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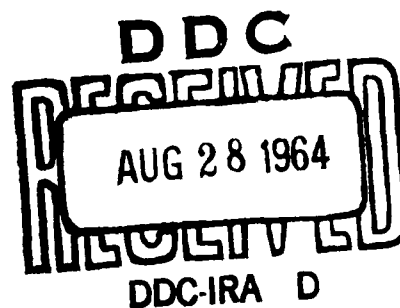
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COMPENSATION EFFECT

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# EFFECT OF PRESSURE ON THE ACID-CATALYZED ENOLIZATION OF ACETONE AND ACETOPHENONE IN VARIOUS ETHANOL-WATER SOLVENTS. ORIGIN OF THE ENTHALPY-ENTROPY COMPENSATION EFFECT<sup>1</sup>

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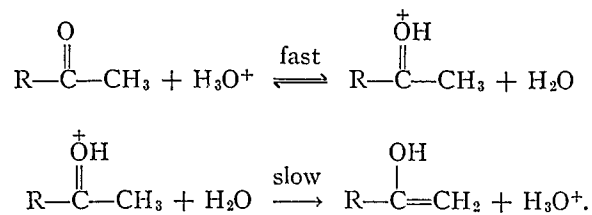
## ABSTRACT

The effect of pressure, temperature, and solvent composition on the rate of the acid-catalyzed enolization of acetone and acetophenone, and the solvent deuterium isotope effect for the enolization of acetophenone, have been measured by following the iodination. The solvent deuterium isotope effect ( $k^{D_2O}/k^{H_2O}$ ) for the enolization of acetophenone in 16.2% w/w ethanol-water is  $2.50 \pm \sim 0.05$ , which undoubtedly proves that there is a pre-equilibrium proton transfer. The effect of solvent in the range water to 33.4% w/w ethanol in water on the rate of enolization of both acetone and acetophenone is small at atmospheric pressure, but is about four times larger at 3 kbar. This cannot be explained on simple electrostatic grounds, and indicates that any simple electrostatic explanation of the solvent effect at atmospheric pressure is invalid. The volumes of activation for the enolizations are strongly dependent on the solvent, that for acetone varying from  $-2.1 \pm \sim 0.5$  to  $-6.9 \pm \sim 0.7$  cm<sup>3</sup> mole<sup>-1</sup> between solvents water and 33.4% w/w ethanol in water.

An examination has been made of the enthalpy-entropy compensation effect. It is shown that in general if the rate or equilibrium constant of a reaction does not change with changing conditions (such as solvent, substituents, etc.) then either the quantities of activation at constant pressure,  $\Delta H_p^\ddagger$  and  $\Delta S_p^\ddagger$ , or the corresponding quantities at constant volume,  $\Delta U_v^\ddagger$  and  $\Delta S_v^\ddagger$ , must vary in a compensating manner, and the existence of an energy-entropy compensation effect is inevitable. For the enolization of acetone and acetophenone in ethanol-water mixtures,  $\Delta U_v^\ddagger$  and  $\Delta S_v^\ddagger$  vary only slightly with solvent, whereas  $\Delta H_p^\ddagger$  and  $\Delta S_p^\ddagger$  vary in a compensating manner. The main causes of the compensation effect in the constant-pressure parameters are, in a sense, the change with changing solvent of the thermal expansion of the solvent and of the volume of activation of the reaction. On the other hand, both the constant-pressure and the constant-volume parameters vary with substituent from acetone to acetophenone, and the constant-volume parameters vary the more.

## 1. INTRODUCTION

The acid-catalyzed enolization of ketones is a well-studied reaction (1). It can be conveniently followed by the halogenation (2-5) and the deuterium exchange (6) of the ketones, and by their racemization (7) if they have an asymmetric  $\alpha$ -carbon atom. The rates of all these processes are usually identical, and when followed by halogenation they are of zero order in halogen, the zero-order rate constant being itself of first order in both ketone and catalyst. The mechanism of enolization when catalyzed by strong acids is accepted on good grounds to be (see ref. 1 for discussions)



Halogenation then occurs by rapid addition to the enol. The incorporation of a molecule of water in the transition state is not kinetically proved. There is, however, little doubt

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that it occurs, on the grounds that analogy with the observed base catalysis (1) suggests that water is itself acting as a base. In addition, the entropy of activation, which is usually about  $-15 \text{ cal deg}^{-1} \text{ mole}^{-1}$  (8), strongly suggests (9-11) that a water molecule is incorporated into the transition state.

Few measurements have been made of the volumes of activation of proton abstraction reactions, and for purposes of comparison with other reactions the volume of activation of the acid-catalyzed enolization of acetone and acetophenone would be interesting. In addition, there are several other points of interest. In the first place, few systematic measurements have been made of the effect of solvent on volumes of activation, and the iodination of ketones is a suitable example of a particular class of reaction that would be worth studying. In the second place, the rate of the reaction is little affected by solvent. It is shown in Section 2 of this paper that for such a reaction, the enthalpy and entropy of activation at constant pressure, or the energy and entropy of activation at constant volume, or both, must vary with solvent so as to compensate one another in the free-energy (energy-enthalpy compensation effect). It is of interest to determine whether only one set of parameters has an appreciable compensation effect or whether both have.

We have therefore measured the effect of temperature and pressure on the rates of the acid-catalyzed iodination of acetone and acetophenone in several ethanol-water mixtures. There was no firm evidence that the iodination of acetophenone goes by a pre-equilibrium proton transfer. The solvent deuterium isotope effect on the rate has therefore been measured to verify it.

## 2. THE ENTHALPY-ENTROPY COMPENSATION EFFECT

It is frequently found that the enthalpy and entropy changes,  $\Delta H$  and  $\Delta S$ , of a reaction, either of its rate or its equilibrium, change with changing conditions in the same direction, so that the changes can be said to compensate one another partially in the free energy  $\Delta G$  ( $= \Delta H - T\Delta S$ ). The changing conditions can be a change of solvent for a given reaction, a change of substituents in a series of compounds undergoing a similar reaction, and so on. This compensation has frequently been called the enthalpy-entropy compensation effect. The existence of this effect is frequently considered surprising. The purpose of the following discussion is to show that it is in fact inevitable for many reactions and other processes except in special circumstances.

We first emphasize that processes can be considered to occur at constant pressure or at constant volume (or of course with neither pressure nor volume constant, but these conditions are less interesting). The most useful free energy for constant-pressure processes is the Gibbs free energy, and we have, using the subscript  $p$  to indicate the constant-pressure condition

$$[1] \quad \Delta G_p = \Delta H_p - T\Delta S_p.$$

The most useful free energy for constant-volume processes is the Helmholtz free energy  $A$ , and we have

$$[2] \quad \Delta A_v = \Delta U_v - T\Delta S_v$$

where  $U$  is the intrinsic energy, and the subscript  $v$  indicates constant-volume conditions. If the rate or equilibrium constant of a reaction is a function of temperature and pressure and not of the extent of reaction then

$$[3] \quad \Delta G_p = \Delta A_v.$$

This condition holds in dilute solution. Both the constant-pressure and the constant-volume parameters are equally fundamental thermodynamic parameters, and there is much to be said for the point of view that the constant-volume parameters are simpler than the constant-pressure parameters.

The relation between the quantities of activation at constant pressure and at constant volume can be derived by applying the operational equation

$$[4] \quad \left( \frac{\partial}{\partial T} \right)_v = \left( \frac{\partial}{\partial T} \right)_p + \frac{\alpha}{\kappa} \left( \frac{\partial}{\partial p} \right)_T,$$

where  $\alpha$  is the isopiestic thermal expansivity of the system and  $\kappa$  its isothermal compressibility. This equation can be applied to any quantity that is a function of the temperature and pressure only. It can be applied to  $\Delta G_p (= \Delta A_v)$  to give

$$[5] \quad \left( \frac{\partial \Delta A_v}{\partial T} \right)_v = \left( \frac{\partial \Delta G_p}{\partial T} \right)_p + \frac{\alpha}{\kappa} \left( \frac{\partial \Delta G_p}{\partial p} \right)_T,$$

from which

$$[6] \quad T\Delta S_v = T\Delta S_p - T\alpha\Delta V/\kappa,$$

and hence,

$$[7] \quad \Delta U_v = \Delta H_p - T\alpha\Delta V/\kappa.$$

We consider first a reaction for which  $\Delta G_p$  and  $\Delta A_v$  do not change with the changing conditions. There is no energy-entropy compensation effect in the constant-volume parameters  $\Delta U_v$  and  $\Delta S_v$  if both are also independent of the changing conditions. There is then, however, an enthalpy-entropy compensation effect in  $\Delta H_p$  and  $\Delta S_p$ , unless the quantity  $T\alpha\Delta V/\kappa$  does not vary with changing conditions. Conversely, if there is no enthalpy-entropy compensation effect in the constant-pressure parameters, there is one in the constant-volume parameters unless  $T\alpha\Delta V/\kappa$  does not vary with changing conditions. If the changing conditions are changing solvent,  $\alpha$ ,  $\Delta V$ , and  $\kappa$  will, in general, all vary and consequently  $\alpha\Delta V/\kappa$  will, in general, vary. If the changing conditions are changing substituents in a homologous series,  $\Delta V$  will, in general, vary. It follows therefore that if  $\Delta G_p$  and  $\Delta A_v$  do not vary or vary only slightly, then either the constant-pressure or the constant-volume parameters will usually tend to vary in a compensating manner because of the variation in  $T\alpha\Delta V/\kappa$ . There may of course be other factors that tend to make the activation parameters vary, and they may dominate the variation in  $T\alpha\Delta V/\kappa$ .

If  $\Delta G_p$  or  $\Delta A_v$  vary strongly there need not necessarily be an enthalpy-entropy or energy-entropy compensation effect unless the variation in  $T\alpha\Delta V/\kappa$  is very strong and of the right sign.

In the rest of this section we shall discuss the inevitability of compensation for the particular case of varying temperature and varying pressure. If the changing conditions are merely changing temperature for the same reaction in the same solvent, the changes of the activation parameters necessarily compensate one another. For example

$$[8] \quad \left( \frac{\partial \Delta H_p}{\partial T} \right)_p = T \left( \frac{\partial \Delta S_p}{\partial T} \right)_p = \Delta C_p$$

and

$$[9] \quad \left( \frac{\partial \Delta U_v}{\partial T} \right)_v = T \left( \frac{\partial \Delta S_v}{\partial T} \right)_v = \Delta C_v.$$

Since  $\Delta C_p$  and  $\Delta C_v$  are related by the equation (21)

$$[10] \quad \Delta C_p - \Delta C_v = \frac{T\alpha\Delta V}{\kappa} \left\{ \left( \frac{\partial}{\partial T} \ln \frac{\alpha\Delta V^2}{\kappa^2} \right)_p + \frac{\alpha}{\kappa} \left( \frac{\partial}{\partial p} \ln \frac{\Delta V}{\kappa} \right)_T \right\},$$

then either  $\Delta C_p$  or  $\Delta C_v$  must differ from zero unless the quantity on the right-hand side of eq. 10 is zero. Consequently, either  $\partial\Delta H_p/\partial T$  and  $T\partial\Delta S_p/\partial T$ , or  $\partial\Delta U_v/\partial T$  and  $T\partial\Delta S_v/\partial T$ , or both, have the same sign, and so there is an energy-entropy compensation effect in at least one of the sets of activation parameters, except in the event that both  $\Delta C_p$  and  $\Delta C_v$  are zero.

The volume change of the reaction can be divided into an enthalpy and an entropy part as follows,

$$[11] \quad \begin{aligned} \Delta V &= \partial\Delta G_p/\partial p, \\ &= (\partial\Delta H_p/\partial p) - T(\partial\Delta S_p/\partial p). \end{aligned}$$

Since for the processes we are considering

$$\Delta G_p = \Delta A_v,$$

we can also write

$$[12] \quad \begin{aligned} \Delta V &= \partial\Delta A_v/\partial p, \\ &= (\partial\Delta U_v/\partial p) - T(\partial\Delta S_v/\partial p). \end{aligned}$$

The relation between  $\partial\Delta U_v/\partial p$  and  $\partial\Delta H_p/\partial T$  is from eq. 7

$$[13] \quad \frac{\partial\Delta U_v}{\partial p} = \frac{\partial\Delta H_p}{\partial p} - T \frac{\partial}{\partial p} \left( \frac{\alpha\Delta V}{\kappa} \right),$$

and the relation between  $\partial\Delta S_v/\partial p$  and  $\partial\Delta S_p/\partial p$  is

$$[14] \quad \frac{\partial\Delta S_v}{\partial p} = \frac{\partial\Delta S_p}{\partial p} - \frac{\partial}{\partial p} \left( \frac{\alpha\Delta V}{\kappa} \right).$$

It follows from these considerations that a zero value of  $\Delta V$  will necessitate a compensation effect either in  $\partial\Delta H_p/\partial p$  and  $T\partial\Delta S_p/\partial p$ , or in  $\partial\Delta U_v/\partial p$  and  $T\partial\Delta S_v/\partial p$ , or of course in both, unless the quantity  $\partial(\alpha\Delta V/\kappa)/\partial p$  is zero. There may, of course, be other factors that tend to induce compensation.

The existence of compensation in the variation of the Arrhenius energy and the pre-exponential factor with pressure was first observed experimentally many years ago (12).

### 3. EXPERIMENTAL

#### *Materials*

Mallinckrodt A.R. acetone and Fisher Certified Reagent acetophenone were used directly. Absolute ethanol was used in preparing ethanol-water solvents. D<sub>2</sub>O (99.6%) was obtained from Atomic Energy of Canada, Ltd. Ethanol-d<sub>1</sub> was prepared in this laboratory according to the method of Burr (13); it was shown by infrared spectroscopy to be at least 95% deuterated in the hydroxyl group. All other chemicals were of reagent grade.

#### *Kinetics at Atmospheric Pressure*

Stock standard aqueous solutions of acetone (0.5 M), iodine (0.01 M), and perchloric acid (1 M) were prepared. A stock solution of acetophenone (0.5 M) was made in absolute ethanol. The reaction solution was made in a 100 ml volumetric flask by pipetting to 50 ml of water, standard solutions of perchloric acid (5 ml), ketone (10 ml), and iodine (10 ml). For experiments in water the solution was made up to 100 ml with water. For experiments in ethanol-water solvents, either 20 or 40 ml of ethanol was added before making up the volume to 100 ml with water to give respectively 16.2 and 33.4% w/w ethanol in water. After thorough mixing, the flask was immersed in a water thermostat whose temperature was controlled to  $\pm 0.005^\circ\text{C}$  and was measured by a platinum resistance thermometer. The temperature was maintained

at 25, 35, and 45 °C for acetone and at 30, 40, and 50 °C for acetophenone. At successive intervals, 10 ml of the reaction solution was removed and titrated with aqueous sodium thiosulphate (0.002 *N*) using starch as indicator. To ensure temperature equilibrium, at least 20 min was allowed before the first sample was removed. About six points were taken and the reaction was followed nearly to completion. Blank experiments without ketone established that iodine did not react with the medium. The absence of iodine at the end of the reaction showed that the reaction went to completion.

For experiments with acetophenone in solvent 16.2% w/w ethanol-*d*<sub>1</sub> in D<sub>2</sub>O, the reaction solution was made in a 25-ml volumetric flask. The acetophenone and perchloric acid (~0.2 g 70.0% w/w HClO<sub>4</sub>) were weighed directly into the flask, which contained 5 ml of ethanol-*d*<sub>1</sub>, and the flask was nearly filled with D<sub>2</sub>O. Three milliliters of a stock iodine solution (~0.008 *M*) in D<sub>2</sub>O was added and the solution was made up to 25 ml with D<sub>2</sub>O. The proportion of deuterium in this solvent was at least 99%. Five milliliters of the reacting solution was periodically titrated with thiosulphate (0.001 *N*). Four points were taken and the reaction was followed nearly to completion.

In the foregoing experiments, the initial concentration of acetone and the concentration of perchloric acid were about 0.05 *M* at 25 °C and 0.025 *M* at the higher temperatures. The initial concentration of acetophenone and the concentration of perchloric acid were about 0.05 *M* at 30 and 40 °C and 0.03 *M* at 50 °C. The initial concentration of iodine was ~0.001 *M* throughout.

#### *Kinetics at High Pressures*

The high-pressure technique was similar to that used previously (14) except for the following modification. Since iodine reacted appreciably with the sampling valve (E of Fig. 1 of ref. 14) a batch method was used to follow the reaction. The reaction vessel was a 2-oz polyethylene bottle provided with a tight-fitting leak-proof cap. The part of the pressure apparatus beyond the junction block F (see Fig. 1 of ref. 14) was eliminated.

The reaction solution was made as in the experiments at atmospheric pressure, a stopwatch being started (stopwatch reading *a*, which is zero) when the iodine solution was added. The polyethylene bottle was filled almost completely with the reaction solution immediately after the solution was mixed, and was placed inside the pressure vessel. The pressure vessel was filled with oil, assembled, immersed in the thermostat, and quickly brought up to pressure. When the desired pressure as read on the Bourdon gauge was reached, the time was noted on the stopwatch (stopwatch reading *b*). After one-half hour (stopwatch reading *c*), the pressure was released and the bottle was removed. The outside oil was wiped off and 10 ml of the solution were pipetted out and titrated (stopwatch reading *d*) with thiosulphate (0.002 *N*). This titer reading was taken as that for zero time. Other samples were put into the bottle and left for different times, i.e., the time interval between *b* and *c* was either 1, 1.5, or 2 h. Four points were taken for each run. The time intervals between *a* and *b* and between *c* and *d* were kept exactly the same for all four samples. In a typical experiment at a pressure of 3 kbar, the time interval between *a* and *b* was 8 min and that between *c* and *d* was 7 min. A blank experiment at 3 kbar without addition of the ketone showed that iodine did not react with the medium. The absence of iodine after a sufficient time at 3 kbar showed that the reaction went to completion. The initial concentration of ketone and the concentration of acid were about 0.05 *M* except for the runs at 3 kbar in 33.4% w/w ethanol in water, for which concentrations of about 0.025 *M* were used.

In all the kinetic experiments the initial concentrations of ketone and acid were kept nearly equal in order to suppress the effect of autocatalysis on the rate of iodination. Further, the molar ratios of ketone to iodine were high enough to exclude the possibility of any di-iodination.

## 4. RESULTS

All kinetic runs were accurately zero order in iodine, and the zero-order rate constants at atmospheric pressure were obtained by least-squares analysis using a digital computer. The reason for this was that the effect of solvent on the enthalpy and entropy of activation was required, and rate constants of maximum accuracy were required to determine this. The rate constants at higher pressures were obtained by the usual graphical method. The second-order rate constants *k*<sub>a</sub> were obtained by dividing the zero-order constants by the product of the concentrations of ketone and perchloric acid. For kinetic runs in water, the rate constants were corrected for compression of the solution (15) which was assumed without significant error to be that of water. Similar corrections for compression could not be applied to rate constants in ethanol-water solvents since compression of these solutions has not been extensively measured. The rate constants in these solvents were therefore only corrected for the thermal expansion of the solvent at atmospheric pressure. The rate constants at atmospheric pressure are given in Table I, and those at higher pressures in Table II. Our mean value for 10<sup>6</sup>*k*<sub>a</sub>/1 mole<sup>-1</sup> s<sup>-1</sup> for acetone (see



TABLE I  
Rate constants for the acid-catalyzed enolization of acetone and acetophenone followed by iodination at atmospheric pressure

Ketone	Solvent	Temp. (°C)	$10^5 k_a / \text{l mole}^{-1} \text{s}^{-1*}$
Acetone	Water	25.00	28.2, 27.4, 27.5, 27.3
		35.00	84.0, 85.1, 85.7, 84.9
		45.00	243, 244, 242, 243
	16.2% w/w ethanol in water	25.00	31.1, 31.6, 31.4, 31.4
		35.00	94.8, 95.0, 93.5, 95.1
		45.00	266, 273, 262, 266
	33.4% w/w ethanol in water	25.00	33.9, 34.3, 34.4, 34.8
		35.00	100, 101, 103, 101
		45.00	276, 278, 282, 281
Acetophenone	16.2% w/w ethanol in water	30.00	21.5, 21.1, 21.3, 21.7
		40.00	66.6, 66.4, 66.8, 67.2
		50.00	198, 200, 198, 197
	33.4% w/w ethanol in water	30.00	23.7, 23.0, 23.1, 23.8
		40.00	71.4, 71.7, 71.2, 72.0
		50.00	211, 205, 209, 208
	16.2% w/w ethanol- $d_1$ in $D_2O$	30.00	54.0, 53.1

\*The rate constants are corrected for thermal expansion of the solvent.

TABLE II  
Rate constants for the acid-catalyzed enolization of acetone at 25.00 °C and of acetophenone at 30.00 °C followed by iodination at different pressures

Ketone	$p/\text{bar}$	Solvent	$10^5 k / \text{l mole}^{-1} \text{s}^{-1*}$
Acetone	500	Water	27.8
		16.2% w/w ethanol in water	35.2
		33.4% w/w ethanol in water	39.9
	1000	Water	30.7
		16.2% w/w ethanol in water	37.8
		33.4% w/w ethanol in water	46.3
	2000	Water	32.9
		16.2% w/w ethanol in water	44.0
		33.4% w/w ethanol in water	58.3
	3000	Water	36.4
		16.2% w/w ethanol in water	51.5
		33.4% w/w ethanol in water	76.5
Acetophenone	500	16.2% w/w ethanol in water	23.8
		33.4% w/w ethanol in water	29.3, 29.1
	1000	16.2% w/w ethanol in water	28.2
		33.4% w/w ethanol in water	33.0
	2000	16.2% w/w ethanol in water	33.8
		33.4% w/w ethanol in water	41.7
	3000	16.2% w/w ethanol in water	36.3
		33.4% w/w ethanol in water	52.2

\* $k$  is  $k_a$  for solvent water, and  $k_a \rho(p)/\rho$  (1 bar), where  $\rho(p)$  and  $\rho$  (1 bar) are the densities of the solvent at pressure  $p$  and 1 bar respectively, for solvents ethanol-water.

Table I) at atmospheric pressure in water is 27.6, which is in good agreement with the literature values; a collection of these can be found elsewhere (16).

The main quantities to be derived from the rate constants that are of interest in this work are the effect of solvent on the enthalpies and entropies of activation at constant pressure, and on the volumes of activation. If  $k_1$  and  $k_2$  represent rate constants at the same temperature in two different solvents, and  $\Delta H_p^\ddagger$  and  $\Delta S_p^\ddagger$  represent the enthalpy and entropy of activation in the same solvents, then

$$[15] \quad \ln k_2/k_1 = \Delta\Delta H_p^\ddagger/RT - \Delta\Delta S_p^\ddagger/R$$

where

$$[16] \quad \Delta\Delta H_p^\ddagger = \Delta H_{p_1}^\ddagger - \Delta H_{p_2}^\ddagger,$$

and

$$[17] \quad \Delta\Delta S_p^\ddagger = \Delta S_{p_1}^\ddagger - \Delta S_{p_2}^\ddagger.$$

Plots of  $\log k_2/k_1$  against  $1/T$  yield  $\Delta\Delta H_p^\ddagger$  and  $\Delta\Delta S_p^\ddagger$ . These are shown in Fig. 1, and the

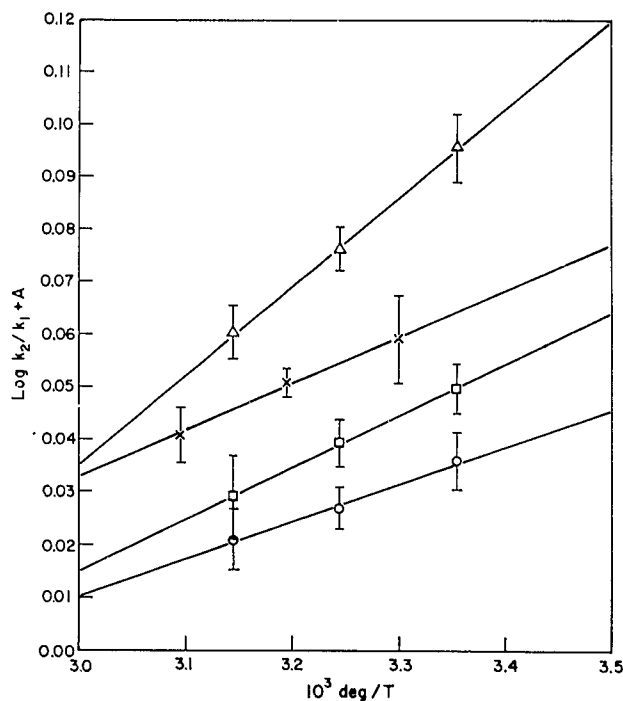


FIG. 1.  $\text{Log}_{10} k_2/k_1$  against  $1/T$  for the acid-catalyzed enolization (iodination) of acetone and acetophenone. Points  $\Delta$ ,  $\square$ , and  $\circ$  refer to acetone, and  $\times$  refers to acetophenone.  $\Delta$  ( $A = 0$ ); 33.4% w/w ethanol in water : water.  $\square$  ( $A = 0.01$ ),  $\times$  ( $A = 0.02$ ); 33.4% w/w ethanol in water : 16.2% w/w ethanol in water.  $\circ$  ( $A = -0.02$ ); 16.2% w/w ethanol in water : water.

quantities  $\Delta\Delta H_p^\ddagger$  and  $\Delta\Delta S_p^\ddagger$  are listed in Table IV together with approximate estimates of their standard errors. The values were verified by plotting (plots not shown)  $T \log k_2/k_1$  against  $T$ . The Arrhenius parameters themselves for the enolization of acetone in water in the range 25–45° obtained by the usual graphical method, are

$$E_A = 20.5 \pm \sim 0.2 \text{ kcal mole}^{-1},$$

$$\log_{10} A / \text{l mole}^{-1} \text{ s}^{-1} = 10.5 \pm \sim 0.1.$$

These are in excellent agreement with the literature values 20.6 kcal mole<sup>-1</sup> and 10.6 respectively (17). The Arrhenius parameters for the enolization of acetophenone in 16.2% w/w ethanol in water in the range 30–50 °C are

$$E_A = 21.5 \pm \sim 0.2 \text{ kcal mole}^{-1},$$

$$\log_{10} A / \text{l mole}^{-1} \text{ s}^{-1} = 10.9 \pm \sim 0.1.$$

Plots of the logarithms of the rate constants against pressure are shown in Figs. 2 and 3. The volumes of activation were obtained by extrapolating plots of  $\log k(p_2)/k(p_1)$

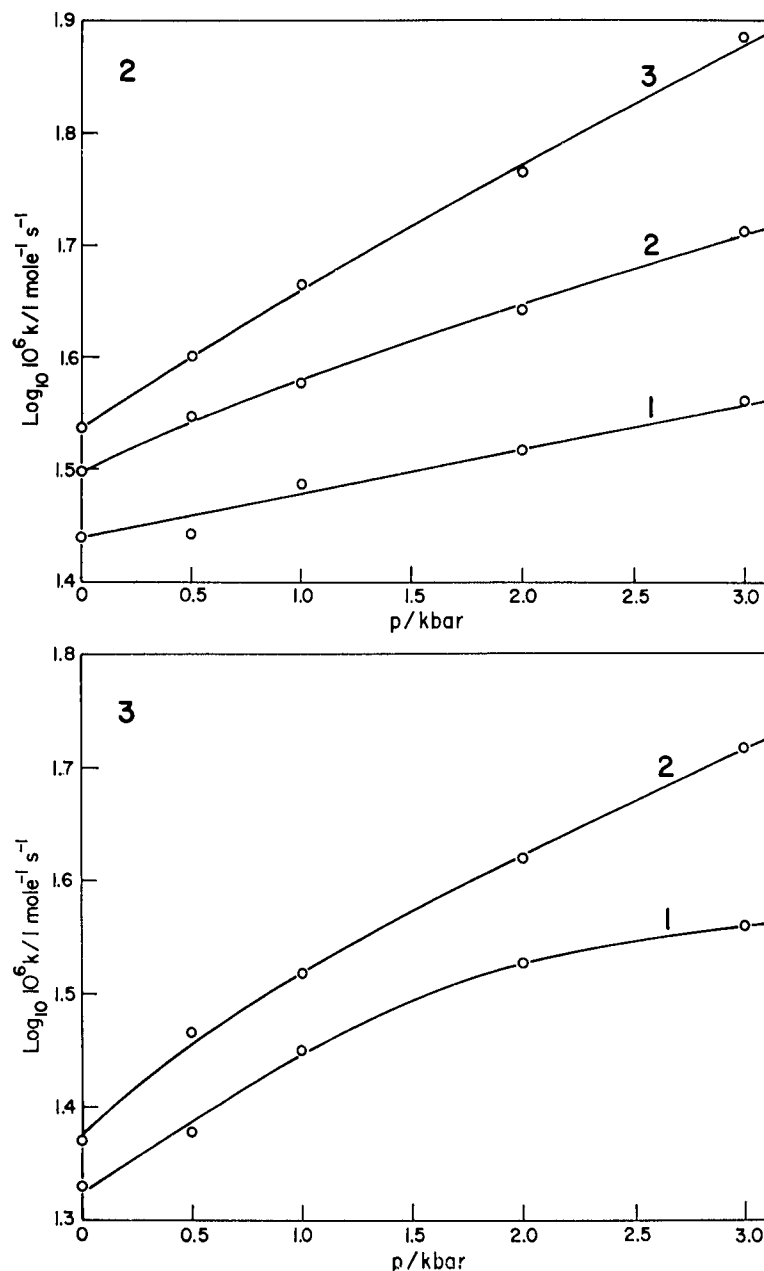


FIG. 2. Effect of pressure on the rate of enolization of acetone at 25.00 °C. Curve 1: in water. Curve 2: in 16.2% w/w ethanol in water. Curve 3: in 33.4% w/w ethanol in water.

FIG. 3. Effect of pressure on the rate of enolization of acetophenone at 30.00 °C. Curve 1: in 16.2% w/w ethanol in water. Curve 2: in 33.4% w/w ethanol in water.

against  $\frac{1}{2}(p_2 + p_1)$  to zero pressure, where  $p_1$  and  $p_2$  are adjacent pressures at which the rate constants were measured. The differences in the volumes of activation in two solvents were verified by plotting  $\log k_1/k_2$ , where  $k_1$  and  $k_2$  are the rate constants in two solvents at the same temperature and pressure, against  $p$ . For ethanol-water solvents the compression of the reaction mixture was allowed for by subtracting  $\kappa RT$  from the value of  $-RT \partial \ln k / \partial p$  at zero pressure (for a similar correction see ref. 18) where  $\kappa$  is the compressibility of the solvent at zero pressure. Using the compressibilities of ethanol-water mixtures as interpolated from Moesveld's data (19), i.e.,  $39.5 \times 10^{-6}$  and  $44.5 \times 10^{-6}$

bar<sup>-1</sup> respectively, the value of  $\kappa RT$  in 16.2% w/w ethanol in water is 1.0 cm<sup>3</sup> mole<sup>-1</sup>, and in 33.4% w/w ethanol in water is 1.1 cm<sup>3</sup> mole<sup>-1</sup>. The volumes of activation are given in Table III.

TABLE III  
Volumes of activation for the acid-catalyzed enolization of acetone and of acetophenone

Ketone	Solvent	Temp. (°C)	$\Delta V^\ddagger/\text{cm}^3 \text{ mole}^{-1}$
Acetone	Water	25.00	$-2.1 \pm \sim 0.5$
	16.2% w/w ethanol in water		$-4.2 \pm \sim 0.7$
	33.4% w/w ethanol in water		$-6.9 \pm \sim 0.7$
Acetophenone	16.2% w/w ethanol in water	30.00	$-6.0 \pm \sim 0.7$
	33.4% w/w ethanol in water		$-8.6 \pm \sim 1.0$

The effect of solvent on the rate constant at various pressures is shown in Fig. 4. The

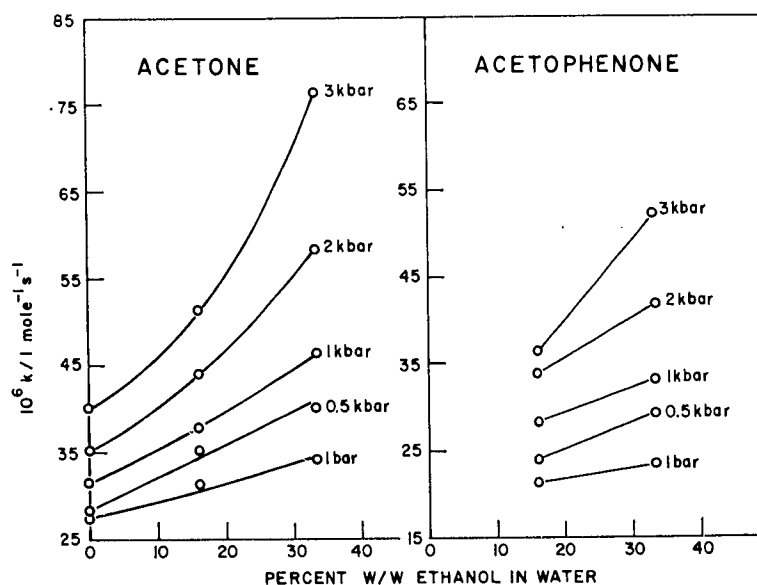


FIG. 4. Effect of solvent on the rate of enolization of acetone at 25.00 °C and of acetophenone at 30.00 °C at different pressures. The definition of  $k$  is given in the footnote of Table II.

rate constants for acetone in water at various pressures shown in this plot are uncorrected for compression of the solution, so that a true comparison with the rate constants in ethanol-water solvents, which are also uncorrected for compression, can be made. Because acetophenone is almost insoluble in water, it was not possible to study its iodination kinetics in water under comparable conditions to those used for acetone. The curves for acetophenone in Fig. 4 were therefore drawn as straight, although by comparison with the curves for acetone, they are probably not accurately straight.

## 5. DISCUSSION

### 1. Solvent Deuterium Isotope Effect for the Enolization of Acetophenone

The solvent deuterium isotope effect for the enolization of acetophenone  $k^{D_2O}/k^{H_2O}$  in 16.2% w/w ethanol in water is  $2.50 \pm \sim 0.05$ . This undoubtedly proves that there is a pre-equilibrium proton transfer to the ketone preceding the rate-determining step. The value is similar to the value 2.1 reported (6) for acetone.

## 2. Effect of Solvent on the Rate of Enolization

The effect of solvent on the rate of enolization is quite small at atmospheric pressure. Between 0 and 16.2% w/w ethanol in water the rate for acetone increases by about 10%, and between 16.2 and 33.4% w/w ethanol in water the rate for both acetone and acetophenone increases also by about 10%. Solvent effects of a similar magnitude were previously observed for the iodination of acetone in ethanol-water (20) and for the bromination of acetone and acetophenone in acetic acid-water (8) at atmospheric pressure. The slight increase in the rate is in the direction expected if it were due mainly to the electrostatic interaction between the reactants and the solvent, and the electrostatic charge were dispersed over a larger volume in the transition state than in the initial state without a significant increase in the dipole and higher moments (21). However, the change of rate is so small that any small electrostatic effects of this kind could easily be swamped by changes of more specific interactions between the reactants and the solvent. The results cannot therefore be taken as indicating the direction of the change of the polarity when the transition state is formed.

Furthermore, the effect of solvent on the rate (see Fig. 4) is about four times larger at 3 kbar than at 1 bar. The effect of solvent on the compression is much too small to account for this effect. It appears from Figs. 2 and 3 that if the rate constant as a function of pressure could be extrapolated smoothly into the region of negative pressures, then the solvent effect would change sign at about -1 kbar, and at pressures below this, increasing the concentration of organic solvent in the mixture would cause the reaction rate to decrease. The pressure at which the effect of solvent on the rate changes sign has actually been observed for the acid-catalyzed hydrolysis of methyl acetate (Withey, Poulton, Whalley, unpublished work), and more detailed comments will be made when this work is published. It is, nevertheless, clear that caution should be used when one is attempting to interpret small effects of solvent on the rate constant.

The large effect of pressure on the solvent effect for both the enolization of ketones and the hydrolysis of methyl acetate cannot be explained on simple electrostatic grounds, and indicates that any explanation of the solvent effect at 1 bar on simple electrostatic grounds is invalid. Rather, the small solvent effect at 1 bar is almost certainly due to two or more larger effects that in large part cancel one another. The relatively large effect of pressure on the solvent effect is probably due to a smaller relative effect of pressure on one or more of these component solvent effects.

The effect of pressure on the solvent effect and the effect of solvent on the volume of activation are, of course, different ways of describing the same thing. Because

$$\frac{\partial}{\partial x} \left( \frac{\partial \ln k}{\partial p} \right)_T = \frac{\partial}{\partial p} \left( \frac{\partial \ln k}{\partial x} \right)_T$$

where  $x$  is the concentration of one component of the solvent mixture, then

$$\frac{\partial}{\partial p} \left( \frac{\partial \ln k}{\partial x} \right) = -\frac{1}{RT} \frac{\partial \Delta V^\ddagger}{\partial x}.$$

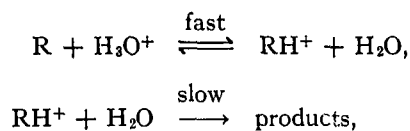
The discussion of the effect of solvent on the volume of activation in Section 5.4 is therefore relevant also to this section.

## 3. Volumes of Activation in Water

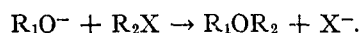
The volume of activation for the enolization of acetone in water is  $-2.1 \pm \sim 0.5 \text{ cm}^3 \text{ mole}^{-1}$ . The volume of activation for the enolization of acetophenone is not known in

water, but it is  $1.8 \text{ cm}^3 \text{ mole}^{-1}$  more negative than that of acetone in both 16.2 and 33.4% w/w ethanol in water. It is likely therefore that the volume of activation for acetophenone in water is about  $-3.9 \text{ cm}^3 \text{ mole}^{-1}$ .

Because the ketones are only slightly protonated under the experimental conditions, the volumes of activation are the difference in partial volume between the transition state and the initial ketone and hydronium ion. The volumes of activation for acid-catalyzed reactions of the kind



where a new  $\text{H}_2\text{O}-\text{C}$  bond is formed in the slow step are usually about  $-8$  to  $-12 \text{ cm}^3 \text{ mole}^{-1}$  (21), and similar values are usually found for reactions of the kind (21)



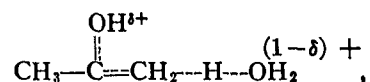
It is therefore at first sight a little surprising to find  $-2.1 \text{ cm}^3 \text{ mole}^{-1}$  for the enolization of acetone. There are probably two reasons for the high volume of activation.

For approximate purposes a volume of activation can be divided into two parts (21),  $\Delta V_r^\ddagger$  which is the change of volume due directly to the changing interaction of the reacting molecules with one another, and  $\Delta V_s^\ddagger$ , which is the change of volume due directly to the changing interaction of the reacting molecules with the solvent. For bimolecular reactions such as we are discussing  $\Delta V_r^\ddagger$  is approximately the contraction (or expansion) of the interatomic distance when a partial valence bond is formed (or broken) multiplied by the cross-sectional area perpendicular to the bond. Both the contraction and the cross-sectional area are probably smaller when a water molecule substitutes at a hydrogen atom than when it substitutes at a carbon atom. Consequently,  $\Delta V_r^\ddagger$  for the acid-catalyzed enolization of ketone is probably less negative than that for bimolecular (A-2) acid-catalyzed hydrolyses.

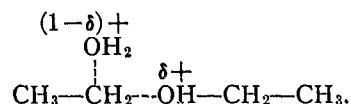
If for approximate purposes we represent part of the interaction between an ion and its solvent by that between a charged spherically symmetrical ion and a continuous dielectric, then  $\Delta V_s^\ddagger$  can be represented in part as the difference between reactants and transition state of the quantity (22),

$$[18] \quad \frac{1}{2}N \frac{z^2 e^2}{a} \left\{ \frac{\partial \epsilon^{-1}}{\partial p} + \left( 1 - \frac{1}{\epsilon} \right) \frac{\partial \ln a}{\partial p} \right\}$$

where  $N$  is Avogadro's number,  $z$  is the number of electronic charges  $e$  on the ion,  $a$  is the radius of the cavity containing the ion, and  $\epsilon$  is the dielectric constant. The transition state for the enolization of acetone can be represented by



and that for a typical A-2 reaction such as the acid-catalyzed hydrolysis of diethyl ether can be represented as



The positive charge is clearly more widely dispersed in the ketone transition state than

in the ether transition state, and consequently the effective radius of the charge can be considered to be greater. In both transition states the effective radius is, of course, greater than in the initial hydronium ion.  $\Delta V_s^\ddagger$  for both reactions will therefore be positive and will be more positive for the ketone reaction than for the ether reaction. The increase of volume is composed of an increase of the volume of both the reactants and the solvent due to the decrease of the interaction between them (22).

We see therefore that both  $\Delta V_r^\ddagger$  and  $\Delta V_s^\ddagger$  are probably algebraically larger for the ketone enolization than for the ether hydrolysis, and so the volume of activation is probably algebraically larger, in agreement with observation. It is clear that where there is a possibility of a large dispersion of charge, caution may be required in using volumes of activation to help determine mechanisms (21).

The fact that the volumes of activation for acetone and acetophenone are not greatly different and that of acetophenone is more negative than that of acetone suggests that there is little dispersion of charge into the benzene ring of acetophenone. The relatively small effect of para substituents on the rate of enolization of substituted acetophenones (8) agrees well with this view.

#### 4. Effect of Solvent on Volume of Activation

The effect of solvent on the volume of activation (Table III) for both acetone and acetophenone is rather large, the volume of activation for acetone in 33.4% w/w ethanol-water being over three times the value for water. The volumes of activation for the acid-catalyzed hydrolysis of methyl acetate (Withey, Poulton, and Whalley, unpublished work) changes by about the same amount in solvent acetone-water as does that for acetone in ethanol-water of similar concentration, although the relative change for methyl acetate is smaller due to its volume of activation in water being four times bigger than that for acetone (23).

The effect of solvent on a volume of activation is almost by definition an effect on  $\Delta V_s^\ddagger$  if the mechanism does not change. We have seen in Section 5.3 that  $\Delta V_s^\ddagger$  is probably positive, and so to explain the observed decrease in  $\Delta V^\ddagger$  with increasing proportion of organic solvent in terms of the ion-dielectric theory represented by equation 18 requires that  $\partial\epsilon^{-1}/\partial p$  should increase in the range of solvent water to 33.4% w/w ethanol-water. This is not a priori unlikely, in spite of the fact that  $\partial\epsilon^{-1}/\partial p$  for ethanol is much smaller than that for water (24) because the initial effect of adding ethanol to water is to cause the compressibility to decrease (19). A little more information can be obtained from theory. The dielectric constant of a mixture of polar substances can be represented approximately by the expression (25)

$$[19] \quad \frac{(\epsilon - 1)(2\epsilon + 1)}{9\epsilon} V = \sum_i \frac{(\epsilon_i - 1)(2\epsilon_i + 1)}{9\epsilon_i} x_i V_i$$

where  $\epsilon$  and  $\epsilon_i$  are the dielectric constants of the mixture and of pure component  $i$ ,  $V$  and  $V_i$  are the molar volumes of the solution and of component  $i$ , and  $x_i$  is the mole fraction of component  $i$ . For ethanol-water mixtures at room temperature the dielectric constants are much greater than unity, and equation [19] can be simplified approximately to

$$[20] \quad \epsilon V = \sum_i \epsilon_i V_i x_i$$

which can also be written

$$[21] \quad \epsilon = \sum_i \epsilon_i \varphi_i$$

where  $\varphi_i$  is the volume fraction of component  $i$ ,

$$[22] \quad \varphi_i = V_i x_i / V.$$

By differentiating equation [21] with respect to pressure and introducing the isothermal compressibility  $\kappa_i$  and the pressure coefficient  $\zeta_i$  of the dielectric constant

$$\zeta_i = \partial \ln \epsilon_i / \partial p,$$

we find

$$[23] \quad \frac{\partial \epsilon^{-1}}{\partial p} = -\epsilon^{-2} \sum \epsilon_i \varphi_i (\zeta_i - \kappa_i + \kappa).$$

The values of  $\partial \epsilon^{-1} / \partial p$  for various ethanol-water mixtures calculated according to equation [23] are as follows.

Solvent	$10^6(\partial \epsilon^{-1} / \partial p) / \text{bar}^{-1}$
Water	-0.74
16.2% w/w ethanol in water	-0.74
33.4% w/w ethanol in water	-0.91
Ethanol	-3.58

It seems likely therefore that  $\partial \epsilon^{-1} / \partial p$  changes little between water and 33.4% w/w ethanol in water, and perhaps slightly decreases. The effect of solvent on  $\Delta V_s^\ddagger$  cannot therefore be explained on the basis of ion-dielectric theory if equation [23] is moderately accurate. It is possible that part of the decrease in  $\Delta V_s^\ddagger$  with increasing proportion of organic solvent is due to there being greater unmixing of water and ethanol around the  $\text{H}_3\text{O}^+$  ion than around the transition state; since water and ethanol have a larger volume when unmixed than when mixed, greater unmixing around the  $\text{H}_3\text{O}^+$  ion than around the transition state would tend to make  $\Delta V_s^\ddagger$  smaller in water-ethanol mixtures than in water. This could, in principle, be treated in terms of the dielectric theory, but it is not worthwhile. There are also other interactions between the reactant and the solvent about which little is known quantitatively, and they are probably playing their part.

##### 5. Quantities of Activation at Constant Pressure and at Constant Volume: Variation with Solvent

The free-energy of activation ( $\Delta G_p^\ddagger$  or  $\Delta A_s^\ddagger$ ) for the enolization of acetone and acetophenone in ethanol-water mixtures changes little with solvent. The volumes of activation for the reactions are not zero, and change considerably with changing solvent. It follows, according to the arguments given in section 2, that there should be compensation either in  $\Delta H_p^\ddagger$  and  $T\Delta S_p^\ddagger$  or in  $\Delta U_s^\ddagger$  and  $T\Delta S_s^\ddagger$ . The differences,  $\Delta\Delta H_p^\ddagger$  and  $T\Delta\Delta S_p^\ddagger$ , in  $\Delta H_p^\ddagger$  and  $T\Delta S_p^\ddagger$  between solvents are listed in Table IV together with the changes in  $T\alpha\Delta V^\ddagger/\kappa$  and in  $\Delta U_s^\ddagger$  and  $T\Delta S_s^\ddagger$ . It is clear that the intrinsic energy and entropy of activation at constant volume change much less with changing solvent than do the enthalpy and entropy of activation at constant pressure. There is therefore a significant energy-entropy compensation in the constant-pressure parameters of activation but not in the constant-volume parameters. There have been several suggestions in the past that quantities of activation at constant volume should be more easily understood than quantities of activation at constant pressure (see ref. 21 for references). There has, however, been no previous reliable test of this suggestion. A test was made 25 years ago using the homogeneous dimerization of cyclopentadiene (26) but doubts have recently been cast (27) on the reliability of the experimental results used (28).



TABLE IV

Changes with solvent of the activation parameters for the acid-catalyzed enolization of acetone and acetophenone. The temperature range was 25–45 °C for acetone and 30–50 °C for acetophenone. Temperature-dependent parameters were evaluated at 25 °C for acetone and at 30 °C for acetophenone

Ketone	Solvent	$\frac{\Delta\Delta G_p^\ddagger (= \Delta\Delta A_p^\ddagger)^*}{\text{cal mole}^{-1}}$ $\pm \sim 5$	$\frac{\Delta\Delta H_p^\ddagger}{\text{cal mole}^{-1}}$ $\pm \sim 120$	$\frac{T\Delta\Delta S_p^\ddagger}{\text{cal mole}^{-1}}$ $\pm \sim 120$	$\frac{T\Delta(\alpha\Delta V^\ddagger/\kappa)^\ddagger}{\text{cal mole}^{-1}}$ $\pm \sim 100$	$\frac{\Delta\Delta U_p^\ddagger}{\text{cal mole}^{-1}}$ $\pm \sim 150$	$\frac{T\Delta\Delta S_p^\ddagger}{\text{cal mole}^{-1}}$ $\pm \sim 150$
Acetone	16.2% w/w ethanol in water	76	325	250	216	109	34
	33.4% w/w ethanol in water	130	775	645	572	203	73
	33.4% w/w ethanol in water	54	405	350	373	32	-23

\*Solvent 1 (eqs. 15–17) for acetone is water and for acetophenone is 16.2% w/w ethanol in water. Solvent 2 is listed in column 2 of this table. The quantities  $\Delta\Delta G_p^\ddagger$  were evaluated from the equation  $\Delta\Delta G_p^\ddagger = RT \ln k_2/k_1$ , where  $T$  refers to the temperature at which  $\Delta V^\ddagger$  has been measured. The quantities  $\Delta\Delta H_p^\ddagger$  and  $T\Delta\Delta S_p^\ddagger$  were obtained from plots shown in Fig. 1. †The thermal expansion ( $10^4 \alpha/\text{deg}^{-1}$ ) for water is 248 (25 °C), for 16.2% w/w ethanol in water is 396 at 25 °C, and 441 at 30 °C, and for 33.4% w/w ethanol in water is 594 at 25 °C, and 613 at 30 °C. These were obtained by plotting  $\log(\text{density})$  against temperature and evaluating the slopes at the temperatures desired. The densities were taken from the literature (31). The compressibilities ( $10^4 \kappa/\text{bar}^{-1}$ ) of these solvents from Moesveld's data (19) are 43.9, 39.5, and 44.5 respectively at 25 °C, and the same values were assumed for 30 °C.  $T$  is the temperature at which  $\Delta V^\ddagger$  has been measured.

TABLE V

Changes with substituent of the activation parameters for the acid-catalyzed enolization of acetone and acetophenone at 30 °C

$(\Delta\Delta = \Delta_{\text{acetophenone}} - \Delta_{\text{acetone}})$							
Solvent	$\frac{\Delta\Delta G_p^\ddagger (= \Delta\Delta A_p^\ddagger)^*}{\text{cal mole}^{-1}}$ $\pm \sim 5$	$\frac{\Delta\Delta H_p^\ddagger}{\text{cal mole}^{-1}}$ $\pm \sim 120$	$\frac{T\Delta\Delta S_p^\ddagger}{\text{cal mole}^{-1}}$ $\pm \sim 120$	$\frac{T\alpha\Delta V/\kappa}{\text{cal mole}^{-1}}$ $\pm \sim 100$	$\frac{\Delta\Delta U_p^\ddagger}{\text{cal mole}^{-1}}$ $\pm \sim 150$	$\frac{T\Delta\Delta S_p^\ddagger}{\text{cal mole}^{-1}}$ $\pm \sim 150$	
16.2% w/w ethanol in water	563	1365	803	-146	1511		949
33.4% w/w ethanol in water	557	1510	953	-170	1680		1123

Many attempts have been made in the past to explain the observed enthalpy-entropy compensation effect in a variety of systems (29, 30 and references quoted there). For the system investigated here, the fact that there is little energy-entropy compensation in the constant-volume parameters seems to require no special explanation. The explanation of the enthalpy-entropy compensation in the constant-pressure parameters requires an explanation of the variation of  $\alpha\Delta V^\ddagger/\kappa$  with solvent, because of the relationship in equations [6] and [7]. For the enolization of acetone in water and in 33.4% w/w ethanol in water,  $\alpha$  changes from  $248 \times 10^{-6}$  to  $594 \times 10^{-6} \text{ deg}^{-1}$  (Table IV, footnote),  $\Delta V^\ddagger$  changes from  $-2.1$  to  $-6.9 \text{ cm}^3 \text{ mole}^{-1}$  (Table III), and  $\kappa$  changes from  $43.9 \times 10^{-6}$  to  $44.5 \times 10^{-6} \text{ bar}^{-1}$ . The changes of these quantities between water and 16.2% w/w ethanol in water for the enolization of acetone, and between 16.2% w/w and 33.4% w/w ethanol in water for the enolization of acetophenone (see Tables III and IV) are similar to these changes. The change in  $\alpha\Delta V^\ddagger/\kappa$  is therefore due about equally to changes in the thermal expansivity and in the volume of activation and hardly at all to changes in the compressibility. The causes of the change of the volume of activation with solvent are discussed in Section 5.4. The change of the thermal expansivity with solvent is undoubtedly due largely to the small thermal expansivity of water due to its peculiar structure. The thermal expansivity of pure water is of course zero near  $4^\circ\text{C}$ , and then the quantities of activation at constant pressure and at constant volume are equal.

#### 6. Quantities of Activation at Constant Pressure and at Constant Volume: Variation with Substituent

Since the intrinsic energy and entropy of activation at constant volume change little with changing solvent (Section 5.5) although the enthalpy and entropy of activation at constant pressure change appreciably, it is worth investigating the change of the two sets of activation parameters with changing substituent. The differences in the activation parameters at constant pressure were obtained from plots analogous to those in Fig. 1. For this purpose, rate constants for acetone at  $30^\circ\text{C}$  were interpolated from Arrhenius plots. The results for both 16.2% w/w and 33.4% w/w ethanol in water are summarized in Table V. There is compensation in both the constant-pressure and the constant-volume parameters, and the compensation in the constant-volume parameters is the greater. There is little doubt that attempts to explain the compensation quantitatively should be based on the constant-volume parameters.

### 6. CONCLUSIONS

The most important conclusions derived from the experiments reported in this paper are as follows:

1. The effect of solvent on the rate of a reaction may be greatly influenced by pressure, and care is required in interpreting solvent effects, particularly small solvent effects, at atmospheric pressure. It is wise to study the effect of both temperature and pressure on the solvent effect.
2. Reactions whose rates change only slightly with changing conditions (such as substituents, solvent, etc.) inevitably will have an energy-entropy compensation effect in either the enthalpy and entropy of activation at constant pressure or in the energy and entropy of activation at constant volume, or, of course, in both sets of parameters. There is no significant compensation in the variation with solvent of the constant-volume parameters for the enolization of acetone and of acetophenone in ethanol-water mixtures; the compensation in the constant-pressure parameters can be ascribed about

equally to changes in the thermal expansion and in the volume of activation with changing solvent. There is more compensation in the variation with substituent of the constant-volume parameters for the enolization of acetone and acetophenone than in the constant-pressure parameters. Attempts to explain the compensation in quantitative terms should doubtless be based on the constant-volume parameters if these differ significantly from the constant-pressure parameters.

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