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# APPLICATIONS OF NUCLEAR MAGNETIC RESONANCE*

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The nuclear magnetic resonance effect was predicted during the 1930's, but it escaped experimental detection until 1946 when the technique for observation was worked out simultaneously by Block at Stanford and Purcell at Harvard. We shall follow the Purcell method here.

Suppose that we place a sample of material in a strong, homogeneous magnetic field which we shall denote by $H_z$. If the nuclei in the sample have magnetic moments and spin I, then they will have $2I + 1$ stable energy states, the lower energy states occurring when the nuclei are more nearly aligned with the field. The nuclei precess about the magnetic field at the Larmor frequency, given by $\omega = \gamma H_z$, where $\omega$ = the angular frequency of precession and $\gamma$ = the gyromagnetic ratio. At room temperature the interaction energy $\mu H$ (where $\mu$ = the magnetic moment of the nuclei) is much smaller than the thermal energy, kT. Thus, there will be only a small excess population in the lower energy states. Let us consider, as an example, protons which have ½ integer spins. In a field of 10,000 gauss, there will be about 1,000,040 protons in the lower energy state as compared to 1,000,000 in the higher energy state. It is this excess of 40 nuclei in the lower energy state which we can observe.

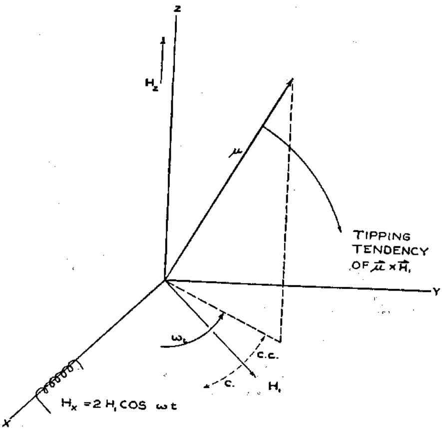

FIG. 1.

If the sample is placed inside a coil which is perpendicular to the applied magnetic field $H_z$, and a radio frequency voltage applied to the coil, there will be a small magnetic field of radio frequency, which we shall denote by $H_1$, inside the sample and perpendicular to the static field $H_z$. The r.f. field may be considered to consist of two circularly polarized components rotating in opposite directions about $H_z$ (fig. 1).

If the r.f. field is applied at the Larmor frequency, then one of the rotating components will produce a torque $\vec{\mu} \times \vec{H}_1$ on the precessing magnetic moments, tending to tip them over. The component of $H_1$ rotating in the same direction as $\mu$ produces a tipping torque; the component rotat-

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ing in the opposite direction cancels out since there will be a torque tending to flip spins up for as much time as there is a torque tending to tip them down.

During the time the spins are being flipped over, power is absorbed in the sample coil. Phenomenologically, this is equivalent to a change in the magnetic susceptibility of the sample. Thus, the effective inductance and resistance of the sample coil change during the flipping of the spins. The spins would all be flipped in a very short time if there were no coupling of the spins to the external environment, and thus, the signal would be very short. However, since there are thermal motions of nuclei in the sample (these will be the lattice vibrations in the case of a solid, and random molecular motions in the case of a liquid) the spin system can interact with these degrees of freedom, and lose its excess energy to it. The spin system, after having absorbed r.f. power, may be thought of as analagous to a piece of hot metal in contact with a thermal bath. The spin system, just as the piece of metal in the analogy, will cool down exponentially. The time required for all but 1/e of the equilibrium excess of spins to reach their lower energy state is denoted by $T_1$, and is referred to as the spin-lattice relaxation time. Obviously, $T_1$ depends upon the structure of the material.

In addition to the spin-lattice relaxation, each nuclear spin interacts with neighboring spins through their magnetic fields. Thus the magnetic field at the nucleus consists of the applied field $H_z$ and the local field caused by neighboring nuclei. The local field is different at different nuclei, owing to the different possible orientations of the neighbor spins. This effect thus leads to a broadening of the line. The magnitude of this local field is of the order of a gauss in solids. One can also assign a time perameter to this broadening effect, since $\omega' = \gamma \, \delta \, H$, where $\delta H$ is the local field variation over the nuclei and $\omega'$ is the corresponding frequency spread. Then we define $T_2 = \frac{2}{\gamma \, \delta \, H}$. This type of interaction is called the "spin-spin" relaxation time.

There are, of course, other sources of line broadening. For example, $T_1$ itself contributes to the line width, as do any inhomogeneities in the applied field $H_z$. Still other sources of broadening are due to the uncertainty principle, saturation broadening and quadrupole broadening, if any nuclei are present which possess an electric quadrupole moment. Thus the line width and shape depend upon the structure of the sample. $T_2$ varies from $10^{-5}$ sec to about 2 sec.

The apparatus used for the detection of the resonance signal is shown in figure 2. (All apparatuses used were based on the same principles but varied somewhat in their details.) The magnetic field $H_z$ is swept back and forth approximately 1 gauss about its normal value. The r.f. signal generator is set on a frequency such that the resonance occurs when $H_z$ is at about the middle of its sweep. A bridge is used simply to prevent saturation of the receiver by the oscillator. The bridge is then balanced, and since the cathode-ray tube sweep may be thought of as

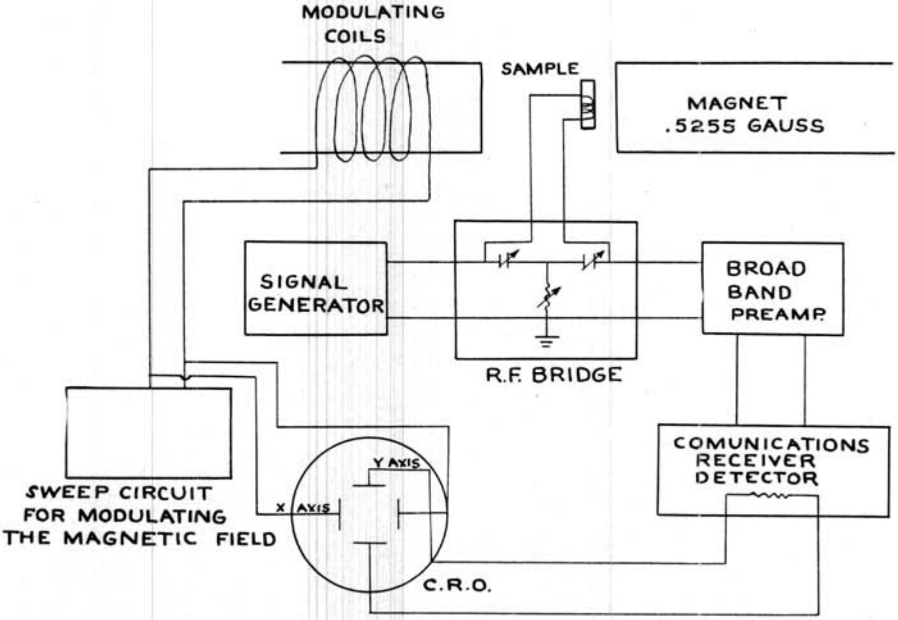

FIG. 2.

plotting gauss on the x axis, a signal appears on the screen as a plot of signal vs magnetic field.

Figure 3 (left) shows such a plot for glycerine. The sweep length is about .4 gauss, and the sweep time about 3 seconds. The line width of about 30 milligauss is here due to the inhomogeneity in $H_z$. Figure 3 (right) shows the dispersion curve, which is obtained by a somewhat different type of bridge unbalance.

There are many applications of the method, such as the study of chemical structure, structure in solids, measurement of diffusion constants, etc.

It was discovered quite early that when paramagnetic ions are added to water, the proton spin-lattice relaxation time decreases from about 2.3 sec to $10^{-3}$ sec, the relaxation time being proportional to the concentration of paramagnetic ions. Selwood and his group utilized this effect to study the rate constant of the reaction $Eu^{++} \rightarrow Eu^{+++} + e^-$ catalyzed by zinc. By simply measuring $T_1$ as a function of time after introducing zinc into the $H_2O + Eu^{++}$, the reaction rate could be determined.

Pake and Gutowski found the line shape for compounds in solid form containing groups with two protons to be similar to that shown in figure 4. (In this case the phase-unbalance,

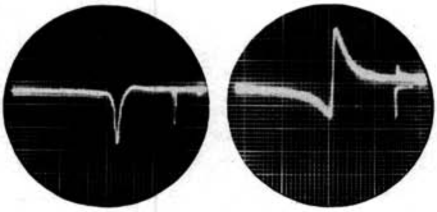

FIG. 3.

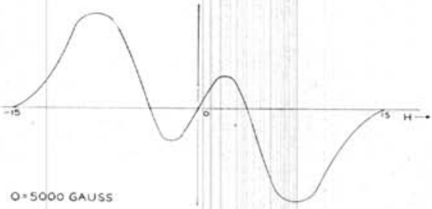

FIG. 4.

or inductive change in the sample, is shown.) An analysis of this system by Van Vleck led to values of the proton-proton bonds distances in 1, 2 dichloroethane. Similar investigations have been carried out with other compounds.

The line shape for a 3-proton system is shown in figure 5. A group at the University of Tokyo utilized this difference in line shape between the two kinds of groups to prove that in hydrogen perchlorate monohydrate (H Cl O4 $\cdot$ $H_2O$), the water of crystallization is bound as the oxonium ion ($OH_3^+$).

In 1949, Knight found that the position of the resonance depends to some extent on the chemical bonding of the nucleus. This effect is due to the small local field produced at the nucleus by the orbital electrons. This "chemical shift" has been studied extensively by Arnold and Packard at Stanford and Gutowski at the University of Illinois. They have utilized this small shift, which ranges from a few milligauss up to a half gauss, to study the electron distributions in a number of organic and inorganic phosphorous and flourine compounds. More recently, it has been found that a number of these compounds do not have single lines, but have a number of lines. From this Gutowski and Slichter have shown the existence of a coupling between nuclei in a molecule through the orbital electrons. Experiments of this type require an extremely homogeneous magnetic field.

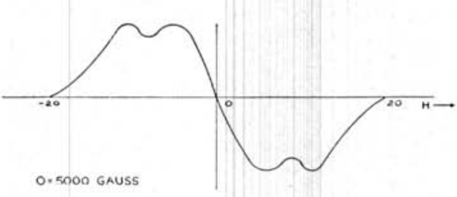

FIG. 5.

Our research program consists of applying these effects to suitable problems in biochemistry and pharmacology. The problem to which we are devoting most of our efforts involves the inactivation of the enzyme cholinesterase by diisopropyl fluorophosphate (DFP). The question is, Is the fluorine transferred to the cholinestarase molecule? Also, we are attempting to measure the rate constant of the reaction. The fluorine resonance in DFP consists of two lines. If the fluorine is transferred to the cholinesterase molecule so that it is bound to a different atom phosphorous, the splitting should disappear, and the resonance position shift

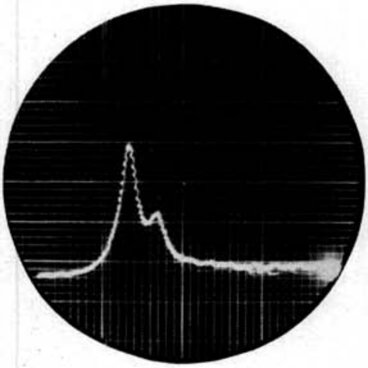

FIG. 6.—Protons in acetic acid showing —COOH peak separated from —$CH_3$ peak.

slightly. The rate of disappearance should be proportional to the rate of change of the relative amplitudes of the signals from the unreacted DFP and the reacted DFP. If the fluorine is merely transferred to the solution as free $F^-$, the shift will be different than if it is transferred to the cholinesterase.

There are a large number of such problems in biology which should lend themselves to solution by this technique.