

THE APPLICATION OF QUANTUM MECHANICS TO CERTAIN CASES OF HOMOGENEOUS CATALYSIS

II. CERTAIN ASPECTS OF ENZYME ACTION

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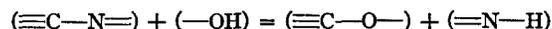
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(A) In a previous paper (1) the catalytic effect of H^+ and OH^- ions on the hydrolytic splitting of the C—N linkage was investigated by means of quantum mechanical considerations. In this paper will be reported investigations as to the effect of foreign rigid dipoles on the energy of the activated configurations, and thus on the energy of activation. If the latter is lowered a positive catalytic effect is noted, and such a dipole might conceivably constitute the prosthetic group of an enzyme for the reaction in question.

The specific problems and method of attack may be briefly sketched as follows:

Given some configuration (we shall limit ourselves to the activated one) of the atoms involved in the reaction



(*i.e.* under certain specific conditions this may represent the hydrolysis of a peptide link), and a separate dipole which may be made to assume and maintain any arbitrary position with respect to this configuration as diagrammed in Fig. 1, then:

1. What will be the nature of the effect of the dipole on the potential energy of the reacting system?

2. How close can the dipole approach the reacting configuration before the increase in potential energy of the six atom group (*i.e.* original four atom system plus the two atoms of the dipole) due to incipient interchange repulsions renders further approach impossible?

3. To what extent may such a dipole alter the activation energy of a reaction?

As examples of dipoles, arbitrary to be sure, we shall consider the C—O (of a carboxyl group for instance), the N=O of a nitro group and the N—H of an amino group, and study their effect in acid and alkaline solutions, since hydrolysis in solutions containing neither H nor OH ion is an idealized case.

(B) The effect of the dipole AB on the energy of the reacting system can be best thought of as consisting of two factors. If it approach sufficiently near it will begin to form part of the reacting system. The bond $A—B$ will begin to weaken and bonds $A—N$, $A—H$, $A—C$, $A—O$, $B—C$, etc., will begin to form and we have a six atom reaction.

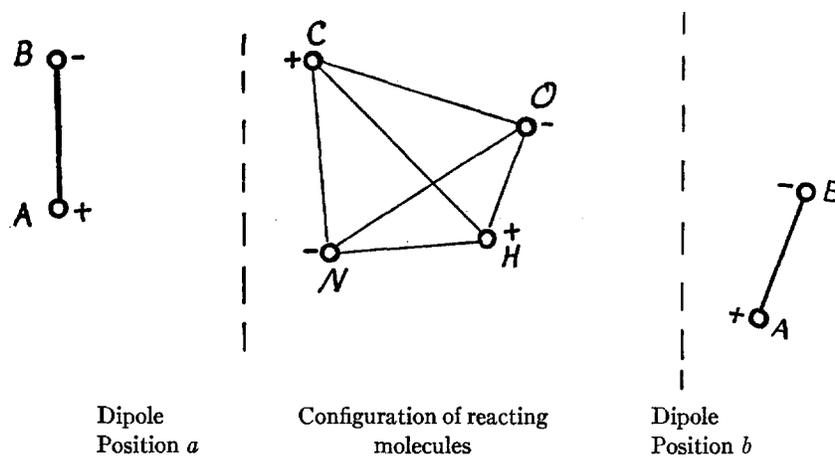


FIG. 1

In general the potential energy of the entire system will rise greatly. On the other hand, if it remains at a sufficient distance its only effect will be an electrostatic or dipole effect on the four atom reacting system. This effect may either increase or decrease the potential energy of the four atom system. As drawn in Fig. 1, Position a , the dipole would increase the potential energy of the reacting configuration. This can be easily seen since there would be an attraction for the C—N group and a repulsion of the O—H group. This means that the reacting configuration of four atoms would be less stable than in the absence of the dipole, or, in other words, the O—H group would have to possess a greater amount of energy to approach the C—N to this position. Such an effect would be a negative catalytic effect. However, were

the dipole AB rotated through an angle of 180° in the plane of the paper a different condition of affairs would result. In such a case the group $C-N$ would be repelled and the $O-H$ group attracted. The net result would be a decrease in the potential energy of the system and positive catalysis should occur. The question remains as to the quantitative significance of the above pictured effects.

(C) The first question which must be answered is how close the catalyzing dipole may approach the reacting system and still be treated separately and not as part of the reacting system. This is done by studying the change in energy of the *six atom* system as the dipole is brought up from an infinite distance. Details of calculation of this secondary problem are not given since it involves the setting up of a secular equation in the form of a symmetrical five row determinant, and the solution of this for the lowest root for every value of dipole distance. Table I gives results of such calculations for the different dipoles approaching the reacting group as shown in Fig. 1 but oriented in every case so as to give a positive catalytic effect. It will be noted that the effect described is a maximum when the dipole is in the same plane as the reacting system. Therefore the values of the dipole distance, r , are taken in the sense of distance from the nearer "edge" of the reacting system, and the dipoles are arbitrarily directed to have the line joining their constituent atoms parallel in every case with this nearer "edge."

From the last column of Table I it will be noted that, while the potential energy does not increase much up to an approach of about 3 Ångström units, the increase is very rapid beyond that and thus the actual approach will depend, among other things, upon the supply of energy available to overcome this repulsion.¹

¹ It is the purpose of the present paper to show that, given the dipole in proper position, the activation energy of the four electron system will be lowered; but not to investigate the cause of the dipole taking such a position against repulsive forces as given in Table I. It is reserved for a future paper to investigate the possible nature of combination between enzyme and substrate from a quantum mechanical point of view. The starting point will be suggested by the nature of the curves of Fig. 4 of the previous paper (1), where especial emphasis will be laid on the basin or saddle in the middle of the curves. If conditions were found such that the entire hill were sufficiently lowered but the basin retained, one might conceivably have the necessary energy for a practically unactivated loose combination between enzyme and substrate.

(D) The effect of these dipoles is therefore investigated from an arbitrarily chosen distance of 3 Ångström units from the reacting system. One could conceivably proceed directly by ordinary dipole theory, having located the elementary dipoles at the proper place between the two atoms involved. The disadvantage of such a method in the present instance lies in the fact that, in aqueous solution, we are

TABLE I

Dipole	Distance of dipole from reacting group	Energy of six atom group	$\Delta E = E_{\infty} - E_r$
	Å.u.	kg. cal.	
C—O (Position a, Fig. 1)	∞	238.7*	—
	4.0	237.5	1.3
	3.5	236.4	2.3
	3.0	233.5	5.2
	2.5	225.4	13.3
	2.0	209.9	28.8
	(Position b)	3.0	233.8
N=O (Position a)	∞	326.6*	—
	4.0	326.1	0.5
	3.5	325.5	1.1
	3.0	323.8	2.8
	2.5	318.4	8.2
	2.0	305.7	20.9
	(Position b)	3.0	324.2
N—H (Position a)	∞	257.0*	—
	3.0	253.0	4.0
	(Position b)	3.0	255.0

* These values for $r = \infty$ are merely the sums of the energy of the activated configuration of the four atom reacting system and the respective bond energies of the dipole bonds.

dealing with distances such that the dielectric constant of the medium is changing rapidly with distance. It was therefore thought better to calculate the magnitude of this dipole relief of stress from

$$- \sum \frac{e_i e_j}{\epsilon r_{ij}} \cos \theta$$

Where ϵ is the dielectric constant and θ is the angle between the dipole and the line joining the charges e_i and e_j the summation being taken

to decrease the potential energy of the four electron system as explained above. Table II gives the basis for choosing the values of dielectric constant as a function of distances (2).

The magnitude of the charges assigned to the C, O, N, and H of the reacting group and of the C—O and N—H dipoles were those worked out in the previous paper (1). In addition, from the effect of the nitro group on the dipole moments of nitro substituted compounds

TABLE II

$r, \text{Å.u.}$	2.0	2.5	3.0	3.5	4.0	4.5	5.0	5.5	6.0
ϵ	3.0	4.0	5.0	6.5	8.0	12.0	17.0	21.0	27.0

TABLE III

Dipole	Position (see Fig. 1)	Reaction	Dipole effect	Lowering of activation energy
			<i>kg. cal.</i>	<i>kg. cal.</i>
C—O	<i>a</i>	Alkaline	0.92	1.1
	<i>b</i>	"	17.3	16.9
	<i>a</i>	Acid	1.1	1.5
	<i>b</i>	"	1.7	2.3
N=O	<i>a</i>	Alkaline	4.7	5.0
	<i>b</i>	"	-0.97	-1.0
	<i>a</i>	Acid	2.1	2.9
	<i>b</i>	"	3.2	4.4
N—H	<i>a</i>	Alkaline	0.3	0.5
	<i>b</i>	"	3.8	4.2
	<i>a</i>	Acid	1.6	2.2
	<i>b</i>	"	0.72	1.1

(3) the charge $+4 \times 10^{-10}$ was assigned to the N of the N=O and -2×10^{-10} to the O, and the added assumption was made that these were not appreciably affected by acidity or alkalinity of solution.

The results of these calculations are given in Table III. In all cases the distance of dipole from the nearer side of the reacting system is 3 Ångström units.

It is realized that the dipoles, their positions, and distances, as given in Table III, are arbitrarily chosen, and that perhaps some of the positions may not be probable ones, but the significant fact brought out is that, given such conditions, there will result a lowering of the

potential energy of the reacting configuration by the amount in the last column. This would result in a specifically increased reaction velocity of from 6- or 7- fold to some 4700-fold at room temperature, and in one case (the second figure) the reaction would be practically instantaneous unless some other configuration should become, in this instance, the activated one.

(E) Northrop and Kunitz (4) have stated that "at present there is no direct evidence of the existence of any peculiar prosthetic group in these active proteins" (*i.e.* pepsin or trypsin) "not found in other proteins, and it is quite possible that their activity depends on some peculiar arrangement of the amino acids." The considerations presented in the present paper demonstrate, it is thought, that groups found in ordinary proteins may be capable of active catalysis if they can be properly placed with respect to the reacting system which is being catalyzed. Some of the necessary functions of the "peculiar arrangement of the amino acids" would, then, be to furnish, with the substrate, enough energy of combination to overcome the repulsive forces encountered by the dipoles in assuming an "active position," as well as to furnish such dipoles at the proper points. The latter named function would involve specific arrangements and is not amenable to general treatment, but the source of enzyme-substrate combination may be investigated and it is hoped in a final paper to indicate the possible source of such bonding.

REFERENCES

1. Stearn, A. E., *J. Gen. Physiol.*, 1934-35, **18**, 171.
2. Debye, P., *Polar molecules*, New York, The Chemical Catalog Company, Inc., 1929.
3. Smyth, C. P., *Dielectric constant and molecular structure*, New York, The Chemical Catalog Co., 1931.
4. Northrop, J. H., and Kunitz, M., *Ergebn. Enzymforsch.*, 1933, **2**, 117.