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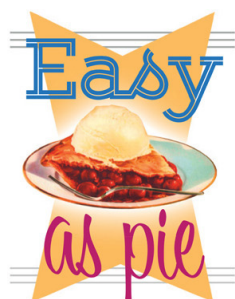
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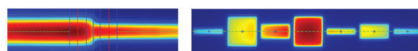
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Solutions of two paramagnetic ions for use in nuclear magnetic resonance phantoms

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The introduction of paramagnetic ions to affect relaxation times has been used in a variety of nuclear magnetic resonance (NMR) applications. All such relaxants used in NMR phantoms to date have consisted of a single paramagnetic ion. The disadvantage of this is that only one relaxation time can be adjusted as desired, either T_1 or T_2 . This study demonstrates that, by properly choosing two paramagnetic ions, it is possible to adjust both T_1 and T_2 independently over a wide range of values. Specifically, solutions of MnCl_2 and NiCl_2 were prepared that simultaneously matched target T_1 and T_2 values to within approximately 6%.

Key words: T_1 , T_2 , relaxation times, NMR phantoms, paramagnetic ions

I. INTRODUCTION

The introduction of paramagnetic ions to affect relaxation times has been used in a variety of nuclear magnetic resonance (NMR) applications including the preparation of phantoms¹⁻⁴ and as the active part of possible contrast agents.⁴⁻¹⁴ In such simple solutions it is possible to adjust either T_1 or T_2 to be as desired. However, the disadvantage of these single ion solutions is that if one prepares a solution with, for example, a given T_1 , then the T_2 of the solution is also fixed and may not be as desired. This is particularly important in attempting to mimic tissues where one must be simultaneously free to select both T_1 and T_2 (as well as possibly other NMR parameters). This study shows that, by using two suitably chosen paramagnetic solutes, solutions can be prepared over a wide range of T_1 's and T_2 's that simultaneously and accurately match target values of both relaxation times.

II. THEORY

It has been known that the presence of paramagnetic ions affects the relaxation times of water. For this paper it is convenient to discuss such relaxation in terms of the relaxation rates, R_1 and R_2 , which are the reciprocals of the more common relaxation times, T_1 and T_2 , respectively. With this notation we may write the expected relaxation rates of a water solution of a single paramagnetic ion A as

$$R_1 = R_{w1} + m_{A1}k_A, \quad R_2 = R_{w2} + m_{A2}k_A, \quad (1)$$

where R_{w1} and R_{w2} are the relaxation rates of pure water, k_A is the concentration of the paramagnetic ions in the solution in units of millimolar (mM) and m_{A1} and m_{A2} are constants. Thus, we see that the relaxation rates are linear with respect to the concentration of ions.^{5,14}

The mechanism for the relaxation is an interaction between the unpaired electrons of the paramagnetic ions and the protons of the water hydrogens.¹⁵ In the case of R_1 the interaction is primarily a classical dipole-dipole interaction. The R_2 interaction is, on the other hand, more complicated. It is hypothesized that protons momentarily "link" them-

selves with the paramagnetic ions. If the duration of this linking is much longer than the correlation time for molecular rotation, then scalar coupling may exist. Depending on the field strength and other factors, this coupling can provide an additional relaxation mechanism for R_2 .¹⁴ Therefore, R_2 can be appreciably different than R_1 and we cannot in general expect the constants m_{A1} and m_{A2} to be equal.

If a second different paramagnetic ion B is introduced, it is reasonable to expect the relaxation rates of the solution to be given by

$$R_1 = R_{w1} + m_{A1}k_A + m_{B1}k_B, \quad (2)$$

$$R_2 = R_{w2} + m_{A2}k_A + m_{B2}k_B.$$

The assumption here is that both ions are at low enough concentrations that they in essence act independently, that is, that there is no interaction between the paramagnetic ions. The constants R_{w1} and R_{w2} and the m 's should be the same as for single ion solutions and can be determined experimentally. In this case it should be possible to produce a solution of two paramagnetic ions that has both a given T_1 and T_2 . The necessary concentration of the two paramagnetic ions are found by solving Eq. (2) for the concentrations. Thus, we have

$$k_A = \frac{m_{B2}(R_1 - R_{w1}) - m_{B1}(R_2 - R_{w2})}{m_{B2}m_{A1} - m_{B1}m_{A2}}, \quad (3)$$

$$k_B = -\frac{m_{A2}(R_1 - R_{w1}) - m_{A1}(R_2 - R_{w2})}{m_{B2}m_{A1} - m_{B1}m_{A2}}.$$

Further, the requirement that the concentrations given in Eq. (3) be non-negative introduces the restriction that

$$\frac{m_{B2}}{m_{B1}} \geq \frac{R_2 - R_{w2}}{R_1 - R_{w1}} \geq \frac{m_{A2}}{m_{A1}}, \quad (4)$$

(or vice versa, depending on whether m_{B2}/m_{B1} is greater than m_{A2}/m_{A1} or not). Thus, we see that, if we wish to mix solutions with a wide range of relaxation rates, then it is desirable to find two paramagnetic ions whose ratios m_2/m_1 are much different in order to make this inequality as wide as possible.

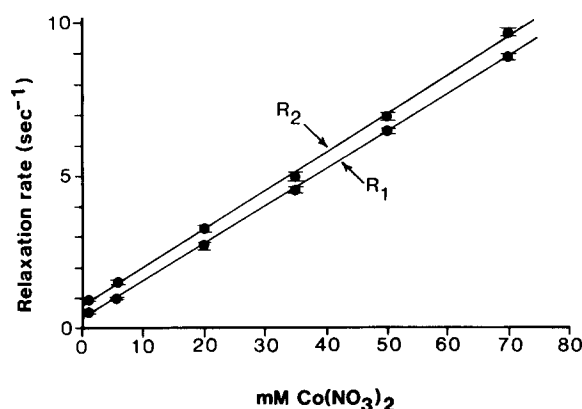


FIG. 1. Plot of measured relaxation rates vs concentration for solutions of $\text{Co}(\text{NO}_3)_2$ with the least-squares fit line.

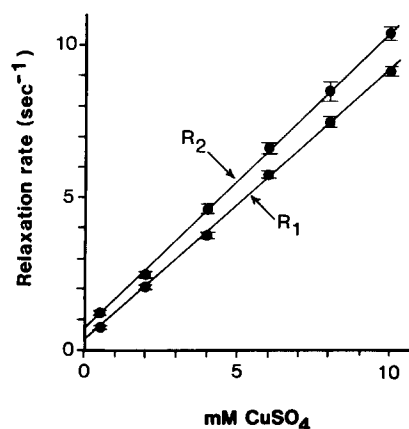


FIG. 3. Plot of measured relaxation rates vs concentration for solutions of CuSO_4 with the least-squares fit line.

III. EXPERIMENT

Ionic compounds of four paramagnetic metals were chosen for investigation: $\text{Co}(\text{NO}_3)_2$, NiCl_2 , CuSO_4 , and MnCl_2 . A compound of manganese, in particular, was chosen because theory indicates that Mn^{++} is probably unique among simple paramagnetic ions in that it relaxes R_1 differently than R_2 ,¹⁵ a point that will be treated in more detail later. Six solutions of various concentrations were made up for each salt. Concentrations were chosen to give R_1 and R_2 roughly in the range of 10^{-3} to 10^{-2} s^{-1} (that is, T_1 and T_2 from approximately 100 to 1000 ms). Each solution was made up independently by weighing out the proper amount of compound and dissolving it in multiply filtered water, rather than by serial dilution from a single stock solution.

The relaxation times of the solutions were determined using an IBM Minispec PC10 desk-top spectrometer (IBM Corporation, P.O. Box 3332, Danbury, CT 06810) operating at 10 MHz and 37 °C and the standard software available on the system. At least three measurements of each T_1 and five of each T_2 were made. Plots of average relaxation rates versus concentration are presented in Figs. 1–4. The error bars around the data points represent plus and minus one standard deviation. The data were least-squares fit to the linear Eq. (1), resulting in the lines shown in the figures. The

parameters of these fits (R_{w1} , R_{w2} and the m values) are given in Table I.

Various combination solutions were then prepared from the stock solutions above and water. The relaxation rates were measured as described above and checked for adherence to Eq. (2). The data from two sets of representative combinations are given here. The first, Fig. 5, is a plot of relaxation rates versus concentration of NiCl_2 in a 4 mM solution of CuSO_4 . Figure 6 is a similar plot for concentrations of $\text{Co}(\text{NO}_3)_2$ in a 5 mM solution of CuSO_4 . As before, the error bars represent plus and minus one standard deviation. The solid lines are plots of the predicted rates as given by Eq. (2). The values for the constants m used in this equation were taken from Table I. The values for R_{w1} and R_{w2} were taken as the average of the values from Table I for the two paramagnetic metals used. That is, the values for R_{w1} and R_{w2} were 0.272 and 0.732 for $\text{Ni} + \text{Cu}$ (Fig. 5) and 0.303 and 0.714 for $\text{Co} + \text{Cu}$ (Fig. 6), respectively. The discrepancy between the measured R_2 data and the theoretical line in Fig. 6 is important and will be discussed at a later point.

Finally, an attempt was made to prepare various solutions with given target relaxation rates. The combination of

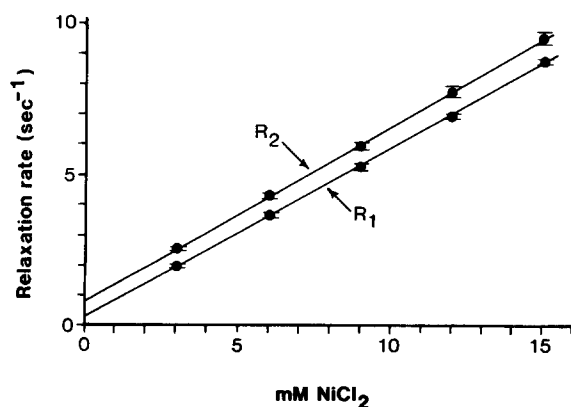


FIG. 2. Plot of measured relaxation rates vs concentration for solutions of NiCl_2 with the least-squares fit line.

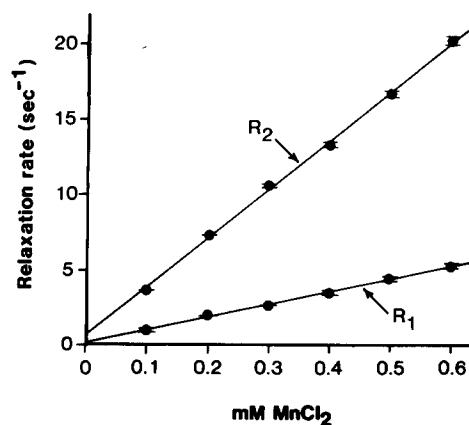


FIG. 4. Plot of measured relaxation rates vs concentration for solutions of MnCl_2 with the least-squares fit line.

TABLE I. Relaxation rates for water, line slopes (m), and slope ratios obtained from measured relaxation rate vs concentration data for four paramagnetic ion solutions.

Solution	R_{w1} s^{-1}	R_{w2} s^{-1}	m_{A1} s^{-1}/M	m_{A2} s^{-1}/M	m_{A1}/m_{A2}
$Co(NO_3)_2$	0.313	0.751	122.8	125.9	1.025
$NiCl_2$	0.250	0.787	565.6	583.1	1.031
$CuSO_4$	0.293	0.678	895.6	977.0	1.091
$MnCl_2$	0.205	0.621	8518	32 470	3.812

$MnCl_2$ and $NiCl_2$ was chosen for this test for the following reasons. First, this combination followed Eq. (2) well and showed no interaction at the concentrations used. Second, Ni and Mn have significantly different ratios of m_1/m_2 , namely, 1.031 and 3.812, respectively. The wider the difference is, the wider the boundaries established by inequality (4). For the Mn + Ni combination, inequality (4) is plotted in Fig. (7). Such a plot is a convenient visual aid in determining which values of R_1 and R_2 are accessible with a given combination of solutes.

Four sets of target R_1 's and R_2 's were arbitrarily selected within the range of values accessible using $MnCl_2$ and $NiCl_2$. These are indicated by the dots in Fig. (7). The target values are given in Table II. The required concentrations of $MnCl_2$ (k_{Mn}) and $NiCl_2$ (k_{Ni}) are also given in the table, as calculated using Eq. (3). For the calculation, m values were taken from Table I and the average R_{w1} and R_{w2} values for $MnCl_2$ and $NiCl_2$ (that is, 0.228 and 0.704, respectively) were used.

The four sets of solutions were prepared using dilutions of the stock solutions prepared when producing the calibration curves for each solute. In the preparation of such mixtures it is useful to note that, if one has a stock solution of concentration C , and one desires a final concentration of solute k , then the fraction of the final volume of the stock solution required is simply k/C . For example, to prepare the first solution in Table II from stock solutions of 0.6 mM $MnCl_2$ and 6 mM $NiCl_2$ requires that the final solution consist of 42.8% (0.257/0.6) of the $MnCl_2$ stock and 26.7% (1.6/6) of the

$NiCl_2$ stock by volume, the remaining 30.5% being additional water. The author has found that when mixing small amounts of solution (under half a liter) that it is preferable to prepare them from dilutions of large volume stock solutions, since the quantities of solute that would need to be weighed are small enough that weighing errors become significant.

The relaxation rates for these solutions were measured as described previously and the average value and percent deviation from intended value are given in Table II.

IV. RESULTS AND DISCUSSION

The relaxation rates of all four sets of solutions containing a single paramagnetic ion as a function of concentration (Figs. 1–4) followed the expected theoretical expressions, Eq. (1). That is, they all are well fit by a straight line. Note that the y intercept of such a fit should be the relaxation rate of the solvent alone. Since this was water in each case, we would expect this value, R_{w1} and R_{w2} , to be the same. However, the y intercept is an extrapolated value and rather sensitive to slight variations in the experimental data. Because of this, some investigators (for example, Brown and Johnson⁵) have obtained clearly nonphysical values, such as negative numbers, for the solvent relaxation rate. Still, the values obtained in this experiment for the four solutions are fairly consistent (Table I), the averages being $0.265 \pm 0.048 s^{-1}$

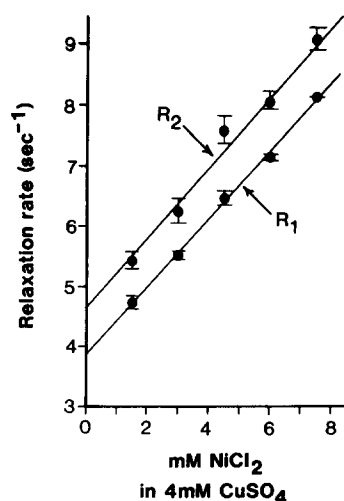


FIG. 5. Plot of measured relaxation rates vs concentration of $NiCl_2$ in a 4 mM solution of $CuSO_4$ with predicted lines from Eq. (2).

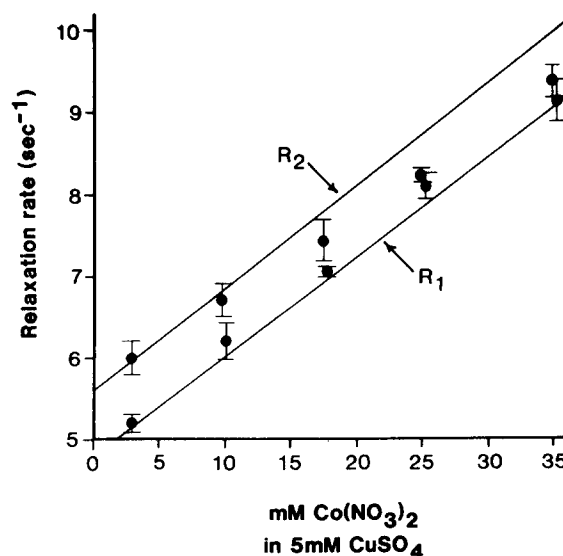


FIG. 6. Plot of measured relaxation rates vs concentration of $Co(NO_3)_2$ in a 5 mM solution of $CuSO_4$ with predicted lines from Eq. (2).

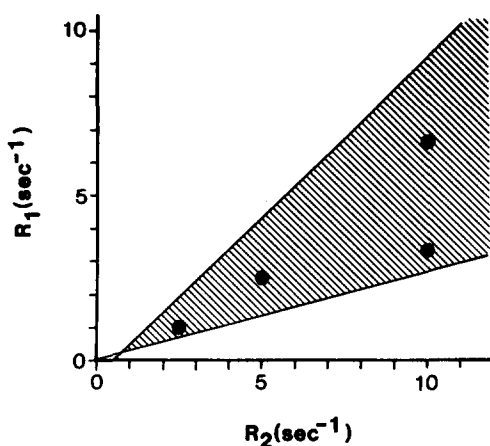


FIG. 7. Plot of inequality (4) for a solution of Mn^{++} and Ni^{++} with arbitrarily chosen target rates for four test solutions (dots).

and $0.709 \pm 0.074 \text{ s}^{-1}$, respectively (corresponding to a T_1 and T_2 for water of 3.77 s and 1.41 s, respectively).

The slope of the fit line, m_{A1} and m_{A2} in Table I, is a measure of the effectiveness of the ion as a relaxing agent; the larger the value, the more effective the ion is as a relaxing agent. Note the almost two orders of magnitude range in these values, extending from Co^{++} to Mn^{++} .

The values calculated for slopes of Cu^{++} and Ni^{++} are less than those obtained by Bucciolini, *et al.*² There are two factors that may account for these differences. First, their values were measured at a resonant frequency of 21.5 MHz compared to 10 MHz used in the present study. Second, the least-squares fit on their data were performed after subtracting an assumed value of $T_1 = T_2 = 3400 \text{ ms}$ ($R_1 = R_2 = 0.294 \text{ s}^{-1}$) for the relaxation of water, rather than obtaining the solution relaxation value from the fit. While the assumed R_1 value they chose for water is close to the average measured here (0.265 s^{-1}), the R_2 value is significantly different (0.709 s^{-1}).

As pointed out previously, the difference between R_1 and R_2 depends on the significance of the scalar interaction to the overall relaxation mechanism. The relaxation rates of most paramagnetic ions are dominated by dipole-dipole interactions and, therefore, have nearly the same R_1 and R_2 values.

TABLE II. Intended relaxations rates, required concentrations (k), measured rates and % error in rates for four sample solutions of MnCl_2 and NiCl_2 .

Solution	Target R_1 target R_2 (s^{-1})	k_{Mn} k_{Ni} (mM)	Measured R_1 measured R_2 (s^{-1})	R_1 % error R_2 % error
1	3.33	0.257	3.32	- 0.3
	10.00	1.600	10.09	+ 0.9
2	6.67	0.112	6.54	- 1.9
	10.00	9.69	9.95	- 0.5
3	2.50	0.083	2.55	+ 2.0
	5.00	2.77	5.31	+ 6.2
4	1.00	0.0425	1.04	+ 3.8
	2.50	0.722	2.61	+ 4.4

In the present experiment, such cases would be indicated by a ratio of slopes (m_{A1}/m_{A2}) of approximately unity. Co^{++} , Ni^{++} , and Cu^{++} (Table I) all lie in this category. Mn^{++} is somewhat unique in possessing a significant scalar interaction term as reflected in the table by a slope ratio different than one. A more detailed theoretical treatment of these interactions can be found in several sources. For example, the reader is referred to the recent paper by Koenig and Brown¹⁵ and references therein.

The value of this slope ratio has additional significance to this investigation. Our goal is to be able to mix solutions with given values of both R_1 and R_2 by combining pairs of paramagnetic ions. However, the range of possible relaxation rates we may achieve is constrained by inequality (4). To allow the widest range possible, the slope ratio of the two ions should be as different as possible, specifically, one should be unity and the other should be as large as possible. In the present case this implies that one of the ions should be Mn^{++} . Combining, for example, Ni^{++} and Cu^{++} would give an extremely restricted range of available relaxation rates.

Another important restriction on combining ions is that their behavior in solution can be modeled by Eq. (2). This implies that at concentrations of interest there be no significant interactions between the ions. A combination that exemplifies such an undesirable significant interaction is Co^{++} and Cu^{++} . The concentration of $\text{Co}(\text{NO}_3)_2$ was varied in a solution of 5 mM CuSO_4 . Relaxation rates were measured as described previously and plotted versus concentration in Fig. 6. The solid lines in the figure were calculated using Eq. (2). At low concentrations of Co^{++} the measured values agree well with the equations. At higher concentrations, the R_1 values still agree well but the R_2 values decrease in a systematic manner, approaching the R_1 value. The important point here is that the R_1 values agree well with Eq. (2) while the R_2 values diverge with increasing concentration. If there were some reaction between the two solutes that was reducing the concentrations of one or both of the ions, for example, a chemical reaction that reduced the solubility and precipitated a small amount of one of the ions then we would expect both R_1 and R_2 to be reduced. On the other hand, the approach of R_2 toward R_1 with increasing concentration suggests an interference with the scalar interaction between water and one or both of the ions, since this interaction is the major reason why R_1 does not exactly equal R_2 for simple solutions. In any case the deviation of the measured values from Eq. (2) makes this combination of ions unsuitable, since the equations used to calculate required concentrations of solute [Eq. (3)] are based on these equations.

By comparison, NiCl_2 and CuSO_4 are an example of a pair of noninteracting ions at the concentrations treated here. Figure 5 plots measurements of R_1 and R_2 for various concentrations of NiCl_2 in 4 mM CuSO_4 . The measured values agree well with the straight lines predicted by Eq. (2).

Finally, an attempt was made to mix solutions with arbitrary given values of R_1 and R_2 . MnCl_2 and NiCl_2 were chosen as solutes since this combination gives a wide range of possible relaxation rates as allowed by inequality (4) [Fig. (7)]. Four target R_1 and R_2 pairs were chosen over a wide

range [as indicated by the dots in Fig. (7) and listed in Table II]. The solutions were prepared and rates measured and compared to the intended target values. The resulting solutions all had rates within approximately 6% of the intended target rates (Table II). Two of the solutions were within 2% of the target values, perhaps because these involved relatively higher concentrations of solute and, therefore, the amount of solute was larger and easier to measure accurately.

Several considerations influence the choice of material used in an NMR phantom. Solutions of two paramagnetic ions are relatively easy to produce, especially when prepared from bulk stock solutions. While two paramagnetic ion solutions have only recently been produced in our laboratory, solutions of single paramagnetic ions used here show no systematic variation over the period of several years; it is reasonable to assume that the two paramagnetic solutions will exhibit similar long-term stability. In short two paramagnetic ion solutions should be suitable for use wherever single ion solutions are currently used.

One disadvantage of any solution as a phantom material is that it is difficult to form irregular objects or thin boundaries between areas of different properties. For these instances, solid phantoms produced from gels of agarose are being investigated.¹⁶⁻¹⁷ Such gels are reportedly able to reproduce a range of relaxation times near that of tissue. However, their calibration and preparation are more difficult than for simple solutions, and the problem of how to best seal the gel to inhibit evaporation and the determination of long-term stability are still under study.

Koenig and Brown¹⁵ state that the T_1/T_2 ratio for tissue in the imaging range of fields strengths is approximately 30. However, the recent extensive compilation of tissue parameters by Bottomley *et al.*¹⁸ indicates much smaller ratios, in the range of approximately 2 (for fat at low fields) to perhaps 12 (for muscle at high imaging fields), the ratio in general increasing with field strength. Clearly, some tissues, especially at higher field strengths, will be beyond the range of relaxation times that can be simultaneously reproduced using the simple solutions dealt with here. The next step is to see whether gels containing two paramagnetic ions might effectively mimic tissue.

V. CONCLUSIONS

Using two different paramagnetic ions in solution, it is possible to prepare samples that accurately match desired values of both R_1 and R_2 relaxation rates. This simplifies the production of phantoms used in testing and calibration by reducing the number of solutions that need be prepared to cover a given range of rates. Further, it is a useful step toward a solution of the much more complicated problem of preparing tissue-equivalent materials that must be simultaneously mimic a wide range of NMR parameters.

ACKNOWLEDGMENT

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