## Co-operative Activation

A CONSIDERABLE number of examples of chemical reactions in organized condensed systems have been observed to occur with activation energies greater than those normally associated with the temperature range at which the reactions occur. These reactions are: (1) the denaturation of proteins, where activation energies of 50–150 k.cal. have been reported[1], (2) $CaCO_3.6H_2O \rightarrow CaCO_3 + 6H_2O$ [2], (3) $K_2SO_4.Cr_2(SO_4)_3 24H_2O \rightarrow K_2SO_4.Cr_2(SO_4)_3 12H_2O + 12H_2O$ [3] and (4) the production of detonation nuclei in solid explosives[4]. On the other hand, in many solid reactions there is no marked deviation from the Polanyi-Wigner equation, the rate in molecules per sq. cm. being given by $\nu.e^{-E/RT}.N$. Thus there is no very large deviation in the case of $Ag_2CO_3 \rightarrow Ag_2O + CO_2$ [5] or $CuSO_4 5H_2O \rightarrow CuSO_4 3H_2O + 2H_2O$ [6], and in exothermic solid reactions; the following figures bear out the same point.

| | Temp. ° C. | Rates (mols./cm.² sec.) | |
|---|---|---|---|
| | | Calc. | Exp. |
| Lead azide | 270 | $1{\cdot}2 \times 10^{13}$ | $5{\cdot}3 \times 10^{15}$ [7] |
| Potassium azide | 251 | $2{\cdot}0 \times 10^{13}$ | $1{\cdot}7 \times 10^{15}$ [8] |
| Nitrogen iodide | −19 | $8{\cdot}5 \times 10^{11}$ | $6{\cdot}6 \times 10^{14}$ [9] |
| Barium azide | 115 | $1{\cdot}8 \times 10^{17}$ | $3{\cdot}1 \times 10^{15}$ [10] |

In all these cases, the thermal decomposition is believed to be simple, the unit processes involving at the most the decomposition or the liberation of one or two molecules. For the decomposition of calcium carbonate hexahydrate, the discrepancy is $10^{23}$ and for chrome alum $10^{11}$ times. For the denaturation of proteins, the discrepancy is variable and sometimes much larger, It would, therefore, appear that the abnormal cases are those for which a large number of molecules or chemical bonds are involved in the unit reaction.

It is possible to explain the rapid rates of these abnormal processes as due to co-operative activation of a number of points $n$ on the surface within a short time interval $\tau$, the activation energy required at each point being $E/n$, where $E$ is the measured activation energy. The magnification of the rate which is thereby attained depends, in a complex fashion, on the type of organization involved, on the number of points $n$ which are activated, the number of points $m$ out of which $n$ are chosen, but is independent of the value of $\tau$. For crystalline substances, $\tau = 1/\nu$, where $\nu$ is the frequency of lattice vibration ($= 10^{13}$ sec.), but for colloidal substances in aqueous media $\tau$ may be so low as $10^{-8}$ sec.

If we consider the 100 face of a cubic lattice with four adjacent lattice points composing a co-operative group, then it can be shown that the rate of reaction is approximately $10^3$ times greater than that for the process of activation of one point with the energy $E$. For five adjacent lattice points the magnification is approximately $10^4$. If we increase either $m$ or $n$ appropriately, then the magnification can be increased to factors of the order of $10^{23}$, which was found for the decomposition of calcium carbonate hexahydrate. In order to obtain magnifications of the correct order, it appears to be necessary to increase $m$, the number of lattice points out of which the $n$ points are chosen. This would mean that the activated points are to be spread over a relatively wide area. Only in the case of detonation nuclei is there any evidence bearing on this point, and this indicates in lead azide and nitrogen iodide that the activated points are spread over an area relatively great compared with the ionic diameter.

For the denaturation of proteins, the process is depicted as the disruption of a small number of bonds within a small time interval of approximately $10^{-8}$ sec., out of a relatively large number distributed over the surface of the protein molecule, the activation energy for the breaking of each bond being $E/n$. If in this case $m$ is 100 and $n$ is 4, then the magnification will be $10^8$ times. For the decomposition of hydrates, the co-operative activation is regarded as being spread over the surface of the crystal, activation occurring at key points in the lattice, the loss of water from these points which follows the activation being imagined to cause the breakdown of the lattice over a relatively wide area.

An alternative mechanism is one proposed by Eyring and Stearn[1], which ascribes the high rates of reaction to the occurrence of high entropy change on passing from the reactant to the activated complex. On the basis of this hypothesis, in the case of changes in the solid state, an abnormally high energy of activation should be found in those cases where there is a high degree of disorder produced during the reaction, that is, when there is an amorphous product, and a more normal value when the product was crystalline. There is, however, at the present time but little evidence bearing on this aspect of the matter.

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[1] These reactions have been summarized by Eyring and Stearn (*Chem. Rev.*, **24**, 253 (1939)).
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## Existence of Several Active Components in Crude Pepsin Preparations

THE original solubility measurements on crystalline swine pepsin led to the conclusion that the crystals consisted of a single pure protein or several closely related proteins[1]. Since that time, it has become apparent in this and other laboratories[2,3] that pepsins prepared from the various commercial products or from pepsinogen differ in solubility, specific proteolytic activity and stability. Solubility measurements have now been made on various partially purified pepsin preparations in order to determine the cause of these variations.

The results show quite clearly that commercial preparations contain more than one protein possessing peptic activity and that the differences between the various preparations are due to differences in the proportion of the components present. Curve I shows the solubility diagram of the total protein fraction from a commercial 1 : 10,000 Cudahy pepsin preparation. When analysed, as described by Kunitz and Northrop[3], this curve indicates that the preparation is a mixture containing 15 per cent of component *A*, having a solubility of about 0·6 mgm. protein nitrogen per ml. in the