

THE APPLICATION OF LANTHANIDE RELAXATION REAGENTS IN CMR

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The possibility of determining geometrical relationships using the  $(3 \cos^2 \theta - 1)/r^3$  dependence of proton nmr shifts on the dipolar interactions induced by lanthanide shift reagents has been widely exploited.<sup>1-3</sup> The utility of the shift reagents in carbon-13 nmr, however, is often mitigated by large contact contributions from delocalization of electronic spin. In extreme cases this can even produce "wrong-way" shifts, i.e., upfield shifts with europium reagents.<sup>4-6</sup> Considering the questions which have arisen regarding the validity of the expression used for calculation of geometry<sup>2,7,8</sup>, we have suggested the complementary use of relaxation reagents for the determination of structure from proton spectra.<sup>9,10</sup> The advantages of a relaxation reagent over a shift reagent for cmr will be demonstrated below.

The low sensitivity of natural abundance cmr spectrometers requires concentrated samples for relatively short acquisition times for spectra. Since the observed shift depends on the ratio of reagent to substrate and the gyromagnetic of  $^{13}\text{C}$  is one-fourth that of  $^1\text{H}$ , a large quantity of shift reagent must be added to produce suitable shifts.\* Conventional proton spectrometers only allow routine determination of relaxation times ( $T_2$ ) by measurements of line widths. Routine use of line widths in cmr is proscribed by the inordinately long acquisition times required to accurately measure the width at half-height of a very broad resonance. The mode of data acquisition in modern pulsed cmr spectrometers, however, readily

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\* The quantities of shift reagents required can become significant. At current prices a one milliliter sample of 10M 1-butanol requires \$4 worth of  $\text{Eu}(\text{fod})_3$  to shift C-1 100 Hz and \$21 worth to shift C-2 100 Hz at 20MHz. The relaxation reagents require one-hundredth these quantities to be useful.

allows the determination of spin-lattice relaxation times. Although the quantitative determination of  $T_1$  and the relative distances may become somewhat involved, the qualitative utility of the  $1/r^6$  dependence of the relaxation time is extremely effective in the assignment of resonances.

Normally one observes a  $^{13}\text{C}$  spectrum by rotating the magnetization of the sample with a  $90^\circ$  pulse of rf power and detecting the resulting signal. The Fourier transform of this time dependent signal produces the spectrum as illustrated for 1-butanol in Figure A. If a  $180^\circ$  pulse is applied, the magnetization is inverted and if it is quickly followed by a  $90^\circ$  pulse to observe the effect, the spectrum will appear upside-down as in Figure B. If a time interval,  $\tau$ , is allowed between the  $180^\circ$  and  $90^\circ$  pulse, the magnetization will have relaxed partially back to its original value. A series of these  $180^\circ$ - $\tau$ - $90^\circ$  or "inversion recovery" experiments with varying  $\tau$ , provides a method of measuring  $T_1$  because the  $\tau$  at which a given resonance crosses through zero equals  $\ln 2 \times T_1$ .

The  $T_1$ 's of most carbon atoms in organic compounds are  $\geq 1$  sec; hence, with a  $\tau$  of less than 0.1 sec one usually observes inverted resonances. Addition of  $\text{Gd}(\text{dpm})_3^*$  drastically

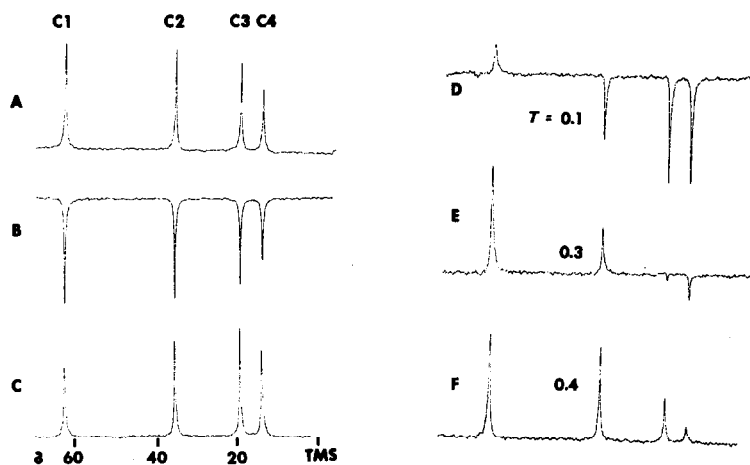


Figure. (A) The 20MHz  $^{13}\text{C}$  nmr spectrum of 11 M 1-butanol in  $\text{CDCl}_3$ . (B) The inverted spectrum following a  $180^\circ$ -0.5 sec- $90^\circ$  pulse sequence. (C) The effect of 0.01M  $\text{Gd}(\text{dpm})_3$  (Note the broadening of C-1 and negligible shifts). (D-F) Variations with  $\tau$  in inversion recovery experiments for the sample containing 0.01M  $\text{Gd}(\text{dpm})_3$ .

\* dpm is the anion of dipivaloylmethane. fod is the anion of heptafluoro-7,7-dimethyl-4,6-octanedione.

shortens the relaxation time of those nuclei near to the binding site of the metal. This is illustrated in the figure, which clearly demonstrates the  $T_1$  ordering of 1-butanol in the presence of the gadolinium reagent to be C-1 < C-2 < C-3 < C-4. The relaxation due to the  $Gd(dpm)_3^*$  should show a close correlation with  $1/r^6$ , where  $r$  is the distance from the metal to the carbon nucleus being relaxed. In quantitative studies the observed relaxation time must be corrected for other sources of relaxation; i.e., the natural relaxation time must be included ( $1/T_{1obs} = 1/T_{1 Gd} + 1/T_{1 nat}$ ).<sup>\*\*</sup> The correlation with distance can be tested with a rigid molecule, such as 4-picoline, where relative distances can be predicted accurately. Reasonable agreement is obtained as can be seen in the following table.

SPIN-LATTICE RELAXATION TIMES OF 4-PICOLINE WITH  $Gd(DPM)_3$

Nuclei	3:2	4:2	Me:2
$(T_1)^{-6}/(T_1)^{-6}$ observed	0.72	0.66	0.60
$r^{-6}/r^{-6}$ calculated	0.72	0.64	0.51

Relaxation times were measured by zero-crossings as well as slopes of  $\ln(2A_0 - A)$  vs  $\tau$  plots.<sup>14</sup> Relaxation times were measured on a sample containing 10 M 4-picoline and 0.02 M  $Gd(dpm)_3$  in deuteriochloroform at 20MHz using a Varian CFT-20.

Errors may arise from additional relaxation by non-bonded species. This problem becomes significant for situations in which a nucleus is distant from the bound metal atom. Some relaxation might also arise from a contact interaction; however, the large change in relaxation time accompanying a small shift of the resonance, as well as the correlation of the data with distance, suggests a small contribution from contact effects.<sup>\*\*\*</sup> It appears that the most serious problems may arise from situations where the relaxation time is not dominated by the dipolar interaction with the metal. Such cases may arise with hindered internal rotations and changes in rotational correlation times which occur on binding to the metal.

\* For other rare earths additional angular factors must be considered.<sup>9,11,12</sup>

\*\* Errors arising from saturation due to inadequate delays between pulse sequences could be eliminated by artificially reducing all relaxation times to one second by the addition of a non-coordinating relaxation reagent<sup>13</sup>. Hence a solution containing both  $Gd(dpm)_3$  and  $Cr(acetylacetonate)_3$  may prove useful.

\*\*\* Shifts of +.29 ppm, -0.20 ppm, +0.19 ppm, and -0.01 ppm for C-2, C-3, C-4 and Me were noted upon the addition of the gadolinium reagent, where a positive shift is downfield. The alternating signs are a definite indication of the contact interaction. Considering the relaxation time of gadolinium III and analogous effects with cobalt and nickel complexes we estimate the contact contribution to the relaxation should be less than 10%.<sup>12</sup>

It should be feasible to correct for second coordination sphere effects by considering the change in a model compound which would not coordinate; *i.e.*, toluene as a model for picoline. The relative magnitudes of the relaxation arising from contact interactions can be readily estimated from the relative sizes of the contact shifts produced. It is of utmost practical importance, nevertheless, that the method withstands the empirical test of working in a large number of cases. This will require extensive study; however, it is clear that the relaxation reagent method is successful with 4-picoline, whereas the europium shift reagent fails<sup>4-6</sup>. Used with adequate precautions and consideration of sources of error, we believe the use of these relaxation reagents will be an extremely valuable tool for the assignment of carbon-13 resonances.

1. R. von Ammon and R.D. Fisher, *Angew. Chem. Internat. Edit.*, 11, 675 (1972).
2. W.D. Horrocks, Jr. and J.P. Sipe, III, *Science*, 177, 994 (1972).
3. B. Bleany, *J. Magn. Res.*, 8, 91 (1972).
4. R.J. Cushley, D.R. Anderson, and S.R. Lipsky, *J. Chem. Soc., Chem. Commun.*, 636 (1972).
5. M. Hirayama, E. Edagawa, Y. Hanyu, *J. Chem. Soc., Chem. Commun.*, 1343 (1972).
6. G.E. Hawkes, C. Marzin, S.R. Johns, and J.D. Roberts, *J. Amer. Chem. Soc.*, 95, 1662 (1973).
7. C.L. Honeybourne, *Tetrahedron Lett.*, 1095 (1972).
8. R.E. Cramer and R. Dubois, *J. Amer. Chem. Soc.*, 95, 3801 (1973).
9. G.N. La Mar and J.W. Faller, *J. Amer. Chem. Soc.*, 95, 3817 (1973).
10. J.W. Faller and G.N. La Mar, *Tetrahedron Lett.*, 1381 (1973).
11. H. Sternlicht, *J. Chem. Phys.*, 42, 2250 (1965).
12. G.N. La Mar, submitted to the *J. Amer. Chem. Soc.*
13. G.N. La Mar, *Chem. Phys. Lett.*, 10, 230 (1971).
14. K. van Putte, *J. Magn. Res.*, 2, 216 (1970).