

Intermolecular Exchange of the Enolic Proton in 1-Formyl-1-Phenylacetone

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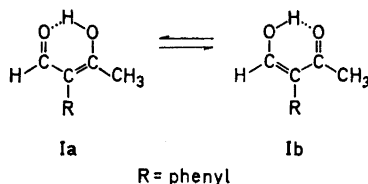
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The rate of the intermolecular exchange of the enolic proton in 1-formyl-1-phenylacetone has been studied with proton magnetic resonance in the temperature region -20°C to $+100^{\circ}\text{C}$. The exchange rates have been obtained from the shapes of the proton magnetic resonance signals by the use of an iterative curve fitting technique employing an electronic computer. The activation energies for the exchange process are given for eight concentrations.

The rate of exchange of protons bonded to oxygen is in many compounds very fast and it is generally not possible to study the exchange with deuterium labelling techniques. Much of the presently available information on proton exchange in such systems has been obtained from proton magnetic resonance (PMR) studies. The PMR procedure almost exclusively used has been to deduce the exchange rates from the changes in the signal shapes in the spectra.^{1,2} This technique is applicable to reactions with half lives in the approximate range 0.001 to 1 sec.

The method has one particularly attractive feature in that proton exchange between identical molecules may also be studied provided that the resonance signal from the proton undergoing exchange in the limit of very slow exchange appears as a multiplet due to spin-spin interaction with one or several nuclei in the molecule. This criterion, however, also limits the number of compounds $\text{R}-\text{O}-\text{H}$ where such "self-exchange" of the OH proton can be studied. As yet only a limited number of primary and secondary alcohols has been investigated.³⁻⁸ In alcohols it appears likely that the proton exchange is facilitated by the presence of intermolecular hydrogen bonds. To illuminate the role of hydrogen bonds in intermolecular transfer reactions it has been considered of interest to investigate the rate of proton exchange between OH protons in compounds where the OH group is involved in a relatively strong *intramolecular* hydrogen bond.

A possibility to perform such an investigation is offered by 1-formyl-1-phenylacetone, which in inert solvents largely exists in the enolic form (I).



The PMR signal of the enolic proton H_B is at room temperature split into a doublet due to spin-spin coupling with the "formyl" proton H_A . At elevated temperatures the H_A and H_B doublets collapse into singlets due to accelerated intermolecular exchange of the enolic protons. The rate of exchange is thus in the range where the PMR technique may be applied.

The hydroxymethylene keto-aldo enol equilibrium and proton exchange in enols of α -formyl ketones has been frequently discussed in recent years.⁹⁻¹⁶ The observed value of the chemical shift of the H_A proton in I is intermediate between that of an aldehyde proton and that of a proton in the fragment

$H-C=O$.⁹ The spin coupling constant J_{AB} between the enolic proton and the "aldehydic" proton in I is also about half of the value observed in enols of formylketones where the hydroxymethylene ketone forms may be assumed to predominate.⁹ An interpretation of these NMR data is that a very rapid interconversion between forms Ia and Ib takes place, the equilibrium at room temperatures being slightly in favor of the form Ia. An alternative interpretation is, however, that the potential energy profile associated with the atomic displacements between the extreme positions in Ia and Ib is of a slightly asymmetric single minimum type, and that the enol thus may be considered to have one structure, presumably with somewhat unorthodox equilibrium bond distances.

The interpretation of the *intermolecular* proton exchange in I will not be affected by a very rapid intramolecular proton exchange. The effective value of J_{AB} may, however, vary with temperature as the equilibrium proportions of Ia and Ib change. Within the accuracy of our measurements no such variations were observed in the temperature range -40°C to $+10^\circ\text{C}$.

In order to obtain information on the activation energy for the overall exchange reaction in I the rates have been studied at a number of temperatures in the interval -20°C to $+100^\circ\text{C}$. The evaluation of the rate data from the signal line shapes is based upon an iterative least-squares fit computer program.

CALCULATION OF EXCHANGE RATES FROM PMR SPECTRA

The first quantitative description of how chemical exchange of resonating nuclei affects the shape of nuclear magnetic resonance signals was presented by Gutowsky, McCall and Slichter.¹ The theory, which is based upon modifications of the Bloch phenomenological equations¹⁷ has later been presented in a simplified form by McConnell.¹⁸ The theory is valid not only for exchange of nuclei between chemically different molecular environments but also for exchange of nuclei between molecules in different nuclear spin states.

The lineshape function v for exchanging protons situated in two magnetically different environments or in two different nuclear spin states is given by eqn. 1, which is derived according to McConnell.¹⁸

$$v = \frac{-\gamma H_1 M_0 \left[\frac{1}{T_2^2} + \frac{2\tau'}{T_2^2} + \frac{\tau' J_{AB}^2}{2} + \frac{(\tau')^2}{T_2^3} + \frac{(\tau')^2 J_{AB}^2}{4T_2} + \frac{(\tau')^2 \omega^2}{T_2} \right]}{\left[\frac{1}{T_2} + \frac{2\tau'}{T_2^2} + \frac{\tau' J_{AB}^2}{4} - \tau' \cdot \omega^2 \right]^2 + \left[\omega + \frac{2\tau' \omega}{T_2} \right]^2} \quad (1)$$

where T_2 = spin-spin relaxation time
 J_{AB} = the spin coupling constant of the exchanging nuclei (H_B to proton H_A)
 ω = the sweep frequency
 τ' = the mean lifetime for the protons in each site
 γ = magnetogyric ratio
 H_1 = the strength of the r.f. field
 M_0 = the equilibrium value of the macroscopic magnetic moment

Eqn. (1) for the collapse of spin doublets is strictly valid only when the chemical shift δ_{AB} between the two kinds of spin-spin coupled protons A and B is large compared to the spin coupling constant J_{AB} . For the AB case, equations relating the shapes of spin multiplets to rate constants, valid for arbitrary values of δ/J , have been derived by Alexander^{19,20} using a density matrix description of the system of exchanging nuclear spins. In the present case, however, δ_{AB} is about 435 c/s at 60 Mc/s. J_{AB} is 6.2 c/s and the ratio δ_{AB}/J_{AB} is then about 70. Therefore eqn. (1) should be valid to a high degree of accuracy. Eqn. (1) gives the lineshape for both the H_A signal and the H_B signal. The exchange rate of the OH proton may thus be evaluated from either signal. In the present case the formyl signal H_A was chosen, as this was found to be slightly sharper than the OH signal (H_B) at slow and fast exchange limits. This difference in line width is probably due to an unresolved spin coupling between the CH_3 group and the OH group in (I).

Eqn. (1) will in the present work be applied only in the range where $\tau \cdot \delta \gg 1$. In the limit of very fast exchange ($\tau \cdot \delta \leq 1$) the equation is no longer strictly valid and a quantum correction must be applied to the above "classical" expression.⁶

Since the probability that an exchange event will lead to spin inversion is 0.5 the exchange probabilities $1/\tau'$ obtained from eqn. (1) will only correspond to half the total exchange probability ($1/\tau$). We thus have

$$1/\tau = 2/\tau'$$

and when the rate of spontaneous spin inversion (characterized by the longitudinal relaxation time T_1) can be neglected the rate of proton exchange $d|\text{ROH}|/dt$ in the enol ROH follows from the relation:

$$\frac{1}{\tau} = K = \frac{d|\text{ROH}|/dt}{|\text{ROH}|}$$

A common way of evaluating exchange rates from experimental PMR-curves has been to use an approximate equation, relating the exchange rate to some shape parameter of the curve. The application of these equations may, however, lead to serious systematical errors in the rate parameters.^{21,22} In the present paper we have evaluated the exchange rate by fitting the theoretical line shape given by eqn. (1) to the experimental PMR signals by means of an iterative computer program [LETAGROP VRID].²³ The amplitudes of the experimental curves were measured at 15 to 30 points. In the iterative curve-fitting programme the lifetimes τ and an amplitude factor (the latter allowing for differences in amplification, amplitudes of the H_1 -field *etc.* among different recorded spectra) are independently varied so as to minimize the least-squares sum. After 4 to 10 iterations the final τ -values were generally reached; the necessary number of iterations depends on how good the initial rough guess of τ actually was. The lifetimes τ obtained from different PMR spectra recorded at the same temperature seldom differed by more than 15 %.

EXPERIMENTAL

The proton magnetic resonance spectra were recorded on a Varian A-60 spectrometer operating at 60 Hz and provided with a variable temperature probe and V-6040 temperature controller. The temperature scale of this controller was calibrated against a copper-constantan thermocouple placed inside a spinning sample tube containing about 1 ml of *m*-xylene. In all complete experimental runs except two (in the following numbered 3 and 7) the temperatures were obtained from this calibrated scale. Temperatures are estimated to be accurate to $\pm 1.5^\circ\text{C}$.

In runs 3 and 7 the temperatures were obtained from the temperature-dependent shift between the CH_3 and the OH signal in a mixture of methanol, hydrochloric acid, and water (1:0.1:1). The mixture was filled in a capillary which in turn was centered in the middle of the sample tube by means of two teflon plugs. The temperature-dependent shift between the CH_3 and the OH signals was calibrated against a copper-constantan thermocouple according to a procedure which has been described in detail elsewhere.²³ The accuracy of the temperature measurements with this method is estimated to be $\pm 0.5^\circ\text{C}$. The calibration of the instrument was frequently checked with the usual sideband technique using a Hewlett-Packard model 200 CD audio oscillator the frequency of which was measured with a Hewlett-Packard model 5512 A electronic counter.

The rate constant obtained at each temperature is the average of at least five determinations. Transverse relaxation times (T_2) were considered to be chiefly due to magnetic field inhomogeneities and were estimated from the line widths of the signal under study in the limit of very slow exchange (at -30°C to -40°C), using the relation $T_2 = 1/\pi\Delta\nu_{1/2}$ where $\Delta\nu_{1/2}$ is the signal line width in Hz at half maximum amplitude.

The T_2 value for the formyl proton signals obtained in this way agreed within experimental error with that obtained from the line width of a signal of tetramethylsilane (TMS) used as an internal reference (1 % by weight) in all samples. In order to keep the value of T_2 as constant as possible at all temperatures at which the rate was studied, the homogeneity of the magnetic field was adjusted so as to keep the line width of the TMS signal constant.

The rate of exchange between hydroxylic protons is extremely sensitive toward acidic and basic catalysts. It has been shown that the exchange between the hydroxylic protons in acetophenone and salicylaldehyde is *ca.* 10 times faster in a 10^{-5} M solution of triethylamine than in an uncatalysed solution.²⁴ Filtering the sample solutions through a cotton or a glass wool plug was found to increase the exchange rate by a factor of two or three. Care was therefore taken to purify the chemicals used and to clean the sample tubes.

The standard Varian pyrex sample tubes were carefully rinsed with acid and distilled water before use. 1-Formyl-1-phenylacetone (I) was prepared according to the method

given in Ref. 25, where the PMR spectrum of this compound is also discussed. The sample used in the kinetic experiments was finally purified by fractional distillation through a 20 cm Vigreux column in a nitrogen atmosphere under reduced pressure (b.p. 100–101°C at 9 mm Hg). The *meta*-xylene used as a solvent in the present investigation was subjected to fractional distillation in a Vigreux column immediately before use. The concentration of the solutions used in the experiments was determined by weighing and the preparation of the solutions took place immediately before the PMR experiments were initiated.

Eight concentrations from *ca.* 8 % to *ca.* 45 % by weight were investigated (Table 1).

Table 1. Summary of activation parameters for the intermolecular proton exchange in 1-formyl-1-phenylacetone at different concentrations.

Expt. No.	Conc. % by weight	E_a^a kcal/mole	ΔH^\ddagger^b kcal/mole	$\Delta F^\ddagger(298^\circ\text{K})^b$ kcal/mole	ΔS^\ddagger^c e.u.
1	8.74	6.1 ± 0.2	5.5	16.0	-35 ± 2
2	45.51	7.9 ± 0.3	7.3	16.5	-31 ± 2
3	19.13	8.5 ± 0.3	8.0	16.4	-28 ± 2
4	24.03	7.9 ± 0.4	7.3	16.1	-30 ± 2
5	9.65	6.0 ± 0.3	5.4	16.5	-37 ± 2
6	18.20	6.8 ± 0.4	6.2	15.8	-32 ± 3
7	17.33	8.0 ± 0.1	7.4	16.7	-31 ± 1
8	33.96	8.0 ± 0.1	7.4	16.5	-31 ± 1

^a The errors are calculated assuming only random errors.

^b The random errors in this parameter can be assumed to be of the same order as in E_a .

^c The errors in this parameter are calculated assuming equal random errors in ΔH^\ddagger and ΔF^\ddagger . More realistic errors in ΔS^\ddagger are about ± 7 e.u.

Each complete run was performed within 24 h in order to minimize the formation of degradation products which might catalyse the proton exchange. The reversibility of the exchange rate and the formation of degradation products formed during the experiment was checked by measuring the coalescence temperature before and after each complete run. In no case did the coalescence temperature change more than 0.3 to 0.5°C.

RESULTS AND DISCUSSION

Graphs of the logarithms of the inverse exchange rate of the OH proton *versus* $1/T$ for all concentrations give reasonably linear plots. Arrhenius activation energies have been calculated for the different concentrations from the slopes of straight lines fitted to the experimental points by the method of least squares, assuming only random errors.

In Table 1 the results of the PMR measurements of the thermodynamic functions for the intermolecular exchange of the enolic proton in 1-formyl-1-phenylacetone are summarized.

In Fig. 1 a plot of E_a *versus* concentration is shown. The scatter in the E_a values makes it difficult to decide whether E_a is concentration dependent or not. If the catalytic effect of impurities is regarded as the largest systematic error, the highest observed value for the energy of activation should presum-

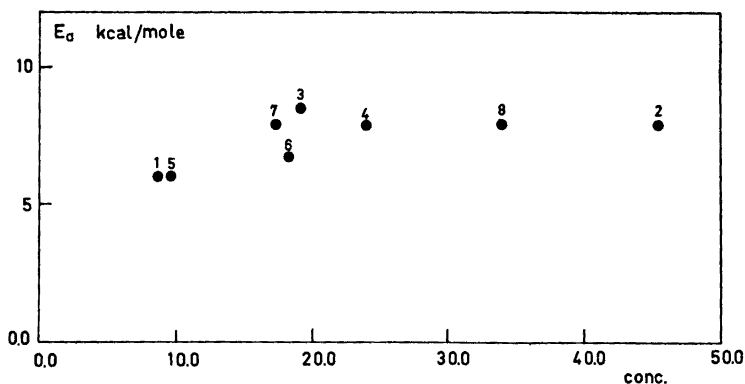


Fig. 1. A plot of E_a versus concentration (in percent by weight) for proton exchange in 1-formyl-1-phenylacetone.

able be the most reliable. In the case of 1-formyl-1-phenylacetone the "best" value for the energy of activation for the overall exchange process should thus be around 8 kcal/mole.

Only a few values of activation energies for proton exchange reactions are at present available for comparison with the above value. For the proton transfer between ethanol and water, activation energies of 10 kcal/mole⁷ and 7.6 kcal/mole²⁶ have been estimated. The values of the activation energy obtained in the present work are thus of the same order as activation energies obtained in systems where no intramolecular hydrogen bonding of the exchangeable protons is present. The strength of the intramolecular hydrogen bond in enolised β -diketones is considerable and from thermochemical data the energies of the intramolecular hydrogen bonds in the enolic forms of acetoacetic ester and analogous compounds have been estimated to be 10 kcal/mole.²⁷

Thus it seems likely that the intermolecular proton exchange in 1-formyl-1-phenylacetone takes place *via* a mechanism whereby the hydrogen bond energy is largely retained. Furthermore the large negative entropies of activation, in spite of the fairly large experimental errors, support the suggestion that the transition state may consist of a bimolecular complex.

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