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Spin-echo Methods for Resolution Control of Lanthanide-shifted N.M.R. Spectra

By J. Mark Bulsing and Jeremy K. M. Sanders*

(*University Chemical Laboratory, Lensfield Road, Cambridge* CB2 1EW)

and Laurance D. Hall

(*Department of Chemistry, University of British Columbia, Vancouver, British Columbia* V6T 1Y6, *Canada*)

Summary At high fields, lanthanide-shifted n.m.r. spectra are severely broadened by chemical exchange; the Carr–Purcell–Meiboom–Gill spin-lock sequence can be used to remove broadened peaks selectively and controllably without distorting the remaining signals.

Following the first reports[1,2] of the use of lanthanide-shift reagents there was much exploration of the potential of these compounds in organic chemistry,[3,4] but little use seems to be made of them now. This is in part undoubtedly because the enhanced chemical-shift dispersion is often obtained at the expense of resolution with concomitant loss of coupling information. We show here that chemical exchange is the prime source of broadening, and that therefore the problem is worse at high field, but that spin-echo techniques can be helpful in controlling the resolution of the final spectrum.

In connection with another study we noticed that Eu(dpm)$_3$-induced (dpm = dipivaloylmethanato) line broadenings in cholesterol and n-alkanols were much more severe at 270 MHz than in the corresponding 'classical' 100 MHz spectra.[1,2] Measurement of T_1 and an estimate of T_2 from linewidths showed that the line broadening could not be attributed to fast T_1 relaxation (Table). Indeed, even the T_1 changes are dominated by the reduced tumbling rate in the adduct rather than by the paramagnetism of the europium ion.[5] If the extra line broadening is due to chemical exchange, then the exchange contribution ($\Delta\nu_{ex}$) should be given[6] by equation (1), where P_B is the fraction of substrate bound to the lanthanide, τ_B is the bound lifetime, and Δ is the chemical shift difference (free — bound) in Hz.

$$\Delta\nu_{ex} = \frac{P_B}{(1 - P_B)^2} \cdot \tau_B \cdot (2\pi\Delta)^2 \qquad (1)$$

This was confirmed by 400 MHz experiments in which the broadening was not only more severe (as Δ is bigger) at low P_B but actually reached a maximum as expected near $P_B = 1/3$ and decreased as further shift reagent was added.† The t-butyl-shift reagent signal was also very broad.

Table. Shift and relaxation properties of n-nonanol protons (0·1 M) in the presence of Eu(dpm)$_3$ (0·03 M).[a]

Proton	δ	Δ[b]	T_1/s	$T_2 (= 1/\pi W)$[c]/s
1	10·90	7·25	0·18	0·02
2	5·75	4·18	0·32	0·03
3	4·19	2·78	0·47	0·07
4	2·77	1·49	0·68	0·09
5	2·18	0·90	0·79	0·1
6	1·86	0·58	1·15	~0·1[d]
9	1·07	0·19	1·51	~0·5[d]

[a] 270 MHz, $CDCl_3$ solution, *ca.* 292 K. [b] Shift from normal position (in p.p.m.). [c] Corrected for 1 Hz linewidth in reference ($CHCl_3$) signal. [d] These apparent linewidths may be large owing to extremely strong coupling of C-7 and C-8 protons.

† At low field, strong binding caused by chelation can give similar effects[4,7] or even slow exchange.[8]

Spin echoes provide a versatile approach to the controlled separation of such sharp and broad signals.[9,10] In the classical experiment [sequence (2)] only the second half

$$90°\text{–}t\text{–}180°\text{–}t\text{–acquire} \quad (2)$$

of the echo is acquired and transformed. Broad signals with short T_2 have relaxed before acquisition begins and are removed from the spectrum. Figure 1 shows a broad

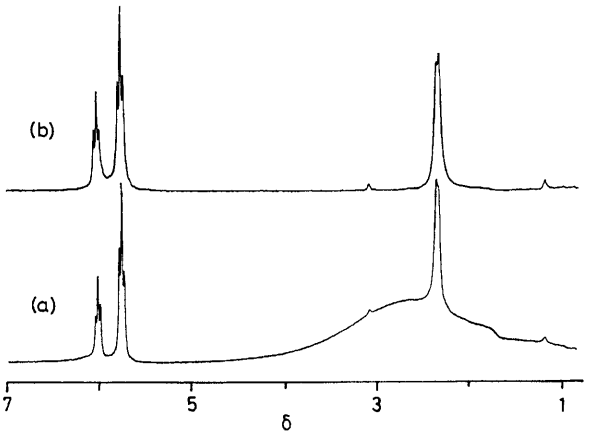

FIGURE 1. 270 MHz n.m.r. spectra of benzyl alcohol ($PhCH_2OH$) and $Pr(dpm)_3$ in $CDCl_3$ solution: (a), normal spectrum; (b), effect of simple half-echo experiment with $t = 5$ ms.

interfering shift-reagent signal being removed with $t = 5$ ms. The sharp signals are retained with better signal-to-noise than if resolution enhancement is used to remove broad peaks mathematically.

More subtle resolution control requires longer t values; if homonuclear coupling is present phase modulation then becomes a problem. Phase modulation may be suppressed by taking the absolute value display of the classical half-echo spectrum but dispersive tails often dominate the spectra. The whole echo can be acquired [sequence (3)] and displayed in the absolute value mode[11] but only in rare

$$90°\text{–}t\text{–}180°\text{–acquire} \quad (3)$$

cases do all the dispersive components actually cancel.

We find that phase modulation is best suppressed by use of a spin lock generated with the Carr–Purcell–Meiboom–Gill (CPMG) sequence [sequence (4)] where t is 1 ms and

$$90^\circ_x\text{–}(-t-180^\circ_y)_n\text{–}t\text{–acquire} \quad (4)$$

n is a variable number.[10,12] Magnetisation isochromats are flipped sufficiently rapidly in the xy plane by the successive 180° pulses that phase modulation has no time to develop, and as n increases the signal intensity decreases smoothly according to T_2. Figure 2(b) and (c) show CPMG resolution control using a n-nonanol–$Eu(dpm)_3$ mixture as example. As n increases successively sharper signals are sequentially removed from the spectrum in a controlled way but *without*

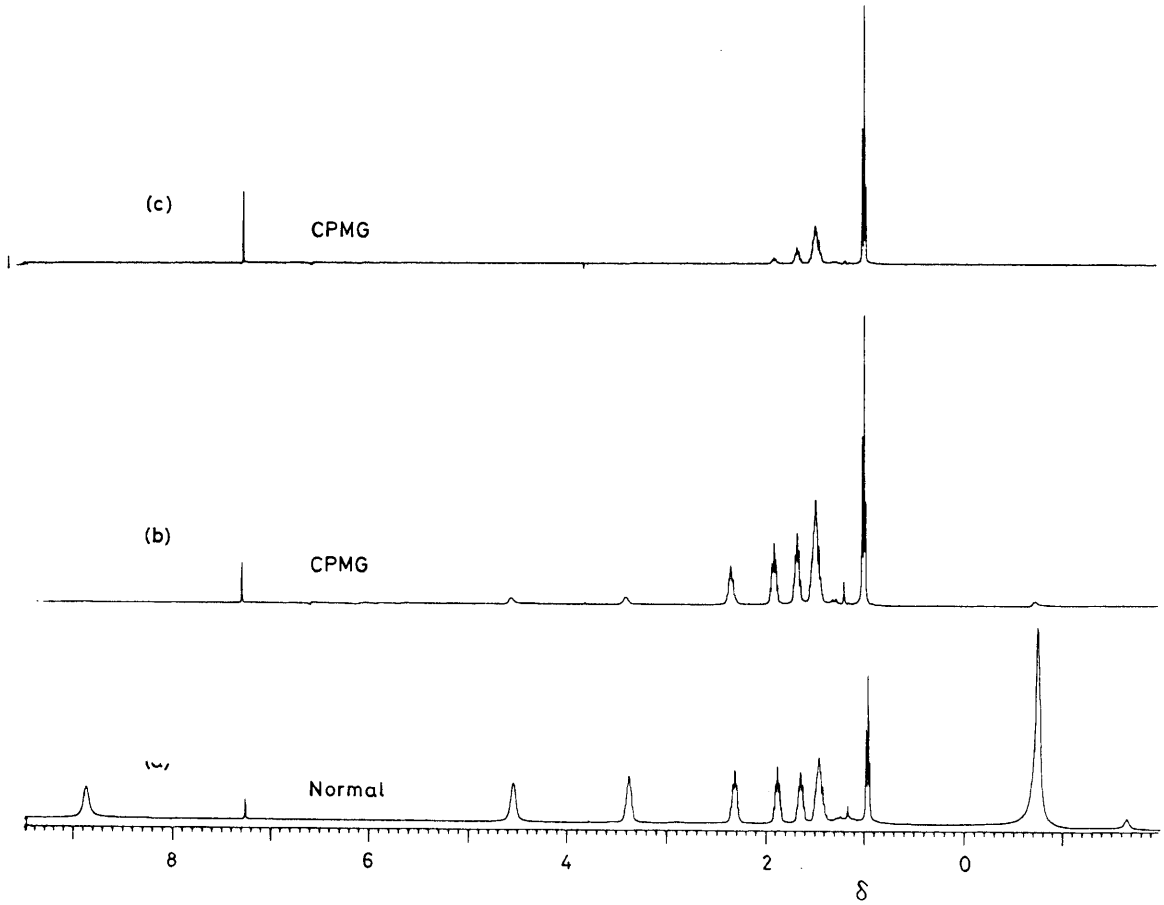

FIGURE 2. 400 MHz n.m.r. spectra of n-nonanol and $Eu(dpm)_3$ in $CDCl_3$: from bottom (a), normal spectrum; (b), CPMG spectrum ($n = 50$); (c), CPMG spectrum ($n = 500$).

multiplet distortion. This promises to be a useful technique in both chemical and biological contexts when relatively sharp signals are obscured by broader ones. Exchange broadening does not affect shifts; the induced-shift ratios given in the Table are identical (within experimental error) to those reported earlier at low fields.[2]

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