

THE APPLICATION OF QUANTUM MECHANICS TO CERTAIN CASES OF HOMOGENEOUS CATALYSIS. I

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A. INTRODUCTION

Recently Eyring and Polanyi (1) have shown how the quantum mechanics can be used to calculate activation energies in good agreement with experimental values. These calculations apply to the large class of reactions which proceed without involving radiation at any step. The energy necessary to break and reform homopolar bonds comes from collisions, and, since the energy found to be necessary is usually not sufficient to break the bonds outright, the bonds must weaken each other as the reacting molecules approach. Thus, upon collision, certain bonds go over into new ones by an adiabatic process.

A very general and extremely satisfactory criterion of stability for any configuration of a system of atoms is the potential energy of this particular configuration with respect to that of slightly varied configurations. The lower the potential energy with respect to its values for the other configurations the greater the stability. This is a general thermodynamic criterion and does away with the necessity of trying to picture models of definite kinds of valence binding, though the usefulness and desirability of the latter from a psychological point of view may remain.

As an example there is plotted in Fig. 1 a graph showing how the potential energy of a system of any two nascent atoms (except those of noble gases) varies with their distance apart. Here it is seen that when the atoms are far apart the energy is constant; *i.e.*, further separation does not alter it. When they approach sufficiently closely, attractive forces begin to be effective and the potential energy decreases. Upon still further approach the curve passes through a minimum representing the most stable configuration, or the equi-

librium distance between the two atoms when the bond is formed. This can be determined in a particular case from X-ray diffraction data. The "depth" of the "trough" measured from the rim when the atoms are far apart is a measure of the stability and is related to the heat of dissociation of the bond. As the atoms approach even more

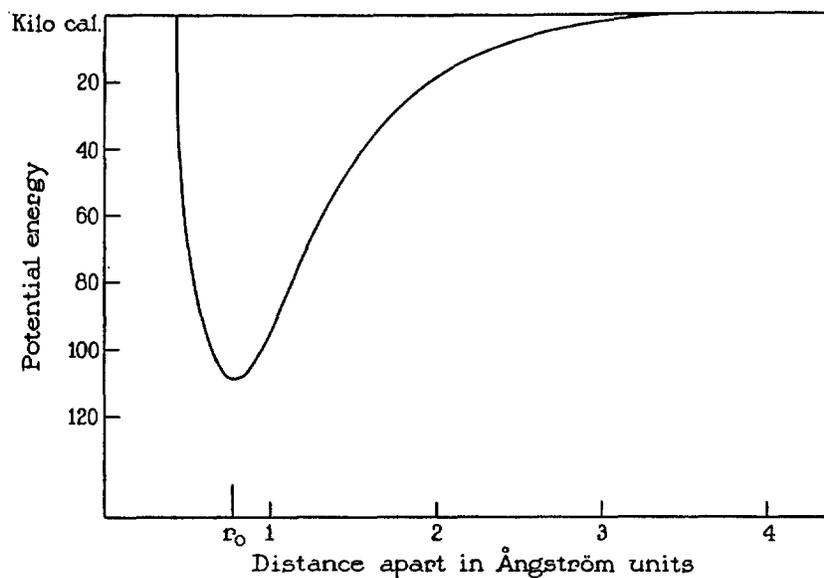


FIG. 1. A typical Morse curve. In this case it is drawn from data on the hydrogen molecule and represents the change in potential energy of the system (ordinates) as a function of the distance between the hydrogen atoms. The point of lowest energy (or greatest stability) comes at the equilibrium distance between the atoms in the ordinary molecule, and the depth of this trough is closely related to the heat of dissociation of the H—H bond; *i.e.*, the energy necessary to separate from a distance apart of r_0 to an infinite distance apart. Analogous curves quantitatively describing any bond of covalent nature between two atoms may be drawn from the proper data.

closely they begin to repel each other strongly, and the potential energy rises very sharply. Curves of this kind which quantitatively describe bonds between any pair of different atoms may be constructed from known data by a simple function proposed by Morse (2) and are called Morse curves.

If, instead of two nascent atoms, two molecules approach and undergo reaction the picture is different. Consider the reaction

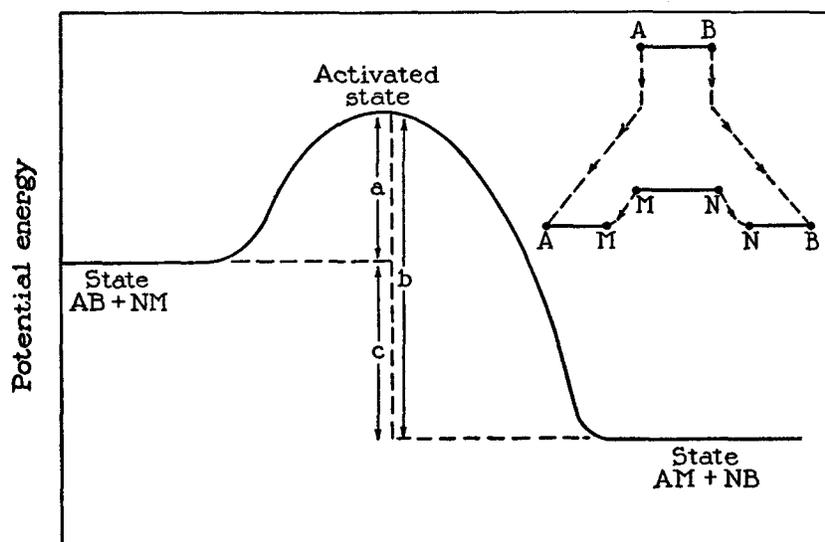
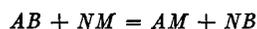


FIG. 2. Showing the change in potential energy (ordinates) of a system of two molecules, AB and NM , as reaction to form AM and NB takes place. Abscissae may be thought of as giving the course of reaction. AB and NM must approach to within a certain distance before any change in energy takes place (left horizontal portion of curve). During reaction the energy rises and then falls to a constant value for the new molecular system AM and NB . The height a measures the activation energy for the reaction AB plus NM equals AM plus NB , while the height b measures this same quantity for the reaction in the reverse direction. The height c is a measure of the heat of reaction. It is exothermic in one direction (as written above) and endothermic to the same extent in the other.

The physical process is pictured in the upper right hand corner.

If we plot the total potential energy of the various configurations of the four atoms, A , B , M , and N , as this reaction proceeds, we obtain the curve given in Fig. 2. Following the course of this curve it will be noted that as molecules AB and NM approach from sufficiently large distances apart there is at first no change in total potential energy

and the curve is flat. Upon closer approach there is a *rise* in potential energy which increases as reaction proceeds until a maximum value is reached. The rise in the curve may be pictured as due to the fact that the incipient breaking of the original bonds against their *full* bond strength is pitted against the incipient formation of new bonds which do not reach their full bond strength until completely formed. The height of the "hill" above the original plain is a measure of the heat of activation and the state of the system at the summit is the activated state. It is a state of "indecision." If the original molecules possess enough energy to carry them over the hill the reaction goes on to completion, if they possess insufficient energy the reaction does not go and they merely collide without reaction.

In passing, one or two facts may be pointed out. (a) In general the heat of activation will not be the same for the reverse reaction as for the original one. The difference, *i.e.* the difference in height of the two flat portions of the curve, is a measure of the heat of reaction. (b) The heat of *activation* is the principal factor in determining whether a reaction will proceed spontaneously or not. (c) The heat of *reaction* is more directly concerned with how nearly a statistical system of reacting molecules will undergo complete reaction before equilibrium is reached. Thus if the heat of *reaction* is zero the heat of activation is the same in either direction and, in the particular example cited equilibrium would be reached, starting with chemically equivalent amounts of reagents, when the reaction had proceeded half way to completion. Such considerations are for statistical systems only. In the individual event the reaction either does or does not go to completion.

Naturally the most satisfactory method of determining any magnitude in which we are interested is by direct experimental measurement. As a second choice we measure some related magnitude whose connection with the one desired involves a minimum of inference. With thermal measurements one runs into many difficulties. It is true that the heats of most reactions might conceivably be directly measured. But these values involve only the system before any reaction has started and after it has gone entirely to completion and give us no information about the *reacting* system. In very simple cases activation energies can be measured. Experimental determinations here

usually involve reaction velocities and thus presuppose a knowledge of reaction mechanism, since, if a reaction takes place in steps it is the velocity of the slowest step which is the determining factor. Even when these values can be given a definite significance, however, they tell us only the maximum height of the "potential hill" (Fig. 2) and say nothing about the course of the reaction nor the configuration of the system in the activated state. Furthermore, since they involve measurements at different temperatures one runs into the possibility that the limiting, or slow step at one temperature may not be the same as that at the other temperature.

By the method of Eyring and Polanyi one calculates the potential energy of any specified configuration of atoms. Even in the present unperfected state the information obtainable in this manner is of high value. Thus, for a particular postulated mechanism of reaction, the complete course from start to finish can be followed; by a sufficiently exhaustive study the actual mechanism can be ascertained (from the possible mechanisms one eliminates all except one, *i.e.* that of lowest activation energy); the calculations are based on very fundamental experimental data of a general nature.

The quantum mechanics has uncovered a hitherto unsuspected source of binding energy—a resonance of electron pairs between atoms due to a rapid interchange of electrons among themselves. This gives a more definite picture of the electron pair bond. The energy of any configuration is, then, given in terms of two contributions—an electrostatic force, always attractive and usually termed the coulombic part, and a resonance force, which may be either attractive or repulsive, depending on whether the electrons are paired or not, usually called the interchange contribution. The pairing of electrons may be roughly thought of as due to the fact that they are all spinning and are thus small magnets. The binding, of course, does not arise from this magnetic effect but is an electrical attraction. Only two electrons of opposite spins pair, and any other electron is then repelled. In the ordinary bond it is found that about 14 per cent of the bond strength is due to the coulombic contribution and about 86 per cent to the interchange. The particular distribution between these two factors makes no difference on any initial or final state of the system but is of significance in the activated state as the value of the activation energy is appreciably affected by this distribution.

By this method calculations are fairly easily made for systems containing four reacting atoms, and they can be quite practically made for those containing five or six atoms. For larger molecules the *complete* problem is, in practice, almost impossible of solution. Even here, however, much valuable information can be obtained by confining oneself to the *reacting groups*.

When we make this simplification the most important factor we are neglecting is the steric effect of the non-reacting parts of the molecule. Such effects are of much more importance in some cases than in others. They are particularly important for certain classes of organic reactions.¹

B. Catalysis

Specific reaction velocities can obviously be increased in two ways. The number of molecules possessing sufficient energy to surmount the barrier, or potential hill, may be increased. The temperature effect on reaction velocity comes through this mechanism, and, as is well known, data from temperature coefficients of reaction velocities are the basis of the ordinary method of measuring activation energies. There may, however, be varying environmental conditions which alter the height of the barrier. These are catalyzing conditions, the catalyst being negative if the height be increased and positive if it be decreased.

The statement was made above that the distribution of energy between coulombic and resonance was quite significant in the activated state; *i.e.* when the system is just at the top of the hill. Large polarizabilities resulting in appreciable permanent dipoles, as well as extra charge due to ionized condition of reacting groups, play a rôle in increasing the per cent of the total energy which is coulombic, and therefore in changing the height of the hill. This energy can be estimated as

$$- \sum \frac{e_i e_j}{r_{ij}}$$

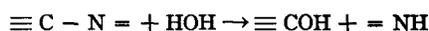
i.e., the product of each pair of charges over their separation in a

¹ In certain cases even these effects can be treated by quantum mechanics and the author has some specific cases under investigation.

dielectric of unit constant. The sum is of course algebraic and is a repulsion for like charges and an attraction for opposite. In any other dielectric medium the constant must be considered, which, for water at the distances involved, approaches the optical value of 3 in place of the static value of 80, which is the constant for larger distances of separation (3).

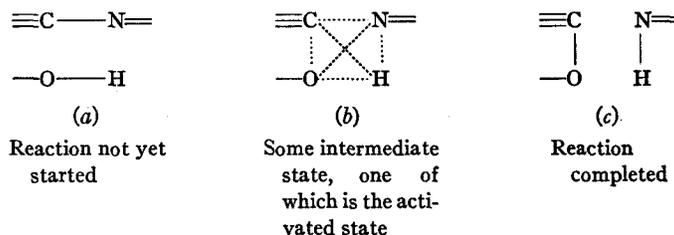
C. Hydrolysis of the Carbon-Nitrogen Linkage

The reaction



was investigated. Thus we are in reality investigating the hydrolytic splitting of a C—N bond and neglecting steric effects of the other groups attached to the carbon and nitrogen. If to the former there is attached a carbonyl oxygen and to the latter one hydrogen we have essentially the peptid linkage. Were we to be interested in the absolute values of the activation energies in this paper such steric effects should not be neglected, though they are by no means easy to estimate.² In this paper, however, we shall be interested in catalytic effects, *i.e.* in lowerings of activation energies rather than in their absolute magnitudes, and the results, it is felt, can be thought of as applicable to the peptid linkage even though the nature of the particular substituents attached to the C and the N are not specified.

The reaction may be diagrammatically indicated as follows:



As the O—H group approaches the C—N group these two linkages tend to weaken and other linkages begin to form namely C—O, C—H,

² Even in such cases the order of magnitude can be obtained. Thus from some unpublished calculations it is found that substitution of a C—O for a C—H bond on one of the carbons of a C—C bond lowers the activation energy necessary to break the C—C bond by about 3 kilo cal.

N—O, and N—H. These are only incipient tendencies and furnish only a small amount of energy whereas the breaking of the original O—H and C—N bonds must be accomplished against their full strength. Thus the potential energy of the system will rise with the approach of the reacting groups so that they will be repelled unless they have sufficient kinetic energy to balance this repulsion. The minimum energy required is the energy of activation. It is the energy just necessary to carry the reacting system over the potential hill (Fig. 2).

Now the binding energy, E , of a configuration of four atoms involving one valence each is given by the expression

$$E = A_1 + A_2 + B_1 + B_2 + C_1 + C_2 + \sqrt{\frac{1}{2}[(\alpha_1 + \alpha_2 - \beta_1 - \beta_2)^2 + (\alpha_1 + \alpha_2 - \gamma_1 - \gamma_2)^2 + (\beta_1 + \beta_2 - \gamma_1 - \gamma_2)^2]} \quad (1)$$

Where $A_1 + \alpha_1$ (see Fig. 3) is the total binding energy of one of the atom pairs and is a function only of the distance apart of this pair. This is directly read from the corresponding Morse curve for the particular atom pair. The same thing is true for $B_1 + \beta_1$, $B_2 + \beta_2$, $C_1 + \gamma_1$, etc. Here the A 's, B 's, and C 's give the coulombic energies and the α 's, β 's, and γ 's give the interchange energies. The distribution of energy in ordinary cases has been found to be 14 per cent coulombic to 86 per cent interchange. Thus it is a comparatively simple matter to get the energy of any configuration. To obtain the activation energy one calculates the energies for a number of configurations as the O—H and the C—N groups approach, varying all the factors including angle of approach. One can then construct a potential surface or series of surfaces and the lowest potential hill over which it is *necessary* for the reacting system to go will measure the activation energy.

The equation proposed by Morse to give the potential energy, E , of a pair of atoms as a function of their distance apart, r , (see Fig. 1) has the form

$$E = D' (2e^{-a(r-r_0)} - e^{-2a(r-r_0)})$$

Here D' is the heat of dissociation of the bond, D , plus the half quantum of vibrational energy it has in its lowest state; *i.e.*, $\frac{1}{2} h w_0$, where w_0 is the vibration frequency in the lowest level. r_0 is the equilibrium

value of r in the fully formed bond, and a is given by $a = 0.1227 w_0 (M/D')^{\frac{1}{2}}$, M , the reduced mass being defined by

$$M = \frac{M_1 \cdot M_2}{M_1 + M_2}$$

M_1 and M_2 being the atomic weights of the two elements forming the bond.

Table I gives the constants used in obtaining the Morse curves for the various bonds involved in the reaction here studied. D and D' are in kilogram calories, r_0 is in Ångström units, and w_0 in wave numbers.

For this reaction the activation energy comes out about 31.9 kilo cal. The potential energy change during the course of reaction is

TABLE I
Constants Used in Morse Equation

Bond	D	D'	r_0	a	w_0
C—N	66.4	67.87	1.47	2.090	1035
C—H	92.3	96.46	1.12	1.874	2930
C—O	81.8	83.27	1.43	1.940	1034
N—H	96.9	101.55	1.06	2.050	3270
N—O	38.5	40.2	1.36	3.357	1191
O—H	113.1	118.3	0.97	2.135	3660

given in Fig. 4, Curve A. The ordinates are potential energy values of the reacting system while abscissae cannot be so easily defined. They really represent the succession of configurations of the system during the course of reaction for which the potential energy is a minimum. The curve consists of two horizontal parts and a center hill. The abscissae along the left hand horizontal part may be thought of as giving the approach of the two original groups, and, those along the right hand horizontal part as giving the separation of the products formed in the reaction. The abscissae in the center give configurations during reaction. Complete graphical representation would require a four dimensional figure and the points on the curve in Fig. 2 are taken from such a figure (or series of three dimensional ones) and selected to give the lowest potential hill over which the reaction must go.

In passing it may be pointed out that the center of the hill seems in reality to be the floor of a shallow basin whose rim is somewhat over 3 kilo cal. above the floor. This might mean a hydration with corresponding heat of dissociation. The interpretation in any case is suggestive. Thus dissociation of this rather unstable complex in one direction would yield water and a peptid while in the other direction it would yield a substituted amine and an alcohol or carboxyl. In the present case this basin is of little importance as its depth is small compared with the height of the hill which must be surmounted before reaching it. However, were the hill itself significantly lowered the same basin would attain much significance and might represent the type of bond which obtains, for example, in the reaction between proteins and dyes. The factors which alter the height of this hill will be treated in the next section. But further consideration of the basin will not be included in the present paper.

D. Catalytic Effect of Hydroxide and Hydrogen Ions on Reaction

The mechanism of the catalytic effect of these ions can be ascribed to a redistribution of charge either entirely or in part by induced polarization, with a consequent increase in coulombic attraction and concomitant lowering of total potential energy. Qualitatively it may be seen at once that the hydroxide ion may be expected to have the greater effect for here we can definitely locate one electronic charge on the oxygen of the reacting O—H group whereas the hydrogen ion produces its effect by induced polarization.³

The calculations under these conditions are by no means as straight forward as for the first case, the results of which have been given above. It is thus worth while to indicate their nature. In the calculations referred to in Section C, the distribution of coulombic and

³ It may be questioned why, if we view the hydrogen ion as essentially OH_3^+ , we might not have the charged hydrogen as an essential constituent of the reacting O—H group with, at first sight, even greater catalytic effect than the hydroxide ion. A writing out of the reacting configuration, however, would show that as the reaction goes to completion one of the other O—H bonds in the OH_3^+ would also have to be broken and for a hydrogen more remote from the reacting one, which is very improbable. The actual effect of this ion may better be looked upon as an induced coulombic effect.

interchange energy was taken as 14 per cent and 86 per cent respectively of the total energy. This has been found experimentally to hold in many of the cases studied. For a bond between two hydrogen atoms where induced polarization is small Sugiura (4) finds a corresponding distribution of 10 per cent to 90 per cent and this changes with polarizability being 22 per cent for the Li—Li bond (5) and 28.3 per cent for the Na—Na bond (6). We shall therefore take 10 per cent and 90 per cent as a starting value and correct for additional coulombic energy. The assignment of charges can be approximated by a knowledge of the dipole moments of the bonds. From the values for these moments (7) the following charges were assigned to the atoms of the reacting groups.

$$\begin{aligned} \text{C} &+ 1.2 \times 10^{-10} \text{ e.s.u.} \\ \text{O} &- 0.6 \times 10^{-10} \text{ " " } \\ \text{N} &- 1.0 \times 10^{-10} \text{ " " } \\ \text{H} &+ 0.33 \times 10^{-10} \text{ " " } \end{aligned}$$

For the activated configuration (Fig. 3) the coulombic energy in kilogram calories per mol is

$$\left(\Sigma - \frac{e_i e_j}{r_{ij}} \right) \frac{14.35}{3}$$

if e is given in e.s.u. and r is in Ångström units. Here 3 is the optical dielectric constant of the medium. This added coulombic energy in the case of the activated configuration amounts to 5.52 kilo cal. This would bring the coulombic per cent from 10 per cent to 13.6 per cent giving an activation energy of 32.7 kilo cal. in place of the 31.9 kilo cal. obtained by using the 14 per cent to 86 per cent distribution. Thus it is thought that one can in this way get a reasonable order of magnitude for catalytic effects.⁴

⁴To verify this it is merely necessary to take the distances given in Fig. 3 and read off the various bond energies from corresponding Morse curves. If R_1, R_2, \dots, R_6 are these readings and if X and Y are the respective fractions giving coulombic and interchange energy then Equation 1 may be written

$$E = X [R_1 + R_2 + \dots + R_6] + Y \sqrt{\frac{1}{2} [(R_1 + R_2 - R_3 - R_4)^2 + (R_1 + R_2 - R_5 - R_6)^2 + (R_3 + R_4 - R_5 - R_6)^2]}$$

In this form the adjustment of X and Y and E for induced coulombic energy becomes quite simple.

Table II gives basic data from which the extra coulombic energy in the polarized systems, *i.e.*, in presence of H^+ or OH^- , are calculated.

Values of α are obtained by assigning the same refraction to every electron in the valence shell of an atom and assuming all unshared electrons to be polarized with the bond. Thus the C—O \vdots bond refraction = $\frac{1}{4} C + 5/6 O$ where C and O are atomic refractions of carbon and oxygen respectively. For alkaline solutions, where the charged oxygen would not polarize its own bond with appreciable increase in energy, the polarized bond would be N—H in configuration 3 and C—N in configuration 10, for examples. The configurations are numbered arbitrarily as plotted as abscissae in Fig. 4 and one of them,

TABLE II

Bond	Atomic distances in Ångström units					Bond polarizability $\alpha \times 10^{24}$
	Equilibrium	Configuration No.				
		3	4	7	10	
C—O	1.43	1.50	1.50	1.60	1.70	0.89
C—N	1.47	1.64	1.63	1.45	1.41	0.77
N—H	1.06	1.06	1.12	1.18	1.18	0.94
O—H	0.97	1.59	1.40	1.10	0.97	1.05
C—H	1.12	2.03	1.90	1.74	1.68	0.65
N—O	1.36	2.07	2.07	1.97	1.96	1.17

configuration 4, is shown in Fig. 3. They are merely different successive configurations of minimum potential energy assumed by the system as the reaction takes place. In the case of acid solutions, where the proton itself is not part of the reacting system, two bonds will be polarized for every configuration; *e.g.*, C—O and N—H in configuration 3, C—N and O—H in configuration 10, etc.

The induced atomic charges, e_a , are calculated from the relations

$$\mu = \alpha F = e_a r$$

(μ = induced dipole moment) whence

$$e_a = \frac{\alpha F}{r}$$

α = polarizability, F = field intensity in e.s.u., and r = distance in centimeters.

But

$$F = \frac{e_p}{3r^2}$$

e_p = polarizing charge in e.s.u., and 3 = dielectric constant in water at distances involved in the configurations studied. Tables

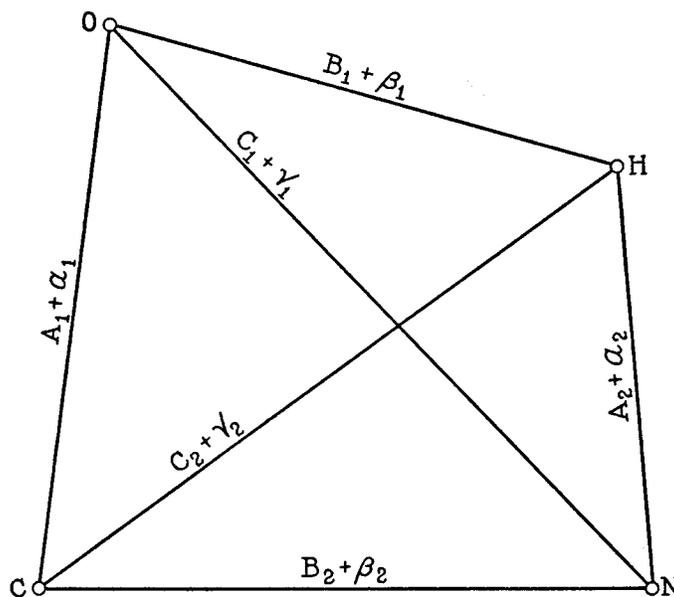


FIG. 3. One of the configurations of the system, drawn to scale, for which the energy was calculated. This, in fact, was the configuration of highest energy, or the activated configuration, for the case under consideration.

may be made for various values of r and thus of F giving the induced and total charges for any configuration. For hydroxide ion a conservative estimate, for all configurations studied, of the value of r is about 2 Å.u. (see bottom row of Table II). This approaches very near to the actual conditions, and Table III contains the results of calculations for certain of the configurations on such a basis.

These energy values (the last column of Table III) are plotted as

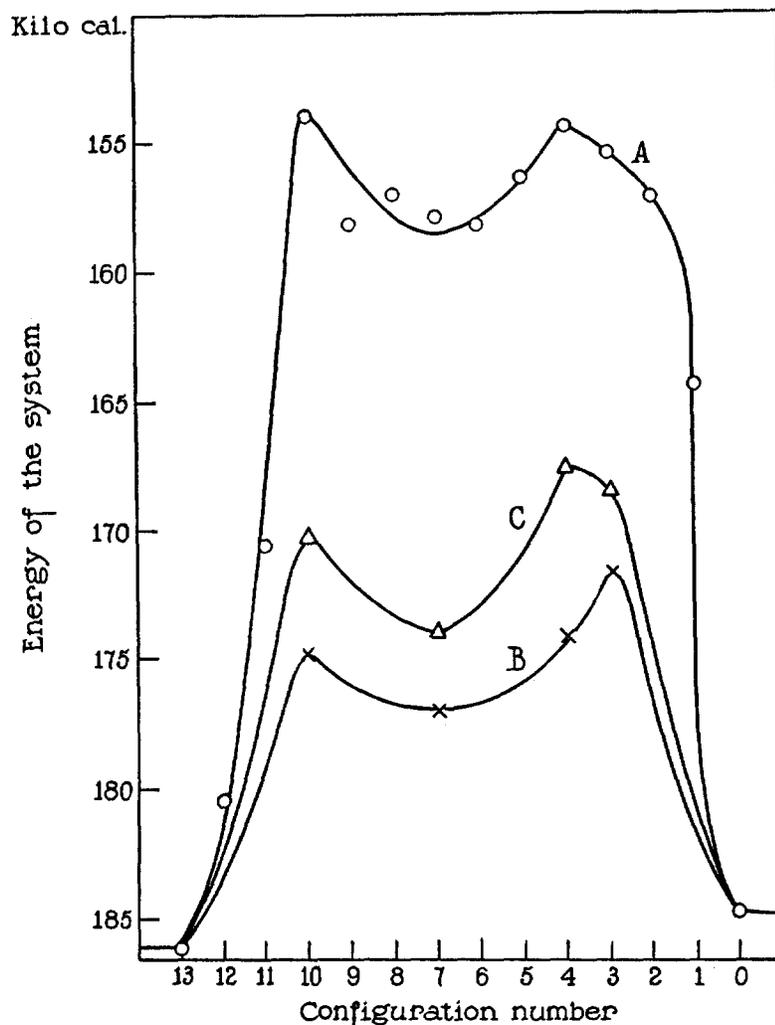


FIG. 4. Showing the potential energy (ordinates) of the system as the reaction $C-N + O-H = C-O + N-H$ takes place. Abscissae represent a succession of configurations of minimum potential energy through which the system must pass in the course of the reaction. Their numbering is arbitrary and happens to correspond to that according to which the reaction was originally worked out. In this figure, configuration 13 represents the state of the system before reaction has begun, and configuration zero the state after the reaction has been completed. Curve A is for neutral water in absence of OH^- or H^+ ions (an ideal case), Curve B is for reaction in alkaline solution, and Curve C for reaction in acid solution. In Case A, configurations 4 and 10 are nearly indistinguishable and the activation energy could be obtained from either. In Case B configuration 3 is the activated state, while in Case C configuration 4 is the activated state. As shown here the reaction is almost isothermic, being endothermic to the extent of about 1.4 kilo cal.

Curve B in Fig. 4. The heat of activation is $186.2 - 171.7 = 14.5$ kilo cal. This value should not be compared directly with the value, *ca.* 32, for neutral water since the OH ion concentration will always be much lower than the effective water concentration in dilute aqueous solutions. Should we arbitrarily take the latter value as 55, then

TABLE III

Hydroxide Ion Catalysis

$F = 4 \times 10^5$ e.s.u. corresponding to polarizing distance of 2 Å.u.

Configuration	Charge $\times 10^{10}$ e. s. u.				Polarized Bond	Polarization coulombic energy	Total energy of configuration
	C	N	O	H			
Before reaction	—	—	—	—	—	<i>kg. cal.</i> —	<i>kg. cal.</i> -186.2
3	Induced....	—	0.34	—	0.34	N—H	-20.0
	Total*.....	1.2	1.34	4.77	0.67		-171.7
4	Induced....	—	0.34	—	0.34	N—H	-20.9
	Total.....	1.2	1.34	4.77	0.67		-174.1
7	Induced....	0.22	0.22	—	—	C—N	-18.4
	Total.....	1.42	1.22	4.77	0.33		-177.0
10	Induced....	0.14	0.14	—	—	C—N	-18.8
	Total.....	1.34	1.14	4.77	0.33		-174.8
After complete reaction	—	—	—	—	—	—	-184.8

* This total charge is obtained by adding the induced charge to the fundamental dipole charges given above. The essential correctness of these values is rendered highly probable since they are in agreement *independently* with the dipole moments involved and the basic 14-86 distribution of coulombic to interchange energy in the neutral system.

Table IV would give the apparent relative activation energies at various pH values.

With acid catalysis we proceed in the same manner. While the problem is slightly more complicated than in the case of alkaline catalysis much of the uncertainty is eliminated by the fact that there

will be no interchange repulsion in the case of the proton. For configurations 3 and 4 it will form part of a substituted ammonium ion while for configuration 10 it will form part of an oxonium ion. Only

TABLE IV

pH	Apparent activation energy
(Non-ionized water)	<i>kg. cal.</i>
10	31.9
11	22.8
12	21.3
13	20.0
14	18.5
	17.0

TABLE V
Acid Catalysis

Configu- ration	Charge $\times 10^{10}$ e.s.u.				Polarized bonds	F	Polarization coulombic energy	Total energy of configura- tion	
	C	N	O	H					
3	Induced.....	0.18	0.89	0.18	0.89	$\left\{ \begin{array}{l} \text{C—O} \\ \text{N—H} \end{array} \right.$	3×10^6 10^6	<i>kg. cal.</i> -16.9	<i>kg. cal.</i> -168.5
	Total.....	1.38	1.89	0.78	1.22				
4	Induced.....	0.18	0.84	0.18	0.84	$\left\{ \begin{array}{l} \text{C—O} \\ \text{N—H} \end{array} \right.$	3×10^6 10^6	<i>kg. cal.</i> -15.8	<i>kg. cal.</i> -167.6
	Total.....	1.38	1.84	0.78	1.17				
7									-174.0*
10	Induced.....	0.17	0.17	1.08	1.08	$\left\{ \begin{array}{l} \text{C—N} \\ \text{O—H} \end{array} \right.$	3×10^6 10^6	<i>kg. cal.</i> -15.8	<i>kg. cal.</i> -170.3
	Total.....	1.37	1.17	1.68	1.41				

* In this configuration neither N—H nor O—H are near their equilibrium bond distances apart (see Table II) so one cannot definitely place the proton either on the N or on the O. Arbitrary calculation on the one assumption leads to a value -173 kilo cal. for the total energy of the configuration while -175 kilo cal. is obtained on the other assumption. This is of minor importance since configuration 4 is the activated state here.

in such a configuration as 7 will there be much doubt, and so far as activation energy is concerned this is of less importance than 4 or 10 (the former being the activated configuration under these conditions).

Thus from the structure of the ammonium ion and oxonium ion we can fairly definitely locate the polarizing charge. Table V gives results for acid catalysis analogous to those of Table IV for alkaline catalysis. We now have two bonds polarized and with different values of field intensity, as the proton will belong either to the ammonium or the oxonium system and will not be symmetrically placed.

The heat of activation, then, is 186.2 – 167.6 or 18.6 kilo cal. These results are plotted as Curve C, Fig. 4.

E. Relative Catalytic Effects of Hydroxide and Hydrogen Ions

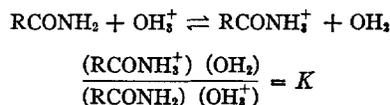
The activation energies of hydroxide and hydrogen ions are, then, respectively 14.5 and 18.6 kilo cal., a difference of 4.1 kilo cal. If pH were in both cases a measure of the effective concentrations this would correspond, at 40°C., to relative speeds of hydrolysis of

$$\frac{4100}{e^{626}} = 700.$$

However, while pH is such a measure for hydroxide ion as it enters as one of the reagents, it is not so for hydrogen ion whose effective concentration is much greater than the value given by pH. This statement must not be interpreted as meaning that catalytic effect in acid solutions is independent of pH. Rather the difference in the two ionic effects can be pictured as follows: The maximum effect of OH ion comes when it enters as one of the reagents rather than plays a purely inductive rôle. As such the pH would measure its effective catalytic concentration. The hydrogen ion, on the other hand, catalyzes by purely induced charges on the reacting atoms. pH measures its activity throughout the solution, but there may be a tendency for it to concentrate selectively at the reacting points in the molecules. If by hydrogen ion one means strictly oxonium ion there will be no such tendency, but if one means, more loosely, proton, then the formation of a basic nitrogen as the hydrolysis proceeds would induce proton concentration in the sense of the proton transferring from oxonium ion to a sort of substituted ammonium ion. If, for a particular configuration such as the activated one, the distribution ratio of proton between water and nitrogen of the substituted ammonia remains sensibly constant, then, even though the catalytically effective con-

centration of proton may differ from that given by pH measurement, nevertheless the change in reaction velocity with hydrogen ion concentration will be proportional to the change of the latter as measured by pH. Thus to get at this effective H ion concentration, even though in a rough way, one must investigate the distribution of proton between water, and a properly substituted ammonia.

In the activated state, configuration 4, we have practically an acetamide nitrogen. Thus we have



But

$$(\text{OH}_3^+) = \frac{K_w}{(\text{OH}^-)}$$

or

$$\frac{(\text{RCONH}_3^+) (\text{OH}^-)}{(\text{RCONH}_2)} = \frac{K K_w}{(\text{OH}_2)} = K_b \text{ and } K = \frac{K_b (\text{OH}_2)}{K_w}$$

where K_b is the basic ionization constant of the amide.

Now at 40.2°C. (8) K_b for acetamide is 3.3×10^{-14} , for acetanilide it is 4.4×10^{-14} , and for urea 3.7×10^{-14} . K_w is *ca.* 3×10^{-14} . Thus, approximately,

$$K = (\text{OH}_2) = 55$$

and the effective concentration of hydrogen ion is not far from 55 times its actual concentration. This would cut down the speed ratio of OH^- to H^+ catalyzed hydrolysis from 700 to around $\frac{700}{55}$ or 13.

One might expect therefore this speed ratio to lie between 13 and 700 and much nearer to the former value at 40°C.⁵

⁵ It may well be suggested that this argument about the proton distribution would not apply to such a configuration as 10 where the O—H separation has its equilibrium value of 0.97 Å.u. and N—H has a separation too great to give it the consideration of an amide configuration. In this case where no doubt the effective and actual H^+ concentration must be considered the same the energy of the system is lower, -170.3 kilo cal. in place of -167.6 for configuration 4.

It is very suggestive that the results of Northrop (9) on the hydrolysis of gelatin at 40° show that, for sufficiently high hydrogen or hydroxide ion concentrations, the velocity ratio, which has been calculated for splitting the peptid linkage as between 13 and 700 and probably much nearer the former value, seems to be about 30.

In nearly neutral solutions the hydrolysis proceeded some 300 to 400 times as rapidly as predicted by linear dependence on H^+ or OH^- concentration. This was attributed to a difference in specific reaction rate between the ions of gelatin and the "uncombined" material though no reason for this was suggested at the time. A ratio of 300 at 40° corresponds to an activation energy difference of about 3.6 kilo cal., an amount easily possible and perhaps due to a combination of two factors. The shortening of protein "spirals" in the isoelectric condition (10) may involve both steric effects in interchange repulsions and valence angle changes. Both involve energy. The order of magnitude may be seen by the facts that: (1) substitution of a C—O bond for a C—H in ethane decreases the activation energy required for hydrolytic breaking of the C—C bond by over 3 kilo cal. (11); the actual rotation of a methyl group about the C—C bond axis in methane through 60° from the stable configuration involves about 0.34 kilo cal. (12); a distortion of 5° in the angle of directed valence in a water molecule involves about 8 kilo cal. (12), etc. Thus, during the pH range through which gelatin is passing from the anion state through the isoelectric state and into the cation state there may well be a goodly portion of this range where the reaction velocity for hydrolysis is nearly independent of pH.

The results of Wijs (13) fit into this picture very suggestively. The bonds involved are not identical, but the values of r_0 are strikingly nearly the same so that the activated configurations will differ only very slightly. This is shown in Table VI. Now in such a case we might well expect the relative effects of OH^- to H^+ to be very nearly

The 55-fold increase mentioned above would correspond to an apparent energy change in the system of 2.5 kilo cal. bringing configuration 4 to an apparent value of -170.2 so that it does not drop under configuration 10. In other words passing through configuration 10, even though we cannot speak of higher effective H^+ concentration, will not "hold up" the reaction with respect to configuration 4.

the same *except* that we have now no amide group to alter the effective H^+ ion concentration. Wijs found, at about $25^\circ C.$, that the OH^- ion was some 1370 times as effective as the H^+ ion. This corresponds to a difference in activation energies of 4.3 kilo cal. as compared with 4.1 kilo cal. calculated here. This does not, of course, mean that the activation energies of the two hydrolyses are the same but that the calculation of the relative catalytic effects of H^+ and OH^- should be the same were it not for the amide N in the activated state of the peptid hydrolysis.

In a second paper the possible prosthetic action of certain groups will be considered from the point of view of their dipole effect on the coulombic energy of an activated configuration.

TABLE VI

Bonds involved in peptid hydrolysis		Bonds involved in hydrolysis of methyl acetate	
Bond	r_0	Bond	r_0
	Å. u.		Å. u.
C—O	1.43	C—O	1.43
C—N	1.47	C—O	1.43
O—H	0.97	O—H	0.97
N—H	1.06	O—H	0.97
C—H	1.12	C—H	1.12
N—O	1.36	O—O	1.32

SUMMARY

1. The activation energy for the hydrolytic breaking of a peptid linkage has been calculated from quantum mechanical considerations.
2. The relative catalytic effects of H^+ and OH^- and the mechanism of these effects have been calculated and discussed.
3. These effects are both qualitatively and semiquantitatively in agreement with experiment.

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