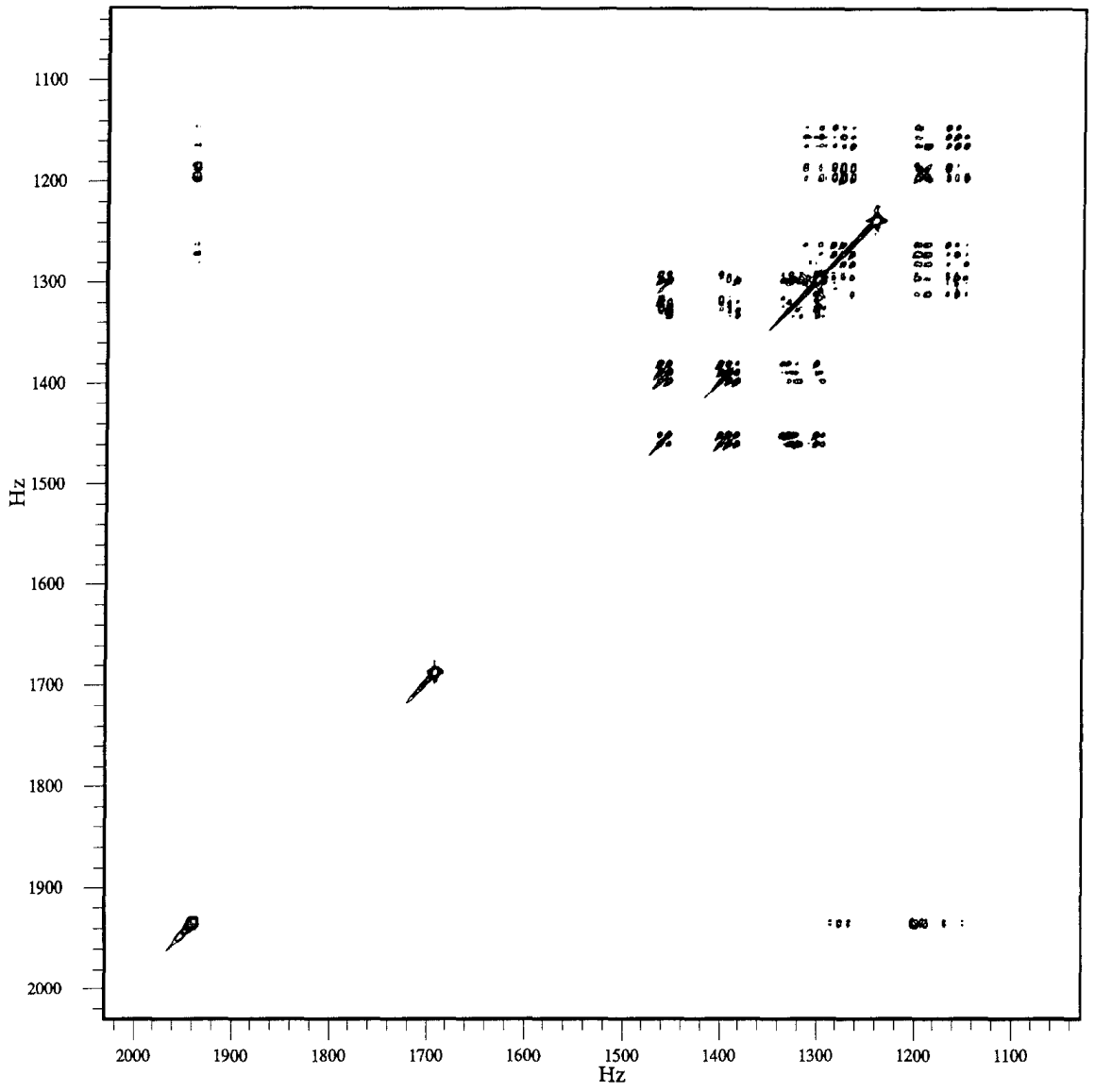

FIG. 5. Same sample and conditions as those in Fig. 4, but with a 20 ms MLEV-17 spin-lock pulse with a $\gamma B_1/2\pi$ strength of 4 kHz and bracketed by a 1 ms half-sinusoid same-sign gradient pair with maximum amplitudes of +2 G/cm.

MLEV-16 (*9*) and MLEV-17 (*10*) as spin-lock pulses. Gradient-enhanced versions of these pulse sequences are shown in Fig. 6. Unlike COSY, the gradient pair can only be of opposite sign for the MLEV-16-based ge-tocsy sequence. The additional pulse (60°) in the MLEV-17 cycle reestablishes both pathways and makes it possible for either a same-sign or an opposite-sign gradient pair to rephase coherence. Data were collected as 512 × 512 matrices with a single acquisition per evolution time (t_1) increment. Spectral width was 1000 Hz in both ω_1 and ω_2 and a 20 ms spin-lock pulse with a B_1 field strength of 4 kHz was used. A 1 ms half-sinusoid gradient pair with maximum amplitudes of 2 and −2 G/cm gave nearly identical results for both

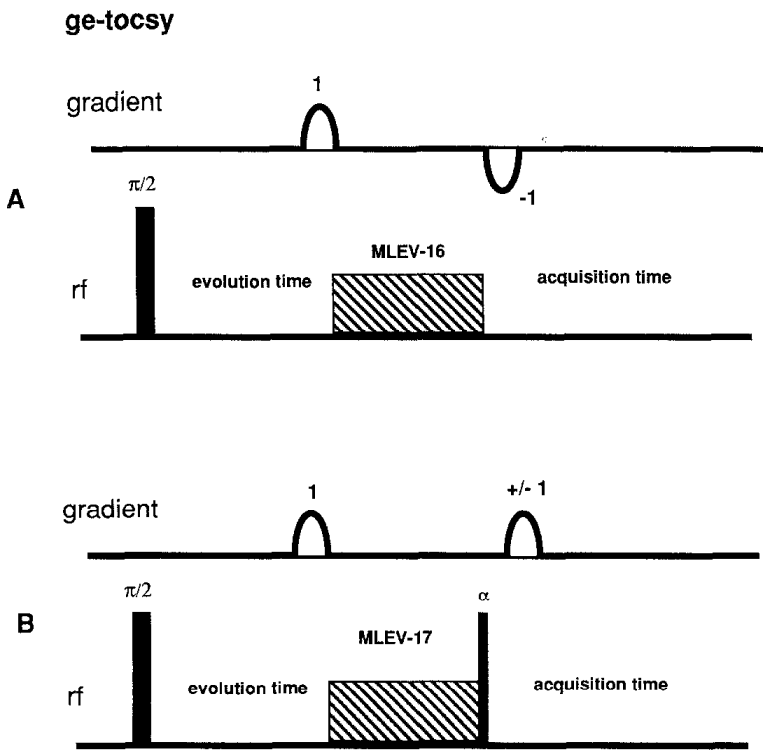

FIG. 6. Gradient-enhanced total scalar correlation experiments (ge-tocsy) with (A) MLEV-16 spin lock and (B) MLEV-17 spin lock. Evolution time includes the first gradient pulse and acquisition time begins after the final gradient pulse.

MLEV-16- and MLEV-17-based experiments (the MLEV-16 result is shown in Fig. 4). A same-sign gradient pair was used to obtain the ge-tocsy spectrum shown in Fig. 5. The most notable difference in the spectra is that peak distortion is observed along ω_1 for the opposite-sign gradient pair and along the diagonal in the same-sign case.

The examples presented here illustrate the potential of gradient-enhanced spectroscopy. The list of advantages includes a significant reduction in measuring time, reduced t_1 artifacts, the elimination of phase cycling and difference methods (which makes these methods less susceptible to vibration), the potential for pure three- and four-quantum editing, and the ability to detect resonances at the same chemical shift as a strong solvent resonance.

Limitations include a requirement for field-frequency-lock blanking during long runs and the possible elimination of useful signals along with those that are unwanted. Also, in the absence of phase cycling, it is important to avoid quadrature artifacts in ω_2 by keeping the two receiver channels balanced.

The benefit of gradient-enhanced spectroscopy should be of particular importance in high-resolution 3D experiments via the reduction in total measurement time associated with the elimination of phase cycling and in proton-detected heteronuclear correlation experiments via the elimination of subtraction-based selection of coherence.

REFERENCES

1. A. A. MAUDSLEY, A. WOKAUN, AND R. R. ERNST, *Chem. Phys. Lett.* **55,** 9 (1978).
2. A. BAX, P. G. DE JONG, A. F. MEHLKOPF, AND J. SMIDT, *Chem. Phys. Lett.* **69,** 567 (1980).
3. P. B. ROEMER, W. A. EDELSTEIN, AND J. S. HICKEY, "Book of Abstracts, 5th Annual Meeting of the Society of Magnetic Resonance in Medicine, Montreal, August 19–22, 1986," p. 1067.
4. C. H. SOTAK, D. M. FREEMAN, AND R. E. HURD, *J. Magn. Reson.* **78,** 355 (1988).
5. R. E. HURD AND D. M. FREEMAN, *Proc. Natl. Acad. Sci. USA* **86,** 4402 (1989).
6. E. O. STEJSKAL AND J. E. TANNER, *J. Chem. Phys.* **42,** 288 (1965).
7. L. BRAUNSCHWEILER AND R. R. ERNST, *J. Magn. Reson.* **53,** 521 (1983).
8. D. G. DAVIS AND A. BAX, *J. Am. Chem. Soc.* **107,** 2821 (1985).
9. M. H. LEVITT, R. FREEMAN, AND T. FRENKIEL, *J. Magn. Reson.* **47,** 328 (1982).
10. A. BAX AND D. G. DAVIS, *J. Magn. Reson.* **65,** 355 (1985).