[CONTRIBUTION FROM THE PHYSICAL RESEARCH DIVISION, CHEMICAL WARFARE LABORATORIES]

Rapid Analysis of Reaction Mixtures by Nuclear Magnetic Resonance Spectroscopy[1]

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Nuclear magnetic resonance spectroscopy is found to be a highly effective tool for the analysis of certain reaction mixtures involving phosphorus compounds. This is shown by the application of this technique to the isomerization of the insecticide β-ethylmercaptoethyl diethyl thionophosphate (Systox). Results indicate that the rate law for the isomerization is intermediate between zero and first order, probably indicating a catalytic effect.

Introduction

The field of high-resolution nuclear magnetic resonance (NMR) spectroscopy has grown rapidly since 1949, when Knight[2] published his discovery of "chemical shifts" of the resonance of P^{31} nuclei. He found that at a fixed radio frequency the precise value of the magnetic field at which resonance occurs depends not only on the nature of the nuclei involved, but also on their chemical environments.

In several more recent papers[3-5] the results of chemical shift measurements of over two hundred phosphorus compounds are presented. These observations show that NMR spectroscopy is potentially a very valuable method of quantitative analysis of mixtures of phosphorus compounds.

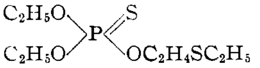
A mixture which is to be analyzed by high-resolution NMR must be a liquid, and the components must have chemical shifts differing by several chemical shift units. The unit usually employed is

$$\delta = \left(\frac{H_c - H_r}{H_r}\right) \times 10^6$$

where H_c and H_r are the resonance field values of the sample studied, and of a reference compound (usually H_3PO_4), respectively.

The strength of each P^{31} resonance should be proportional to the number of nuclei contributing to it. Thus relative concentrations may be deduced from relative signal strengths, without a need for absolute intensity measurements.

Since the sample is not destroyed during the analysis, the NMR method is particularly useful in following the changes of concentrations in reacting mixtures without disturbing the course of the reaction. This paper reports such an application to the study of the kinetics of the isomerization of the insecticide β-ethylmercaptoethyl diethyl thionophosphate ("Systox," I) to the thiol isomer ("Isosystox," II).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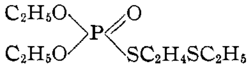
II

Each of these molecules exhibits a single P^{31} resonance, somewhat broadened by indirect spin-spin coupling between the phosphorus nucleus and nearby protons. Analysis is readily possible, since the two signals are obtained at values of the magnetic field differing by about forty parts per million, which is well above the resolving power of the instrument.

Experimental

Measurements were made with a commercial high-resolution NMR spectrometer obtained from Varian Associates, Palo Alto, California. The fixed radio frequency used was 17 mc./sec., with magnetic fields near 9850 gauss in the twelve-inch electromagnet. The amplified magnetic resonance signal was displayed as needed either on an oscilloscope or on a Sanborn industrial recorder.

Differences in the extent of indirect spin–spin interactions, and in relaxation times, make it unlikely in general that different P^{31} resonance signals will have the same width. Therefore, the areas rather than the heights of resonance peaks should be used as a measure of signal strength. We found that this could most conveniently be done by recording the spectrum and cutting out the individual peaks, and then weighing them on an analytical balance. Since both materials have the same molecular formula, the mole or weight fraction of isomer I in the mixture should be given simply by the ratio of the weight of its own peak to the total weight of the peaks.

To minimize random errors caused by transient electrical effects and human fallibility in locating the base line, six or more recordings were always taken and the peaks corresponding to each component weighed together. Values of the mole fraction of isomer I were reproducible to within one or two hundredths.

Systematic errors might arise either from non-linearity in the response of the amplifier and recorder, or from a possible variation of the relative relaxation time (T_1) for the two isomers. To show that such errors were unimportant, measurements were made on samples prepared from known weights of the purest available Systox and Isosystox. The mole fractions found agreed within two or three hundredths with the calculated values.

The Systox used in these studies was prepared in the organic branch of these laboratories, and distilled through a falling-film molecular still at 58° and 10^{-4} mm. Its refractive index was 1.4865. The P^{31} NMR spectrum showed initially a small amount, perhaps 3% of Isosystox, and no detectable trace of other impurities. Contaminants not containing phosphorus would not be expected to affect the P^{31} NMR spectrum, though they might influence the course of the isomerization reaction.

Each sample consisted of about 1.5 ml. of the material sealed under vacuum in a Pyrex tube of 8 mm. outside diameter. The isomerization was followed at 100° and at 115° by immersing the samples in constant temperature baths for appropriate time intervals. After each heating period the samples were cooled to quench the reaction, and the concentrations determined by NMR analysis.

Results and Discussion

The chemical shifts of Systox and Isosystox, measured by a method based on that of Arnold and Packard,[6] were $\delta = -67.7$ and -25.9, respectively. The data were typical of those obtained in Table I.

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(1) (a) This article was presented as a paper at the Pittsburgh Conference on Analytical Chemistry and Applied Spectroscopy, February 27, 1956. (b) Department of Chemistry, Purdue University, Lafayette, Indiana.

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TABLE I

ISOMERIZATION OF SYSTOX AT 115°

Heating time, hr.	% Systox remaining Sample 1	Sample 2
0.5	87%	87%
1.1	77	77
2.0	61	63
3.0	47	50
4.0	35	36
5.0	24	26
6.0	18	20

Analysis of the data shows that the rate law for the reaction is intermediate between zero and first order, rather than simply first order, as had been reported by Fukuto and Metcalf.[7] Their method involved the use of Systox labeled with radiophosphorus; samples withdrawn from the reaction mixture were analyzed by separating the isomers chromatographically and measuring the radioactivity of each fraction.

Our own data may be represented by a rate law of the form

$$-\frac{dc}{dt} = \frac{k_1 c}{k_2 + c}$$

The best values for the k's were found by the method of least squares, using two runs at each of the two temperatures. The unit of time used was hours and the concentration, c, was expressed as mole per cent. The numerical values of the k's are shown in Table II

The equation is of a form discussed by Laidler,[8] which corresponds to a reaction scheme in which a rapid equilibrium is first set up between the reagent and a small amount of catalyst, reacting to form an intermediate, the decomposition of which is relatively slow. In this scheme, k_2 is the reciprocal of the equilibrium constant for the first reaction, while k_1 is the product of the rate constant for the decomposition of the intermediate and the catalyst concentration. Although this equation may also be derived on other assumptions, it seems likely that a catalytic effect is involved. This idea receives further support from the fact that our measured half-life of about 11 hours at 100° is *longer* than the 8.8 hours calculated from Fukuto and Metcalf's data at 95°. Their material was prepared by a method which would not be expected to yield very pure products.

TABLE II

	k_1	k_2
Run 1, 100°	0.071	0.49
Run 2, 100°	.078	.59
Run 1, 115°	.25	.42
Run 2, 115°	.26	.49

NMR spectrometry is found to be a very convenient tool for analytical problems of the type encountered here. The fact that all samples are sealed in glass throughout the study reduces the danger of working with these toxic materials, and the chances of having the samples contaminated. Other advantages are the small amounts of material required, and the convenience with which data may be obtained. The accuracy of NMR analytical methods will undoubtedly be improved as the instruments are further developed, but it is already as good as or better than that of most rapid methods used in kinetic studies.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF ILLINOIS INSTITUTE OF TECHNOLOGY]

The Purification and Specific Conductivity of Anhydrous Hydrofluoric Acid

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Improvements in the methods for the purification of anhydrous hydrofluoric acid have yielded acid of much lower specific conductivity than reported previously.

The ion product for hydrofluoric acid was estimated by Kilpatrick and Luborsky[1] to be 2×10^{-10} at 20°. On the basis of this value a specific conductance for pure anhydrous hydrofluoric acid of 7×10^{-6} ohm^{-1} cm.$^{-1}$ at 20° was calculated.[1] This conductance was considerably lower than the value 1.4×10^{-5} ohm^{-1} cm.$^{-1}$ at $-15°$ previously reported by Fredenhagen and Cadenbach.[2] However, in practice, it has not been experimentally feasible to obtain and handle hydrofluoric acid of purity even similar to that of Fredenhagen and Cadenbach.[2] Kilpatrick and Luborsky[3] used hydrofluoric acid that had a specific conductivity of 1×10^{-4} ohm^{-1} cm.$^{-1}$ at 20° and more recently the conductivity measurements of Rogers, *et al.*,[4] were carried out in hydrofluoric acid of similar purity. Since techniques for fabricating equipment of Fluorothene or Kel-F plastic (trifluorochloroethylene polymer) had been developed at this Laboratory,[5] the construction of hydrofluoric acid purification equipment of plastic was undertaken. We have found that with this equipment, relatively large volumes of hydrofluoric acid of specific conductivity lower than the above value calculated by Kilpatrick and Luborsky[1] are obtainable by fractional distillation.

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