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Citation: *J. Chem. Phys.* **5**, 113 (1937); doi: 10.1063/1.1749988

View online: <http://dx.doi.org/10.1063/1.1749988>

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# The Deduction of Reaction Mechanisms from the Theory of Absolute Rates

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(Received October 7, 1936)

The limitations of the simple collision theory for reactions are discussed. The Menschutkin and related reactions are shown to involve the formation of an activated complex with an electric moment of a magnitude which is calculated for the various cases. The free energy of activation for proton transfer is found from the experiments on conductance in water and the dispersion effects on polarization in ice. A partition function for liquid H<sub>2</sub>O and D<sub>2</sub>O based upon experimental quantities is given. The abnormal rapidity of the denaturation of proteins in spite of an enormous activation energy is typical of reactions, involving the simultaneous breaking of many bonds.

## INTRODUCTION

WE shall use as the general equation for the specific reaction rate constant<sup>1</sup>

$$k' = \frac{\kappa kT}{h} \frac{F_a'}{F_n} \exp(-E_0/kT) \quad (1)$$

or the equivalent forms<sup>2</sup>

$$\begin{aligned} k' &= \frac{\kappa kT}{h} K^\ddagger = \frac{\kappa kT}{h} K^{0\ddagger} \left( \frac{\alpha_1 \alpha_2 \cdots \alpha_n}{\alpha^\ddagger} \right) \\ &= \frac{\kappa kT}{h} e^{-(\Delta H^{0\ddagger}/RT)} e^{\Delta S^{0\ddagger}/R} \left( \frac{\alpha_1 \alpha_2 \cdots \alpha_n}{\alpha^\ddagger} \right) \\ &= \frac{\kappa kT}{h} e^{-(\Delta F^{0\ddagger}/RT)} \left( \frac{\alpha_1 \alpha_2 \cdots \alpha_n}{\alpha^\ddagger} \right) \\ &= \frac{\kappa kT}{h} e^{-\Delta H^\ddagger/RT} e^{\Delta S^\ddagger/R} = \frac{\kappa kT}{h} e^{-(\Delta F^\ddagger/RT)}. \quad (2) \end{aligned}$$

The superscript zero indicates the standard state for the rate process. The other symbols are largely self-explanatory and in any case have been repeatedly defined in the literature so that we shall only define them here as use is made of them. If leakage through the barrier is important (but not too large) an additional factor  $(1 + 1/24(h\nu_n/kT)^2)$  should be introduced into the above equations, where  $\nu_n$  is the imaginary frequency associated with crossing the barrier.<sup>3</sup>

<sup>1</sup> H. Eyring, *J. Chem. Phys.* **3**, 107 (1935).

<sup>2</sup> a. Wynne-Jones and Eyring, *J. Chem. Phys.* **3**, 492 (1935); b. Evans and Polanyi, *Trans. Faraday Soc.* **21**, 875 (1935).

<sup>3</sup> Wigner, *Zeits. f. physik. Chemie* **B19**, 203 (1932).

If leakage through the potential barrier is very great, as for example in the rapid oscillation of ammonia between the two mirror image forms, we can best start from the specific rate expression in the form proposed by Tolman,<sup>4</sup>

$$k' = \frac{\sum k_i \rho_i \exp(-E_i/kT)}{\sum \rho_i \exp(-E_i/kT)}, \quad (3)$$

where  $k_i$ ,  $\rho_i$  and  $E_i$  are specific rate, statistical weight and energy respectively for the  $i$ th level. This can be written in the more convenient form

$$k' = F_n^{-1} \left( \sum k_i \rho_i \exp\left(-\frac{E_i}{kT}\right) + \frac{\kappa kT}{h} F_a' \exp(-E_0/kT) \right), \quad (4)$$

where we have added together the rates for the discrete levels and the continuum on our potential energy surface.

An interesting example of the solvent effect in preventing leakage is supplied by  $-CR_1R_2R_3$  which does not racemize in solution<sup>5</sup> but in the gas phase would probably racemize in a time not very different from the  $\sim 10^{-10}$  seconds required for ammonia. Thus we know that this radical does not exist in the free state, and should not be thought of as uncombined with solvent or other

<sup>4</sup> Tolman, *Statistical Mechanics*. (The Chemical Catalog Co., New York, 1927), p. 261. LaMer has used this equation to develop an expression for the temperature coefficient of the entropy of activation and related quantities; *J. Chem. Phys.* **1**, 289 (1933).

<sup>5</sup> Jones and Wallis, *J. Am. Chem. Soc.* **48**, 169 (1926).

molecules even for such very short times as  $10^{-10}$  seconds.

### The collision theory

It has been customary to interpret the specific reaction rate constant for bimolecular reactions by the equation

$$k' = PZ \exp(-E/RT) \quad (5)$$

where  $Z$  is the number of collisions calculated by using diameters more or less appropriate for momentum transfer,  $E$  is  $RT^2 d \ln k'/dT$ , and  $P$  is whatever is left over to make (5) true. Clearly there can be no objection to this on the basis of its correctness. The equilibrium constant for a reaction of the type



can be written as

$$K = \frac{k_i}{k_f} = \frac{P_i Z_i}{P_f Z_f} \exp((-E_i + E_f)/RT), \quad (7)$$

$$\text{i.e.,} \quad \frac{P_i Z_i}{P_f Z_f} = \exp(\Delta S/R). \quad (8)$$

Here the subscript  $f$  refers to the final products and  $i$  to the initial reactants. The  $E$ 's are defined as in (5). Since, in any actual case,

$$\Delta S = \int_0^T \Delta C_p dT/T$$

always depends on the temperature while  $Z_i/Z_f$  does not, then  $P_i/P_f$  must. Equating  $K$  of (7) to the statistical expression, one obtains

$$K = (F_f/F_i) \exp(-E_0/RT), \quad (9)$$

where  $F_i$  and  $F_f$  are the partition functions for the initial and final states and  $E_0$  is the excess energy of the final over the initial states at the absolute zero of temperature. The point to be emphasized is that (9) shows that  $K$  is inversely proportional to all the properties of the initial molecules, such as their diameters, frequencies, etc., which enter into the partition function  $F_i$ , while in (8), since the momentum transfer diameters are used,  $K$  is calculated as directly proportional to the collision diameters of the initial molecules. The two equations are to this extent contradictory and of course (9) is correct.

If one tries to remedy this by taking the reaction rate proportional to the actual diameters in the activated state and inversely proportional to those in the normal state, as one must as indicated in (9), one can get Eq. (1), but there then isn't much left of the collision theory in its original form.

In spite of these logical difficulties the collision theory is useful if it provides a way of estimating reaction rates with reasonable accuracy. It certainly will not give the rate correctly in both directions, however, unless it leads to the right value for the equilibrium constant. This is by no means a sufficient condition for a reaction theory to satisfy, but it is a necessary one. As an example we calculate the equilibrium constant for the reaction  $H_2 + I_2 = 2HI$  by both methods. Statistical mechanics gives

$$K = \frac{4r_3^4}{r_1^2 r_2^2} \frac{m_3}{(m_1 m_2)^{1/2}} \exp\left(\frac{2S_3 - S_1 - S_2}{R}\right) \times \exp\left(-\frac{\Delta H}{RT}\right), \quad (10)$$

where the entropy of vibration

$$S_i = R \left[ \frac{h\nu_i/kT}{\exp(h\nu_i/kT) - 1} - \ln \left( 1 - \exp \frac{-h\nu_i}{kT} \right) \right].$$

The collision theory gives

$$K = \frac{2\sigma_1 \sigma_2^2}{\sigma_3^2} \frac{m_3}{(m_1 m_2)^{1/2}} \exp(-\Delta H/RT). \quad (11)$$

Here the subscripts 1, 2 and 3 refer to  $H_2$ ,  $I_2$  and  $HI$ , respectively, and  $r$ ,  $\sigma$ ,  $m$ ,  $\nu$ , and  $\Delta H$  are the distance between atoms in the molecule, the collision diameter, molecular mass, molecular frequency and change in heat content, respectively. At 0°A Eq. (10) yields  $K = 37.4 \exp(-\Delta H/RT)$ , while, taking  $\sigma_1 \sigma_2^2 = \sigma_3^2$  (which seems as good a guess as any) we get from equation (11)  $K = 11.35 \exp(-\Delta H/RT)$ . At 440°C the collision value has not changed, while the correct expression has been decreased by the term  $\exp(-S_2/R)$  to  $K = 5.88 \exp(-\Delta H/RT)$ . This is not bad agreement with the collision theory value, and would be better at a higher temperature and of course much worse at lower ones. At constant volume  $\Delta E = \Delta H$ .

Since the activated complex is the same for the forward and the reverse reactions, it is possible to choose  $\sigma_1, \sigma_2 = \sigma_3^2$  equal to some value  $r^2$  such that one gets correct rates in one direction and almost the correct ones in the other, i.e., within a factor of 3 at 440°C. At least for some reactions  $r$  is about the kinetic theory collision diameter at reaction temperatures. For other reactions such a value of  $r^2$  will not be even approximately correct. The equilibrium  $N_2 + O_2 = 2NO$  illustrates one other shortcoming of the simple collision theory.<sup>5a</sup> In this case the entropy corresponding to the additional factor  $(2+4 \exp(-343.8/RT))^2$  must be introduced into (10) for the electronic states in the  $NO$  molecules. Thus, at 27°C statistical mechanics gives the value  $K = 297 \exp(-\Delta H/RT)$ , while the collision theory gives  $K = 2 \exp(-\Delta H/RT)$ . Certainly there is a better way of estimating ( $PZ$ ) than the collision theory for  $Z$  and no theory for  $P$ . Even if we had to guess the properties of the activated complex, just as we must guess collision diameters in the kinetic theory, at least by using (1) we avoid the inconsistencies of the collision theory. Eq. (1) necessarily leads to correct equilibrium constants for reactions. For further examples of large  $P$ 's in gas reactions see a paper by Bawn.<sup>6</sup>

In view of these considerations it must be clear that the procedure of taking a standard  $Z$  factor for gas reactions is of very doubtful significance. In the liquid phase there are added complications. It has been recognized that for reactions where the reactants are ionized while the products are not the same  $Z$  for both reactions is not to be expected. However, it has often been assumed that where two reactions are of the same type with respect to charge the  $Z$ 's and the  $P$ 's should be at least nearly the same, i.e., for such an equilibrium there should be very little change in entropy (cf. Eq. (8)). This is occasionally, but by no means always, true as Table I for proton migration reactions shows. The data in Table I were calculated from the work of White and Jones.<sup>7</sup> Many more are available but the above suffice for our purpose.

The first ten of these reactions simply involve

<sup>5a</sup> Gershinowitz and Eyring, J. Am. Chem. Soc. **57**, 985 (1935).

<sup>6</sup> Bawn, Trans. Faraday Soc. **32**, 178 (1936).

<sup>7</sup> White and Jones, Am. Chem. J. **44**, 159 (1910).

the transfer of a proton from some negative ion to one of its isomers, and should therefore fulfill the criteria for "similar reactions" as well as possible.  $\Delta S = 4.6$  e.u. corresponds to a ratio of 10 for the factor  $P_i Z_i / P_j Z_j$ . The assumption that this factor should be unity (nearly) for similar reactions is satisfactorily fulfilled in the case of reaction 9, but fails by factors of from 3 to 30 for the other ten reactions. In each of the first six reactions there is the alternative of hydrogen bonds forming between a carboxylate ion and some other group such as  $NH_2$ ,  $COOH$ ,  $OH$ , inside the molecule or forming this bond with the surrounding water molecules. The first alternative, if a satisfactory bond can be formed, will lead to the higher entropy for the dissolved acid molecule. This explains the higher entropies of the *ortho* over the corresponding *meta* ions, and that of the *meta* over the *para*, and of the *cis* over the *trans*. In the toluic acids where no internal hydrogen bond is possible the situation is reversed. Reaction (11) is about as serious a violation of the simple collision theory as we have found in this type of reaction. Here  $P_i Z_i / P_j Z_j = 2.5 \times 10^{-6}$ . Thus if this reaction obeys the collision theory in one direction it is off by almost a million times in the other. If the same collision diameter be taken for reactants as for products then the calculated value of  $Z_i / Z_j$  will be practically unity. It is not possible here to throw the responsibility for the small  $P$  on some nonthermodynamic quantity (such, for example, as failure to dissipate the activation energy). The different rates arise, rather from the fact that when butyric acid ionizes, the surrounding solvent molecules have the forces holding them increased by much more than do the water

TABLE I. For reactions of the type:  
 $acid_1 + ion_2 = ion_1 + acid_2$ .

No.	ACID	ION	$\Delta S$	$\Delta H$	$K$
1	<i>o</i> -amino-benzoic	<i>p</i> -amino-benzoate	6.29	1912	0.94
2	metanilic	sulfanilate	0.87	969	0.304
3	maleic	fumarate	4.84	-179	15.25
4	citraconic	mesaconate	3.23	42	4.70
5	salicylic	<i>m</i> -hydroxy-benzoate	5.87	208	13.28
6	salicylic	<i>p</i> -hydroxy-benzoate	6.79	-128	37.19
7	<i>o</i> -toluic	<i>m</i> -toluate	-3.19	-1484	2.45
8	<i>o</i> -toluic	<i>p</i> -toluate	-3.89	-1849	3.16
9	<i>n</i> -butyric	isobutyrate	0.16	26	1.034
10	<i>p</i> -toluic	phenylacetate	2.28	818	0.794
11	<i>n</i> -butyric	metanilate	-24.51	-5777	0.077
12	sulfanilic	hydroxide	17.62	-9775	$6.55 \times 10^{10}$
13	acetic	hydroxide	-3.57	-13750	$1.8 \times 10^9$

molecules surrounding the metanilic acid when its ionization occurs. Thus an ice-like sheath gathers round the butyrate ion as it forms. This sheath is at a lower "effective" temperature and is thicker than that which forms when metanilic acid ionizes. This is because in the latter ion the charge can distribute itself over a larger volume through a reorganization of the bonds in the aromatic residue, i.e., resonance between the different bond structures. The larger the sphere over which a charge is distributed the less the force with which surrounding molecules are held and the less the decrease in entropy as the ion is formed. We can then state the general proposition. *Any ion which can resonate between a variety of bond structures is provided with a mechanism which distributes the charge over a larger volume thus reducing the potential at the surface of the ion and therefore the binding with the solvent. As a result such ions exhibit a comparatively low entropy of ionization.* Conversely the entropy of ionization provides a criterion of the amount of internal bonding of a type not seriously restricting the freedom of relative motion of the parts which form the ion. This last qualification is necessary, since, for example, a hydrogen bond between two points on a long chain decreases the entropy more than if the two points made bonds with the solvent.

Frequently a reaction shows marked changes in the "collision factor" with a change in solvent. In general this is accompanied by a compensating change in the activation energy with the result that the over all change in rate is comparatively small. Using the language of Eq. (2) we can say that an increase (or decrease) in the entropy of activation,  $\Delta S^\ddagger$ , is in general accompanied by a more or less completely compensating change in the heat of activation,  $\Delta H^\ddagger$ , which leaves the free energy of activation,  $\Delta F^\ddagger = \Delta H^\ddagger - T\Delta S^\ddagger$ , but slightly changed. The explanation of this may be seen as follows: Suppose first we have the case in which two ions with unlike charge (or two polar molecules) combine to form a neutral molecule (or one with a smaller dipole moment). In polar solvents the ions will, of course, tend to be more solvated than the activated complex. This will result in a large value for the absolute entropy of activation. The point to be explained is why the changing of solvation by changing to a new

solvent will affect  $\Delta F^\ddagger$  much less than it affects  $\Delta S^\ddagger$ . When a liquid solidifies by freezing there is a large decrease in both the entropy and the heat content without *any* change in the free energy, the one exactly compensating the other. Now if all the forces between the molecules could be increased, the liquid would freeze at some higher temperature with, however, this same compensation between heat content and entropy. This is just what an ion or dipole does when it is introduced into a polar solvent. It increases the forces acting on neighboring solvent molecules, and if this increase is great enough, and the temperature not too far above the melting point of pure solvent, a certain number of solvent molecules "freeze," thus decreasing the entropy of the system but giving off a compensating heat of solidification which more or less completely balances the entropy change. Thus in transferring a mole of ions from one solvent to another where the forces between ions and solvent molecules will in general be different and where solvent melting points are different, there will, on the whole, be a different amount of solvent frozen before and after the transfer. This results in comparatively large changes in the partial molal heat content and entropy and a comparatively small change in the partial molal free energy. Thus, if  $S_{ij}$  is the partial molal entropy associated with taking a mole of reactant  $i$  from the gas phase and introducing it into solvent  $j$ , and if  $S_j^*$  is the same quantity for the activated complex, then the entropy of activation,  $\Delta S^\ddagger$ , in solvent  $j$  exceeds that in solvent  $k$  by the quantity

$$\begin{aligned}\Delta S_j^\ddagger - \Delta S_k^\ddagger &= S_j^* - \sum_i S_{ij} - (S_k^* - \sum_i S_{ik}) \\ &= S_j^* - S_k^* - \sum_i (S_{ij} - S_{ik}).\end{aligned}\quad (12)$$

Further

$$P_j Z_j / P_k Z_k = \frac{\kappa_j}{\kappa_k} \exp (R^{-1}(\Delta S_j^\ddagger - \Delta S_k^\ddagger)).\quad (13)$$

Here  $\kappa_j$  and  $\kappa_k$  are the transmission coefficients in solvents  $j$  and  $k$ , respectively. If a reaction involves changes in multiplicity, the paramagnetism of the two solvents would have an important effect on the  $\kappa$  values. Conceivably, also, the  $\kappa$  values may vary considerably due to a difference in the facility with which solvent molecules supply or absorb the energy of activa-

tion, but in the great majority of reactions in solution the important factor influencing this ratio seems to be  $\exp(R^{-1}(\Delta S_j^\ddagger - \Delta S_k^\ddagger))$ . Understanding this factor, as we have seen, reduces simply to understanding the change in partial molal entropy with change in solvent for the activated complex and for the reactants. Equations exactly analogous to (12) can be written for the difference in heat content and free energy in two solvents.

$$\Delta H_j^\ddagger - \Delta H_k^\ddagger = H_j^* - H_k - \sum_i (H_{ij} - H_{ik}), \quad (14)$$

$$\Delta F_j^\ddagger - \Delta F_k^\ddagger = F_j^* - F_k^* - \sum_i (F_{ij} - F_{ik}). \quad (15)$$

For the relative specific rates in the two solvents we obtain

$$k_j'/k_k' = (\kappa_j/\kappa_k) \exp((RT)^{-1}(-\Delta F_j^\ddagger + \Delta F_k^\ddagger)). \quad (16)$$

It is of interest to examine the experimental work of Muchin, Ginsberg and Moissejewa<sup>8</sup> who measured the rate of the addition reactions pyridine to benzyl bromide and triethyl amine to benzyl bromide to give the two corresponding salts. These reactions were each measured in benzene-alcohol mixtures and also in benzene-nitrobenzene mixtures, where the mole fractions of the solvent components were varied from 1 to 0. The free energy of activation

$$\Delta F^\ddagger = -[RT \ln k' - RT \ln kT/h] \quad (17)$$

of these are plotted against the reciprocal of the dielectric constant,  $1/D$ , in Fig. 1. Curve III of Fig. 1 is based on the work of de Hemptinne and Bekaert<sup>9</sup> on the Menshutkin reaction  $((C_2H_5)_3N + C_2H_5Br \rightarrow)$  measured in a benzene-acetone solvent, the mole fraction of both components being varied from 1 to 0. All the values are for 27°C, and the transmission coefficient,  $\kappa$ , is taken as unity. The free energies of activation are plotted against  $1/D$  since the Debye Hückel theory gives the expression

$$\frac{Ne^2}{2Da} - \frac{Ne^2}{3D} \left( \frac{4\pi\epsilon^2}{DkT} \sum_i n_i z_i^2 \right)^{\frac{1}{2}} \quad (18)$$

for the electrical work required to charge a mole of ions  $N$ . Here  $a$ ,  $e$ ,  $\epsilon$ ,  $n_i$ ,  $z_i$  are the radius of the

ion, its charge in electrostatic units, the charge on an electron, the number of ions of type  $i$  per cc, and the charge on the  $i$ th ion in multiples of the unit charge. At the beginning, at least, of the above reactions the last term of (18) is negligible, there being no ions. If we extrapolate curve IV (Fig. 1) to  $1/D=0$  we get 22.07 kcal. for the free energy of activation, while at  $1/D=1$  we get 25.65 kcal., an increase in  $\Delta F^\ddagger$  of 3.58 kcal. for the electrical part of the free energy of activation if it were carried out at unit dielectric constant, i.e., in the gas phase, as compared with its value if carried out in a solvent of infinite dielectric constant. We compare this value with  $Ne^2/a = 329.5/a$  kcal., the energy of charging up two ions with radii of  $a$  angstroms in a medium of unit dielectric constant. Since, if ions were formed, the ionic radii would not exceed a few angstroms and so give a very large energy of charging, the process of activation clearly does not involve the formation of ions, but does involve a considerable increase in the electric moment of the reactants. We next modify Kirkwood's Eq. (26) slightly<sup>10</sup> to obtain the electrical part of the free energy for a multipole, and combine such expressions for the reactants and the activated complex to obtain the free energy of activation,  $\Delta F_{D1}^\ddagger$  in a solution of dielectric constant  $D$ , where the value  $\Delta F_{11}^\ddagger$  is the value in a solution of dielectric constant 1. The relation is

$$\Delta F_{D1}^\ddagger = -N/2 \sum_{n=0}^{\infty} \frac{(n+1)(D-1)}{(n+1)D+n} \times \left[ \frac{Q_n^*}{b^{*2n+1}} - \sum_i \frac{Q_{ni}}{b^{2n+1}} \right] + G + \Delta F_{11}^\ddagger, \quad (19)$$

where the term  $G$  is the part of the free energy change (in going from  $D=1$  to  $D=D$ ) not depending on the electrostatic forces. Thus the relative solubilities of the reactants and the activated complex will change with composition of solvent due to changes in the van der Waals' forces and chemical combination with the solvent, and so contribute to  $G$ . Such effects are discussed in detail by Hildebrand.<sup>11</sup>

<sup>8</sup> Muchin, Ginsberg and Moissejewa, Chem. Zentr. II, 2376 (1926).

<sup>9</sup> de Hemptinne and Bekaert, Zeits. f. physik. Chemie 28, 225 (1899).

<sup>10</sup> Kirkwood, J. Chem. Phys. 2, 351 (1934). See also R. E. Bell, Trans. Faraday Soc. 27, 797 (1931).

<sup>11</sup> Hildebrand, Solubility (Reinhold Publishing Co., New York, 1936).

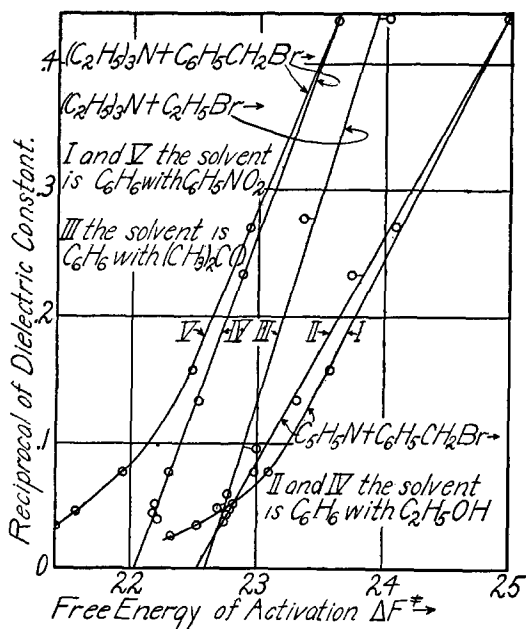


FIG. 1. Adding ethyl alcohol or acetone to benzene changes the rate of the above reactions only by changing the dielectric constant. Nitrobenzene has an additional effect.

In (19)  $N$ ,  $D$ ,  $b_i$  and  $b^*$  are Avogadro's number, dielectric constant, the radius of the hypothetical sphere from which a reactant molecule excludes solvent molecules, and the same radius for the activated complex. The subscript  $i$  is to be summed over all the reactants and the asterisk indicates the activated complex.

For a molecule with two charges,  $+e$  and  $-e$ , separated by a distance  $R$  and situated at equal distances,  $r$ , from the center of a spherical molecule with radius  $b$ , Kirkwood finds:

$$\begin{aligned} Q_0 &= (\sum e_i)^2 = 0, \\ Q_1 &= \mu^2 = \epsilon^2 R^2, \\ Q_2 &= 3\mu^2(r^2 - R^2/4), \\ Q_3 &= 6\mu^2(r^4 - 5r^2R^2/8 + 5R^4/48). \end{aligned}$$

$\mu$  and  $\epsilon$  are the electric moment of the molecule and the charge on the electron, respectively.

$$\begin{aligned} \text{Now } \frac{\partial(\Delta F_D^\ddagger)}{\partial(1/D)} &= \frac{ND^2}{2} \sum_{n=0}^{\infty} \frac{(2n+1)(n+1)}{((n+1)D+n)^2} \\ &\times \left[ \frac{Q_n^*}{b^{*2n+1}} - \sum_i \frac{Q_{ni}}{b_i^{2n+1}} \right] + \frac{\partial G}{\partial(1/D)}. \quad (20) \end{aligned}$$

From (20) we see that when  $\partial G/\partial(1/D)$  can be neglected and when  $D$  is reasonably large compared with the highest  $n$  that need be con-

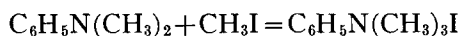
sidered, then  $\Delta F_D^\ddagger$  is a linear function of  $1/D$ . The reaction of benzyl bromide with triethyl amine and with pyridine in solvents varying from pure benzene to pure alcohol satisfy this linear relationship quite well. The same reactions are approximately linear up to moderate concentrations of nitrobenzene in benzene. We shall therefore use the following modification of (20) to estimate  $\mu^*$  of the activated complex from the slope of  $\Delta F^\ddagger$  against  $1/D$  at the point  $D=5$ . All  $Q$ 's except  $Q_1$  have been neglected since, in the reactions under consideration this is probably a good approximation.

$$\frac{\partial(\Delta F_D^\ddagger)}{\partial(1/D)} = \frac{24N^2D^2}{(2D+1)^2} \left[ \frac{\mu^{*2}}{V^*} - \frac{\mu_1^2}{V_1} - \frac{\mu_2^2}{V_2} \right]. \quad (21)$$

Here  $b$ , the hypothetical molecular radius, has been estimated by means of the equation  $8b^3N = V$ . Using (21) we calculate the values for  $\mu^*$  given in Table II. Here the subscript 1 refers to pyridine in I and II, and to triethyl amine in the other three. The subscript 2 indicates ethyl bromide in III and benzyl bromide in the remaining reactions.  $V^*$  is taken as the sum of the molal volumes of the reactants. Without a knowledge of the effect of pressure on reaction rate, or a calculation of the potential surface, this is the best we can do as an estimate of  $V^*$  and is probably not far from right. The fifth column gives the amount by which the free energy of activation in the gas phase would exceed that in a solvent of infinite dielectric constant if  $\partial F^\ddagger/\partial(1/D)$  were constant and had the value possessed at  $D=5$ . If the dielectric constant of the solvent and the moments of the reactants and activated complex were the whole story, then simply changing the solvent should make no difference in the values in column 5, i.e., I is to be compared with II and IV with V. At least, at  $D=5$  the change in dielectric constant seems to be the principal effect. At high concentrations of nitrobenzene (see Fig. 1) some additional factor enters which seems best interpreted as compound formation between the activated complex and the nitrobenzene. This might have been anticipated since the plot of dielectric constant against mole fraction of nitrobenzene when mixed with benzene shows a rise considerably more rapid than linear, indi-

cating association of the nitrobenzene. Such association may well be considerably more pronounced with a very polar substance such as the activated complex. Compound formation should be signaled by  $\Delta S^\ddagger$  becoming rapidly more negative with the added nitrobenzene and  $\Delta H^\ddagger$  decreasing and over compensating the entropy change. Fig. 2 shows that this is what happens in the case of pyridine reacting with benzyl bromide in a benzene-nitrobenzene solvent. Similar effects are present in the other cases. The significance of this for the "collision number" has already been discussed.

The values found for  $\mu^*$  as given in the last column of Table II are near those to be expected for the resultant molecule. Thus the activated complex must have very nearly the same configuration as the final molecule. That this is true in a closely similar reaction can be shown by comparing the entropy of activation and the entropy of reaction. Thus Essex and Gelormini's results<sup>12</sup> for the reaction



give  $\Delta S^\ddagger = -36.1$  and  $\Delta S = -37.06$  at  $60^\circ\text{C}$ .<sup>13</sup>

This also indicates that the activated configuration is very like the final one.

If ions are added to the reacting system we must add another term to (19) depending on the ionic strength. We then obtain

$$F_D^\ddagger = -\frac{N}{2} \sum_{n=0}^{\infty} \frac{(n+1)(D-1)}{(n+1)D+n} \left[ \frac{Q_n^*}{b^{*2n+1}} - \sum_i \frac{Q_{ni}}{b^{2n+1}} \right] + \Delta F_1^\ddagger + G + RT \ln \frac{\gamma^*}{\prod_i \gamma_i}, \quad (22)$$

where we refer back to Kirkwood's Eq. (21) for the explicit form of  $\gamma$ .

#### REACTIONS INVOLVING THE BREAKING OF HYDROGEN BONDS<sup>14</sup>

Bernal and Fowler<sup>15</sup> have given arguments for thinking of ice as possessing a structure such that

<sup>12</sup> Essex and Gelormini, J. Am. Chem. Soc. **48**, 882 (1926).

<sup>13</sup> Wynne-Jones and Eyring (J. Chem. Phys. **3**, 492 (1935)) give too large a value for  $\Delta S$  because of an incorrect interpretation of the equilibrium results of Essex and Gelormini.

<sup>14</sup> W. M. Latimer and W. H. Rodebush, J. Am. Chem. Soc. **42**, 1419 (1920).

<sup>15</sup> Bernal and Fowler, J. Chem. Phys. **1**, 515 (1933).

each oxygen is surrounded by four hydrogen atoms at approximately tetrahedral angles. Two of these hydrogen atoms are to be thought of as belonging to a particular oxygen atom and are about 0.95Å from it—the normal distance in steam—and the other two are about 0.86Å further away and belong to neighboring oxygens.<sup>16</sup> This same structure is assumed to persist in water near the melting point and to be superseded by a state of increasing disorder with rising temperature. Ionization results when an oxygen gains a third near hydrogen by one of its two far neighbors coming 0.86Å closer, leaving an O-H behind. The  $\text{H}_3^+\text{O}$  can now lose an  $\text{H}^+$  to each of three neighbors. The return migration of the one proton simply reverses the ionization. However, migration of the other two corresponds to migration of the  $\text{H}_3^+\text{O}$  and by repetition of the process the positive charge can travel to a distant electrode. In a similar way O-H by acquiring neighboring protons can transfer the negative charge to any distance. This process of a negative ion acquiring a proton from a neutral molecule is the type reaction considered in Table I, so that the free energy of activation  $\Delta F^\ddagger$  is a matter of considerable interest. The migration of a proton from  $\text{H}_3^+\text{O}$  to a neutral molecule is also of very wide occurrence. It is therefore important to ascertain what value the conductance gives for the free energy of activation.

If direct current is to be carried through water by proton transfer then since protons are liberated at one electrode and oxygen at the other, the process will come to a standstill unless some mechanism exists whereby protons after having passed from one oxygen to a neighboring one are then able to pass this oxygen. The rotation of molecules provides such a mechanism. Thus a combination of proton transfer with rotation of

TABLE II.

REACTION	$V_1$	$V_2$	$V^*$	$\frac{\partial(\Delta F^\ddagger)}{\partial(1/D)}$ CAL.	$\times 10^{18}$	$\mu^2$ $\times 10^{18}$	$\mu^*$ $\times 10^{18}$
II	80.5	118.9	200	5650	2.1	1.81	6.52
I	80.5	118.9	200	5050	2.1	1.81	6.30
IV	139.9	118.9	259	3650	0.8	1.81	5.48
V	139.9	118.9	259	4075	0.8	1.81	5.71
III	139.9	76.2	216	3150	0.8	1.83	5.11

<sup>16</sup> Pauling, J. Am. Chem. Soc. **57**, 2680 (1935).



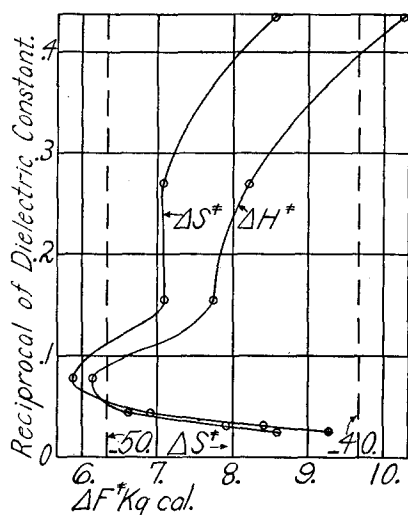


FIG. 2. Changes in  $\Delta H^\ddagger$  and  $\Delta S^\ddagger$  nearly compensate each other.

molecules constitutes one mechanism of conductance in water while the usual bodily transport of the ion is another.

Huckel,<sup>17</sup> Bernal and Fowler<sup>15</sup> and Wannier<sup>17a</sup> have discussed this process. If the barrier which the proton passes over is flat a classical treatment is sufficient for the reaction rate. If it were high, since it is certainly thin, quantum-mechanical leakage would be important and as Bernal and Fowler point out the abnormally large mobility of the hydrogen ion would in that case not be present for deuterium ion. Subsequently, Lewis and Doody<sup>18</sup> have shown that  $K^+$ ,  $Cl^-$  and acid ion have the mobilities 64.2, 65.2 and 315.2, respectively, in ordinary water and 54.5, 55.3 and 213.7 in heavy water. Thus the  $D_3^+O$  ion has nearly as great a mobility relative to  $K^+$  and  $Cl^-$  as  $H_3^+O$  has so that we are dealing with a very flat barrier. We therefore calculate the height of the potential barrier neglecting quantum mechanical leakage by a method similar to that of Huckel. Our treatment differs slightly from his in that we regard rotation of the molecules and proton transfer as two successive steps of the same process. The slower of the two steps is the rate determining one.

We first consider the frequency  $k'$  at which a proton crosses a barrier under an effective potential gradient of  $B$ . Using the theory of

absolute reaction rates we obtain:

$$k' = (\kappa kT/h) \exp(-(\Delta F^\ddagger - B23,060 \cos \theta 0.43 \times 10^{-8})/RT).$$

Here  $0.43 \times 10^{-8}$  is the distance to the top of the energy barrier, i.e., half the distance the proton must travel in crossing a symmetrical barrier.  $\theta$  is the angle which the particular hydrogen bond in question makes with the potential gradient. The factor 23,060 converts electron volts to calories. Effectively the distance the charge travels after the  $H_3^+O$  has rotated is from one oxygen center to the next, i.e.  $[18(6.06 \times 10^{23})^{-1}]^{1/3} = 3.1 \times 10^{-8} \text{A}$ . This distance must be multiplied by  $\cos \theta$  to give the distance traveled along the potential gradient. The average distance per second along the gradient which the charge is carried by each proton on  $H_3^+O$  is (averaging over all angles  $\theta$ ) then

$$\begin{aligned} & (\kappa kT/h) \exp(-\Delta F^\ddagger/RT) \int_0^\pi \exp(B23,060 \cos \theta \\ & \times 0.43 \times 10^{-8}/RT) \cos \theta \sin \theta d\theta \\ & \times \left( \int_0^\pi \sin \theta d\theta \right)^{-1} = (\kappa kT/h) \\ & \times \exp(-\Delta F^\ddagger/RT) 3.1 \times 10^{-8} 23,060 B \\ & \times 0.43 \times 10^{-8} (RT)^{-11/3}. \end{aligned}$$

The three protons give three times this value for  $H_3^+O$ . The molal conductance due to proton transfer is then

$$\begin{aligned} \Lambda' &= 96,500 (\kappa kT/h) \exp(-\Delta F^\ddagger/RT) \\ & \times \frac{3.1 \times 0.43 \times 23,060 \times 10^{-16} B}{RT} \\ & = 3.106 \times 10^3 \kappa B \exp(-\Delta F^\ddagger/RT). \quad (23) \end{aligned}$$

We take the transmission coefficient  $\kappa=1$ . By using (23) with Huckel's estimate for  $(\Lambda_H - \Lambda_{Na})$  as the molal conductance due to proton transfer  $\Lambda'$  where  $\Lambda_H$  and  $\Lambda_{Na}$  are the measured molal conductance of  $H_3^+O$  and  $Na^+$ , respectively, we obtain Table III.

There is considerable uncertainty as to what value should be taken for  $B$  the effective potential gradient along the potential barrier when the overall potential gradient is one volt per centi-

<sup>17</sup> E. Huckel, *Zeits. f. Electrochemie* **34**, 546 (1928).

<sup>17a</sup> C. Wannier, *Ann. d. Physik* **24**, 545 and 569 (1935).

<sup>18</sup> Lewis and Doody, *J. Am. Chem. Soc.* **55**, 2616 (1933).

meter.<sup>19</sup> Huckel assumed  $B = (D+2)/3$  where  $D$  is the dielectric constant which varies from 88.2 at 273°K to 47.1 at 429°K. Using this relationship at 298°K where  $D = 78.8$  we obtain  $\Delta F^\ddagger = 3350$  cal. Now if the slow process is the rotation of the molecules our formal expression for  $\Delta'$  would be but slightly changed and consequently we would obtain nearly the same value for  $\Delta F^\ddagger$ . Since we are measuring the slow process it seems clear that the free energy of activation for the reaction  $H_3^+O + H_2O = H_2O + H_3^+O$  is less than 3.5 kcal. and lies between this value and 1 kcal. The same treatment of the conductance of O-H will give a  $\Delta F^\ddagger$  for the reaction  $H_2O + O-H \rightarrow O-H + H_2O$  lying in this same range. The next to last row in Table III gives the heat of activation calculated from successive pairs of points if  $B$  could be taken equal to unity. Otherwise it must be corrected for the temperature dependence of  $B$ .

We next consider the relaxation time in ice as revealed by the dispersion of the dielectric constant.<sup>20</sup> Murphy<sup>21</sup> found that if  $\tau$  expresses the relaxation time of the polarized condition of the dielectric that the dispersion formulae obeyed in ice are

$$\epsilon' = \epsilon_\infty + \frac{\epsilon_s - \epsilon_\infty}{1 + \omega^2 \tau^2} \quad \text{and} \quad \epsilon'' = \frac{(\epsilon_s - \epsilon_\infty) \omega \tau}{1 + \omega^2 \tau^2},$$

where  $\epsilon'$  and  $\epsilon''$  are the real and the imaginary parts of the dielectric constant respectively. These are the formulae Debye showed<sup>22</sup> apply to rotation of molecules if the relaxation time of the individual molecules is given by

$$\tau_1 = \frac{\epsilon_\infty + 2}{\epsilon_s + 2} \tau. \quad (24)$$

Here  $\omega$  is  $2\pi$  times the frequency of the applied potential  $\epsilon_s$  and  $\epsilon_\infty$  are the dielectric constants for static and infinite frequency respectively. Murphy points out that the same formulae apply to a variety of types of polarization.

<sup>19</sup> J. G. Kirkwood, J. Chem. Phys. **4**, 539 (1936); Lars Onsager, J. Am. Chem. Soc. **58**, 1486 (1936); Hans Mueller, Phys. Rev. **50**, 547 (1936).

<sup>20</sup> Errera, J. de phys. **5**, 304 (1924); Smyth and Hitchcock, J. Am. Chem. Soc. **54**, 4631 (1932). We also want to express our appreciation for the opportunity of discussion with Professor Smyth.

<sup>21</sup> E. J. Murphy, Trans. Electrochem. Soc. **65**, 133 (1934).

<sup>22</sup> Debye, *Polar Molecules* (Chemical Catalog Co., 1929).

We shall now consider what Debye's model of dipoles orienting in an electric field enables us to say about the relaxation time. We write

$$\tau_1^{-1} = k' = \frac{\kappa k T}{h} e^{-(\Delta F^\ddagger / RT)} \quad (25)$$

the specific reaction rate for rotation. From (25) and Murphy's value of  $\tau$  calculated from  $\partial(\epsilon''/(\epsilon' - \epsilon_\infty))/\partial\omega$  we obtain Table IV.

In calculating  $\tau_1$  we used  $\epsilon_\infty = 2.2$  and used Murphy's Table II, column 5, to get  $\epsilon_s$ . There is the same kind of uncertainty in the formula to be used for calculating  $\tau_1$  from  $\tau$  that existed in the  $B$  for conductance. We, however, use the formula (24) proposed by Debye. Larger values of  $\tau_1$  of course would mean larger  $\Delta F^\ddagger$  values. The values calculated from Smyth and Hitchcock's experiments agree quite closely with Murphy's in spite of a considerable difference in the purity of the water used and in methods of measurement.

The free energy of ionization of water at the freezing point is  $\Delta F = 18.68$  kcal. Hence

$$\frac{(H_3^+O)(O-H)}{(H_2O)^2} = e^{-(\Delta F/RT)}$$

and if  $(H_3^+O) = (O-H)$  then  $(H_3^+O)/(H_2O) = e^{-(\Delta F/2RT)}$ . Now the concentration of ions in ice at the freezing point is probably not very different from that in water. Hence  $\Delta F/2$  is approximately equal to the free energy of activation  $\Delta F^\ddagger$  for the relaxation process. The concentration of activated complexes is therefore about the same as the concentration of  $H_3^+O$  and of  $O-H$  ions, i.e., about  $10^{-8}$  to  $10^{-7}$  times the concentration of water molecules. Our results for water show that proton conductance should set in for somewhat lower frequencies, i.e., such relaxation times will correspond to free energies of activation of about 1.5 to 3.5 kcal. higher than that for the relaxation times measured in ice. Debye has pointed out that the observed polarization with an applied

TABLE III.

$T$ (abs.)	273	291	298	323	348	373	401	429
H	222.5	314	350	465	565	644	722	777
Na	26	43.5	50.9	82	116	155	203	249
H-Na	196.5	270.5	299	383	449	489	519	528
$RT^2 \frac{d \ln k^\ddagger}{dT}$ cal.	2822	2482	1907	1430	886	636	211	
$\Delta F^\ddagger - RT \ln B$ cal.	1508	1431	1409	1352	1346	1389	1435	1521

potential of 1 volt/cm could be accounted for by one molecule in  $5 \times 10^6$  orienting. If the ions present in  $H_2O$  migrated toward the electrodes until space charge stopped them (even if there were no discharge) the apparent polarization and conductance would far exceed that observed. This is clear since if pairs of ions moved one space further apart under unit potential gradient it would approximately account for the observed polarization.

Since the observed polarization in ice is probably due to rotation, and therefore faster than proton transfer, our assumption that in water proton migration is slower than rotation and therefore is rate determining seems reasonable. This argument is far from conclusive, however. Thus the fact that  $H_2O$  in ice rotates with a lower free energy than the observed value for conductance in water does not, of course, prove that  $H_3O^+$  ions in water also rotate with a lower free energy of activation. As a matter of fact, Wannier<sup>17a</sup> from a comparison of his quantum-mechanical calculations with the experiments on conductance concludes that rotation is slowest. Whichever process is the slow one our conclusion that the free energy of activation for proton transfer is not in excess of about 3.5 kcal. is a necessary one.

Having considered the simplest reaction involving the breaking of a hydrogen bond we next consider another type—the vaporization of water. Since the activated complex is simply the vapor molecule, the rate of vaporization from a square centimeter of surface in moles per second is given by the expression  $\kappa C_g (2\pi mkT)^{\frac{1}{2}}$ , where  $\kappa$  is the transmission coefficient,  $C_g$  is the equilibrium vapor concentration in moles per cc, and  $(2\pi mkT)^{\frac{1}{2}}$  is the average velocity normal to the surface.<sup>22a</sup> The only novel feature in this calculation is the partition function used for the liquid

water,

$$F_l = \frac{(2\pi m_l kT)^{\frac{3}{2}}}{h^3} V_f (1 - \exp(-500hc/kT))^{-1} \times (1 - \exp(-167hc/kT))^{-2} F_{\text{vib}}. \quad (26)$$

Here  $m_l$  is the effective translational free mass,  $V_f$  is the free volume of the liquid and  $c$  is the velocity of light. The frequency  $500 \text{ cm}^{-1}$  is Cartwright's observed value<sup>23</sup> for the oscillation in which only hydrogen atoms move, interpreting his results in accordance with the model of Bernal and Fowler. He finds the corresponding frequency in  $D_2O$  to be nearly  $500 \times 2^{-\frac{1}{2}}$ . The oscillation  $167 \text{ cm}^{-1}$  is also his observed value for the other pair of approximately equal oscillational frequencies in which the effective mass is about that of the oxygen. He found this frequency to be not appreciably changed in heavy water. In our partition function for heavy water we take these frequencies to be  $167 \times (18/20)^{\frac{1}{2}} \text{ cm}^{-1}$ . Because of the way the water is constrained to oscillate by its neighbors the effective translational mass is considerably less than 18. The free volume is taken to be  $V_f = bT^n$ , where  $n$  is found to be 5.029 from the condition that  $(d/dT)(RT^2 d \ln F_l/dT) = 18.0$ , the molal heat capacity of water. For  $D_2O$  we use 18.32 for the heat capacity per mole. This gives  $n = 5.024$ . The value 18.32 was obtained by finding  $\Delta C_p$  for liquid over vapor from the vapor pressure measurements of Miles and Menzies<sup>24</sup> and adding this to  $C_p$  for gaseous  $D_2O$  assumed equal to Lewis and Randall's value for  $H_2O$  vapor.<sup>25</sup> Brown, Barnes and Maass<sup>26</sup> find by direct measurement a heat capacity for  $D_2O$  of 20. We are unable to reconcile these two results. The partition function

<sup>23</sup> Cartwright, Phys. Rev. **49**, 470 (1936).

<sup>24</sup> Miles and Menzies, J. Am. Chem. Soc. **58**, 1067 (1936).

<sup>25</sup> Lewis and Randall, *Thermodynamics* (McGraw-Hill, New York, 1923), p. 80.

<sup>26</sup> Brown, Barnes and Maass, Can. J. Research **12**, 699 (1925); **13B**, 167 (1935).

<sup>22a</sup> K. F. Herzfeld, J. Chem. Phys. **3**, 319 (1935).

TABLE IV.

T (abs.)	272.3	270.5	269.3	265.7	264.7	261.3	252.6	240.6	227.3	266.0	261.1	227.3
$\tau \times 10^8$	2.06	2.31	2.69	3.74	3.90	6.27	18.9	66.4	434	3.47	5.45	208
$T_l \times 10^7$	8.65	9.49	10.5	15.5	16.1	25.3	76.2	268	1750	19.3	23.2	964
$\Delta F^\ddagger$	8390	8390	8400	8490	8470	8620	8850	9010	9340	8610	8350	9070

for the gas is

$$F_g = \frac{(2\pi mkT)^{\frac{3}{2}} V 8\pi^2 (8\pi^3 ABC)^{\frac{1}{2}} (kT)^{\frac{1}{2}}}{h^3 2h^3} \times F_{\text{vib}} \exp(-E_0/kT). \quad (27)$$

$F_g = F_l$  so that we obtain for the concentration of light or heavy water in the gas:

$$C_g = \frac{1}{V} = \frac{p}{RT} = \frac{m^{\frac{3}{2}} 8\pi^2 (8\pi^3 ABC)^{\frac{1}{2}} (kT)^{\frac{1}{2}}}{2h^3 (m_l^{\frac{3}{2}} b) T^n \prod_{i=1}^3 (1 - \exp(-h\gamma_i/kT))^{-1} e} \times \exp(-E_0/kT), \quad (28)$$

where  $p$  is the vapor pressure. We use the moments for light and heavy water tabulated by Topley and Eyring.<sup>27</sup> Two quantities remain to be determined from the vapor pressures. These are  $E_0$  and  $(m_l^{\frac{3}{2}} b)$ . For  $\text{H}_2\text{O}$  these values are, respectively, 13042. calories and  $8.43 \times 10^{-14}$ , and for  $\text{D}_2\text{O}$  13426. calories and  $1.352 \times 10^{-13}$ . Here  $m_l$  and therefore  $m$  are in atomic units. Newton and Eyring<sup>28</sup> find that for a variety of gases the intermediate value of  $b$  is about  $10^{-14}$ , so that an effective translational mass for  $\text{H}_2\text{O}$  and  $\text{D}_2\text{O}$  of around 10 and 14, respectively, is reasonable. Table V shows the agreement between the experimental and the calculated vapor pressures. The experimental values for  $\text{D}_2\text{O}$  are those given by Miles and Menzies.<sup>24</sup> Since we have not taken account of holes as seems necessary to understand critical phenomena our equation must necessarily give too low vapor pressures at high temperatures.<sup>29</sup>

The abnormally large value of the entropy of vaporization of water arises from the fact that, unlike many liquids, the molecules are unable to rotate freely because of hydrogen bonds. The vapor pressure is about six times as large as for a normal liquid with the same heat of vaporization, and of course this appears as a correspondingly large value for  $\Delta S^\ddagger$  in the expression for the rate of evaporation.

<sup>27</sup> Topley and Eyring, *J. Chem. Phys.* **2**, 217 (1934).

<sup>28</sup> Newton and Eyring, *Trans. Faraday Soc.* In press.

<sup>29</sup> Eyring, *J. Chem. Phys.* **4**, 283 (1936).

TABLE V.

T°C	0	20	40	60	80	100	110	140
$\text{H}_2\text{O}$ obs.	4.58	17.54	55.3	149.4	355.1	760	1074.6	2710.9
	4.596	17.58	55.65	150.3	356.9	760.4	1070.5	2708.3
$\text{D}_2\text{O}$ obs.		15.06	49.13	136.4	331.6	722.3	1028.9	2640.4
		15.10	49.36	136.9	332.5	723.9	1026.4	2633.4

We now consider as our final example of a reaction with a really abnormal entropy of activation the denaturation of proteins. Such reactions have been discussed recently by Anson,<sup>30</sup> Mirsky and Pauling,<sup>31</sup> and by Wrinch.<sup>31a</sup>

The results for the rate of denaturation of hemoglobin and of egg albumin, both of which proceed unimolecularly are presented in a comprehensive survey of the subject by Chick and Martin.<sup>32</sup> Both are first order with respect to the proteins and from their results the following tables have been prepared.

Here the specific reaction rate is expressed in reciprocal seconds.

$$\Delta F^\ddagger = -RT \ln k' + RT \ln (kT/h)$$

$$\Delta H^\ddagger = -T^2 \frac{d}{dT} \left( \frac{\Delta F^\ddagger}{T} \right)$$

$$\text{and} \quad \Delta S^\ddagger = \frac{(\Delta H^\ddagger - \Delta F^\ddagger)}{T}.$$

The steric factor is  $\exp \Delta S^\ddagger/R$ . Clearly the activated complex possesses enormously greater randomness than does the original molecule. This must be due to the breaking of many bonds or the opening of rings or both.

The denatured molecule as well as the activated complex has a much greater entropy than the native protein as is shown by the equilibrium results of Anson and Mirsky on trypsin.<sup>33</sup> Thus their experimental results yield for the reaction native trypsin  $\rightarrow$  denatured at 45° the values  $\Delta F = -190$  cal.;  $\Delta H = -67,600$ ;  $\Delta S = 213$  e.u.

<sup>30</sup> Anson, *The Chemistry of Proteins*, Chap. IX, edited by C. L. A. Schmidt.

<sup>31</sup> Mirsky and Pauling, *Proc. Nat. Acad. Sci.* **22**, 439 (1936).

<sup>31a</sup> D. M. Wrinch, *Nature* **137**, 411; **138**, 241, 651 (1936).

<sup>32</sup> Chick and Martin, *Kolloid chemische Beihefte V*, 49 (1913).

<sup>33</sup> Anson and Mirsky, *J. Gen. Physiology* **17**, 393 (1934).

TABLE VI. Hemoglobin.

$T$ (abs.)	$k'$	$\Delta F^\ddagger$	$\Delta H^\ddagger$	$\Delta S^\ddagger$	STERIC FACTOR
340.7	$1.23 \times 10^{-3}$	24,700	58,000	98	$1.89 \times 10^{21}$
338.7	$7.33 \times 10^{-4}$	24,900	58,700	100	$5.14 \times 10^{21}$
335.7	$3.17 \times 10^{-4}$	25,300	60,300	105	$6.25 \times 10^{22}$
333.1	$1.55 \times 10^{-4}$	25,600	60,400	105	$6.25 \times 10^{22}$

Egg Albumin					
344.2	$1.18 \times 10^{-4}$	26,600	135,800	317	$6.66 \times 10^{68}$
346.1	$4.41 \times 10^{-4}$	25,850	140,900	332	$1.20 \times 10^{72}$
349.4	$25.4 \times 10^{-4}$	24,880	128,100	295	$1.11 \times 10^{64}$

Here the entropy change for the equilibrium falls in between the two previous values for the activated complexes. Unfortunately there are no data on the equilibrium and the reaction rate for the same reaction. One other well established fact is that acid and alkali affect both the equilibria and rates profoundly and this effect is usually to lessen  $\Delta F$ ,  $\Delta H$  and  $\Delta S$  each in much the same way as it affects the three corresponding rate quantities.

Mirsky and Pauling's suggestion that denaturation involves the breaking of hydrogen bonds provides a reasonable picture of the rate process. Let us assume that the 60,000 calories for  $\Delta H^\ddagger$  in hemoglobin comes from breaking 12 hydrogen bonds of 5000 calories each. If these are between an amino and a carboxyl group then since there is only an oscillation of these groups before the bond rupture while there is rotation afterwards we should expect an increase in entropy. The rotational entropies of an amino and carboxyl group are 4.1 and 7.4 e.u. respectively or 11.5 for the sum. Twelve such pairs would give an entropy of 138 e.u. Before comparing this with the observed 100 e.u. of activation we should subtract something for the oscillational entropy of the groups before rupture and add something for the increased freedom given the other groups. All we can say then is that the increase in entropy seems quite reasonable on the basis of the hydro-

gen bond mechanism. The same calculation for egg albumin gives 312 e.u. to be compared with 317 at 344.2° (abs.) with similar results at the other two temperatures. In estimating the entropy we have assumed the amino and carboxyl groups in the activated complex stage are unable to form new hydrogen bonds with water. In solutions containing acid, alkali or urea, however, such bonds probably do form causing  $\Delta H^\ddagger$  and  $\Delta S^\ddagger$  to drop greatly in such a way as to largely compensate each other and so give only moderate decreases in  $\Delta F^\ddagger$  as is observed.

The results on the heat and entropy of activation do not provide a basis for a decision between the hydrogen bond theory and the cyclization theories of Dr. Wrinch providing the latter bonds are not much stronger than the hydrogen bonds. The only requirement is that the bonds broken in denaturation are such as to provide a degree of randomness unusual in chemical reactions and more nearly comparable with the breaking of bonds three or four times as strong as those broken in the melting of ice.

In previous papers a steric factor of about  $10^{-6}$  for the unimolecular reaction by which a hexyl radical closes a five-membered ring simultaneously expelling a  $\text{CH}_3$  group has been calculated and compared with experiment.<sup>2a</sup> (See also reference 6 for additional examples.) In denaturation we have a factor acting in the opposite direction making the reaction abnormally rapid by a factor of about  $10^{22}$  and  $10^{70}$ , respectively. The activated complex theory provides a means of understanding these and of estimating the factor to be expected in other cases. The problems of reaction rates are, in fact, principally those already met in equilibrium problems, so that methods or information useful in one field have an obvious application in the other. Each peculiar type of equilibrium is apt to be exhibited somewhere as an equally peculiar reaction rate.

We want to thank Dr. Anson for many helpful discussions on denaturation.