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Some Observations on Present Day Chemical Kinetics.

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IN what follows I propose to make some observations upon certain aspects of chemical kinetics. These relate not so much to details of recent advances as to the general structure of the subject, which, like everything else, is gradually changing.

The study of kinetics in its earliest stages was, one may suppose, stimulated by the fascination which exists in surveying the unfolding of phenomena in time. In a slow chemical reaction a sort of microcosm of history evolves as it were before our eyes, and it is not surprising that the first of all objects was to find and interpret the law according to which the amounts of substance changed with time. The law of mass action and the conception of reactions of different orders, based upon the theory of probability, seemed to give a satisfactory explanation of what occurred and to offer a basis for a rational classification of reactions. But we have seen this idea sadly disappointed, and today it must be recognised that from the point of view of concentration–time relationships chemical kinetics seems sometimes to present a picture of almost forbidding complexity. Yet the very reason for this at first sight discouraging result lies in a circumstance which itself is gradually leading to major simplifications and generalisations of a different kind. It has transpired that most reactions take place in a series of stages : it appears that many are chain reactions. They are chain reactions because the intermediates are free atoms or radicals, that is to say entities which have been formed by the primitive process of severing a bond. Now what the studies of many experimenters have combined to show, and what several authors have been at pains to point out in individual cases in detail, is that, even in non-chain reactions, the sequence of steps by which most reactions accomplish themselves is one in which each successive member is of extreme simplicity, involving, for example, the reaction of the fewest molecules, the breaking of a single bond, or the transfer of a single atom or electron from one reacting partner to another.

This seems to open up a possibility of some magnitude, namely that the work of these various authors may be generalised and that we may presently be able to formulate rules, based upon our general knowledge of structure and properties, and according to which, looking at a given complex reaction, we shall be able to predict what in fact constitutes the simplest series of steps into which it should be resolved. Once this is done the whole kinetic scheme can be worked out from first principles. This subject at any rate seems to constitute a very fruitful field of enquiry at the present time. In this connexion I might refer to the discussion by Evans (*Trans. Faraday Soc.*, 1944, **40**, 120) of the action of nitric acid on metals which gives a good idea of the way in which order may be brought out of chaos. Following this general idea I have tried in another lecture to show that even the manifold and at first sight mysterious phenomena exhibited by the hydrogen–oxygen reaction are, in the light of modern ideas, almost if not quite predictable from first principles (*Proc. Roy. Soc.*, 1946, *A*, **188**, 1).

We are witnessing the gradual emergence of a new kind of classification of chemical reactions. It may be worth while to consider this briefly from a very general point of view. Spontaneous changes proceed with diminution of free energy; but if they are of the kind whose progress can be measured there are nearly always energy barriers separating the initial and the final states. The overcoming of these barriers depends upon strong local fluctuations whereby one or both of two things may happen : (*a*) abnormal amounts of energy are accumulated in a few molecules, and (*b*) there is a momentary occurrence of unusual spatial distributions of molecules. If a great deal of energy has to be concentrated locally we speak of a high energy of activation : if many molecules have to come together, or if they need to assume highly specialised positions and orientations, then we speak of a low entropy of activation. Both of course represent entropy decreases from the point of view of the system as a whole.

The first major division of reactions depends upon whether this local fluctuation is dissipated after a single act of chemical transformation, or whether its effect persists through a series of such acts so as to give rise to a chain reaction. The commonest form of such reactions involves a succession of steps each with a high entropy of activation. And the overall kinetics are affected more perhaps by the mode in which the dissipation of the original fluctuation occurs— that is, by the mode of chain breaking—than by any other factor.

In the pyrolysis of organic compounds striking differences in kinetics arise from the different modes of radical re-combination (for example, in the decomposition of ethers, whether two

light radicals, or a light and a heavy one, combine). In the important class of reactions in which successive steps of the chain build up polmeric molecules of increasing size, the whole kinetic classification depends essentially upon the mode by which the chains are ended, and in the detailed study this usually constitutes one of the main problems to be solved. It has been the subject of close analysis by Flory, Melville, and others and now constitutes almost a separate chapter of physical chemistry. In most chain reactions what persists is the effect of the original local energy fluctuation—that is, an effect connected with the activation process. A persisting effect of a low entropy of activation is a characteristic of the reactions of living matter, a topic to which I shall return presently.

To turn, however, to those reactions in which the initial energy fluctuation does not persist—that is, to non-chain reactions—it is obvious that if they were in fact all reduced to the simplest possible form, even they would consist of sequences involving at each step only the breaking of a single bond, the transfer of a single atom, or a simple flow of electrons. But the energy conditions would usually be very unfavourable. The energy barriers are lowered when suitable receptor molecules are present and suitably disposed to take up atoms or radicals released by the breaking of bonds, and when suitable complexes are formed which obviate the need for the appearance of unnatural charges on atoms. But these conditions inevitably demand precisely defined and specialised configurations at the moment of reaction—that is to say, greatly lowered entropy of activation. In the same way the unfavourable energy conditions attending the reaction of particles bearing like charges are improved when these charges are screened by the presence of suitable ions (as exemplified by the salt effect) : but here again the need for extra particles in the transition state introduces an unfavourable entropy factor. The antagonism of the energy factor and the entropy factor dominates the whole of the phenomena of kinetics, and one of the great needs, if a satisfying edifice of theoretical chemistry is to be constructed, is for the rules governing the balance to be formulated in a clearer way than has hitherto been possible.

Among the consequences of this antagonism is the change of mechanism which is sometimes observed at a certain point in a related series of reactions. The well-known example is the hydrolysis of the alkyl halides, which changes from a bimolecular to a unimolecular mechanism as the nature of the alkyl radical is varied (cf. Hughes, Liversidge Lecture, *J.*, 1946, 968). Such a change of mechanism with relatively small changes in the reactant would be likely only if the advantage which one mode possessed over the other were rather nicely balanced.

Without actually revealing changes of mechanism, series of reactions in which one reactant is progressively changed by the introduction of substituents not infrequently show parallel increases of activation energy and of the non-exponential term, *i.e.*, as the energy factor becomes less favourable to reaction the entropy factor in compensation becomes more favourable. When a high degree of activation is required the configuration at the moment of transition needs to be less precisely defined than when a low degree of activation is needed. In a general qualitative way this can be understood, but more detailed knowledge is desirable about the conditions which determine when this phenomenon is observable and when, on the other hand, changes in the rate are determined wholly by the change in activation energy. One example only need be mentioned. In the alkaline hydrolysis of benzoic esters, changes in the substituent cause changes in rate wholly accounted for by changes in the activation energy. In the acid hydrolysis of esters and also in the acid catalysed esterification reaction there is a marked compensation of the energy and the entropy terms. The alkaline and acid hydrolysis reactions may be formulated as follows :

Alkaline.   Acid.

$$
\begin{array}{cc}
\underset{\text{O\bar{H}\quad H·OH}}{\overset{\overset{\text{O}}{\|}}{R·C—OR'}} & \underset{\text{H·OH\quad H}^{+}}{\overset{\overset{\text{O}}{\|}}{R·C—OR'}}
\end{array}
$$

$$
\begin{array}{cc}
\underset{\underset{\quad\text{O\bar{H}}}{\text{O\bar{H}}}}{\overset{\overset{\text{O}}{\|}}{R·C}}\ R'OH & \underset{\underset{\quad\text{H}^{+}}{\text{O\bar{H}}}}{\overset{\overset{\text{O}}{\|}}{R·C}}\ R'OH
\end{array}
$$

The chief resistance to reaction is represented by the energy required to bring the hydroxyl ion or the water molecule up to the carbonyl carbon. This energy is less with the hydroxyl ion, and one might suppose the reaction to approximate to the two stage process :

(*a*) $R·\overset{\overset{\text{O}}{\|}}{C}—OR' + O\bar{H} = R·COOH + O\bar{R}'$

(*b*) $O\bar{R}' + H_2O = R'OH + O\bar{H}$
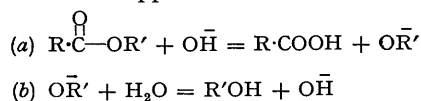
(*b*) being rapid compared with (*a*). If this is so, the orientation and distance of the water molecule become irrelevant, and the only influence of changes in R is on the energy term. In acid hydrolysis the water molecule is a much less active agent, the activation energy is greater, and the co-operation of the hydrogen ion is required. Furthermore, we might suppose the link between the carbonyl carbon and the alkoxyl group to weaken in different degrees according to the magnitude of the repulsion overcome by the approaching water. If this repulsion is great, the transition state may well be attained when the water is at a greater distance than when the repulsion is weaker; the entropy of the transition state is thus greater, and compensates to some extent the more adverse energy. This idea involves an assumption which may be stated in more general terms as follows. In a transition state $A\ B\ C$ a given weakening of the bond BC

$$A \ . \ . \ . \ . \ . \ . \ B\text{-------------------}C$$
$$\quad\quad\quad r_1 \quad\quad\quad\quad\quad\quad r_2$$
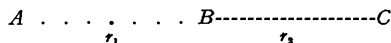
caused by the approach of A will have occurred at a greater value of r_1 when the repulsion of A by B is large, than when it is small. Whether or not this idea is sound (though it seems plausible) is difficult to say, but what is certain is that a series of propositions of this kind based upon theoretical studies of bond energies and their variations would be of the greatest help in systematising kinetic phenomena still further. This is a developemnt to which we must look forward in the decade before us.

I should like to consider briefly a few typical chemical reactions with the object of considering how far we are able to imagine which is the simplest possible series of steps into which they can be resolved, subject always to the condition that the best balance between the entropy and the energy factors is achieved. This discussion must at the moment be a good deal less systematic than one would like, but it may serve to reveal some of the ways in which order is gradually emerging.

Certain reactions of the halogens will first serve for the present purpose. A reaction to which a great deal of patient study has been devoted (Griffith, McKeown, and Winn, *Trans. Faraday Soc.*, 1932, **28**, 107) is the oxidation of oxalic acid by bromine. It transpires that the complicated rate–concentration relations can be well accounted for by the assumption that the rate is proportional to

$$[HC_2O_4^-]\ [HBrO]$$
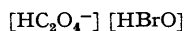
The usual conclusion would perhaps be that the two molecular species here represented are those between which the determinative reaction step occurs. The process by which these two structures yield carbon dioxide, bromide, and water involves, however, several simultaneous events which do not look so natural and inevitable as to seem those which would be predicted from first principles. It is of some interest to pursue here the idea of maximum simplicity and to see to what it leads. Halogens are to some extent amphoteric, and a small dissociation of bromine according to the equation

$$Br_2 = Br^- + Br^+$$
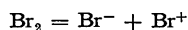
is very likely, and involves no more than an electron redistribution. The cross equilibria which are immediately established in aqueous solution between Br^- and H^+ and between Br^+ and OH^- give at once, and in the most natural way, the bromine–bromide–hypobromite equilibrium.

We may now consider the behaviour of the positive bromine ion when it encounters the oxalate ion $C_2O_4^{--}$.
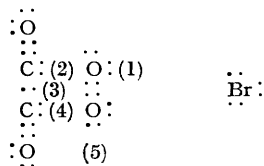
If a positive bromine ion approaches the electron pair labelled (1) in the diagram it can remove them and become a negative ion, :Br:, with a complete octet. Electron pair (3) now joins pair (2) with rupture of the bond between the two carbon atoms and formation of the double bond of CO_2. Then pair (5) joins pair (4) and the second molecule of CO_2 is formed, the whole process amounting to a simple flow of charge. The only step here which may be objectionable on energy grounds is perhaps that of the small amphoteric ionisation of the halogen, but in view of the extreme simplicity of everything else it is tempting to assume it.

However this may be, the scheme I have outlined, even if it does not correspond to reality, exemplifies the type where the various entropy of activation terms are the greatest possible. It is easily shown that reaction of positive bromine with oxalate ion leads to precisely the kinetic scheme referred to above.

Arguments have been adduced (J. C. Morris, *J. Amer. Chem. Soc.*, 1946, **68**, 1692) to show that the hydrolysis of chlorine is best explained by the mechanism $Cl_2 + O\bar{H} = HOCl + Cl^-$. This may be a stage easier from the energy point of view, and is a stage more difficult from the point of view of entropy.

The oxidation of arsenious acid by iodine also exhibits rather complex kinetics, but these have been shown to depend upon the control of the key concentrations by various subsidiary equilibria. The observed rate seems to be governed by the bimolecular action of H_3AsO_3 and HIO giving H_3AsO_4 and HI. Here we have a simple atomic transfer, which, in view of the formulæ of the two arsenic compounds, is again seen to be from the entropy point of view among the least elaborate processes possible.

Perhaps in contrast with the above we might consider the reaction by which phenols are iodinated. According to the work of Li (*J. Amer. Chem. Soc.*, 1942, **64**, 1146) and of Soper and Smith (*J.*, 1927, 2757) the relation between the reaction rate, the pH, and the various concentrations indicates the mechanism by which the molecule HOI reacts both with ϕOH and (much more readily) with $C_6H_5O^-$. If we wished here to postulate I^+ as one reactant it would be necessary, to preserve the form of the kinetic equations, to assume $C_6H_4^-O^-$ as the reaction partner—that is, to suppose that the replaceable proton of the aromatic compound ionised in a separate step. There are of course serious objections to this view. Thus, what seems to be preferred is, in this case, not

$$\geq C - H \longrightarrow \geq C^- + H^+$$
$$\geq C^- + I^+ \longrightarrow \geq C - I$$

but

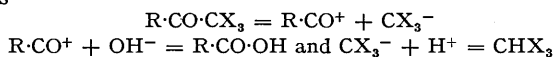$$\geq C - H + I^+ - OH^- = \geq CI + H_2O$$
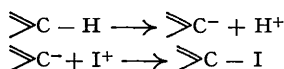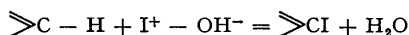
In other words the positive iodine ion prefers to react with its hydroxyl attached, rather than free, in order that the proton may be duly removed and accommodated. Now this process involves two simultaneous operations instead of a single one. It is therefore less favourably placed from the point of view of the entropy change. On the other hand, the formation of water gives an important compensation in the energy term. Here it must be admitted that an attempt to predict the course from first principles would encounter an ambiguity, only resolvable with the aid of more satisfactory theoretical propositions about bond energies, which once again appear as one of the greatest desiderata in the subject.
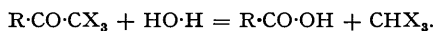
Another interesting reaction of the halogens is the haloform reaction. In this the overall change appears to be of some complexity. But it is known, on the one hand, that under suitable conditions mono-, di-, and tri-halo-ketones can be formed : and on the other hand, it has been found that the reaction may be of zero order with respect to the halogenating agent and of the first order with respect to the ketone and to hydroxyl ions (Bell and Longuet-Higgins, *J.*, 1946, 636). These facts point to the steps :

$$R \cdot CO \cdot CH_3 + OH^- = R \cdot CO \cdot CH_2^- + H_2O$$
$$R \cdot CO \cdot CH_2^- + X^+ = R \cdot CO \cdot CH_2X$$
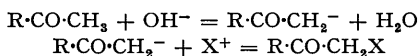
and then two repetitions of similar reactions till $R \cdot CO \cdot CX_3$ is formed. For the final stage we have the alternatives

$$R \cdot CO \cdot CX_3 = R \cdot CO^+ + CX_3^-$$
$$R \cdot CO^+ + OH^- = R \cdot CO \cdot OH \text{ and } CX_3^- + H^+ = CHX_3$$

or

$$R \cdot CO \cdot CX_3 + HO \cdot H = R \cdot CO \cdot OH + CHX_3.$$

In all this we see that the rational classification of the reactions is somewhat as follows :

(1) Internal re-distribution of electrons with breaking of a bond and the appearance of a charge, or of a free bond in a new place.

(2) Transfer of charge from one atom or molecule to another.

(3) Transfer of an atom from one molecule to another.

(4) Exchange of partners according to the scheme

$$\frac{A-B}{X-Y} = \frac{A \quad B}{X \quad Y}$$
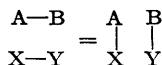
These represent a series in which the requirements in the way of low entropy of activation progressively increase. Many reaction steps can be classified under one or other of these headings. In time we hope to be able to predict which sequence is appropriate to any given case.

Another principle which helps in interpreting the mass of facts is that, in general, reactions will occur between uncharged molecules, an uncharged molecule and an ion, or oppositely charged molecules, in preference to reactions between molecules of like charge. Let us consider what is likely to happen when hydrogen bromide reacts with bromic acid to give bromine. In the first place reaction is more likely to occur between the ion pairs H^+Br^- and $H^+BrO_3^-$ than between Br^- and BrO_3^-. When the ion pairs meet, the simplest reaction is the transfer of a single atom of oxygen from one to the other giving HBrO and $HBrO_2$. The latter must be very unstable and will at once react again with HBr with a further single atom transfer giving 2HBrO. HBrO and HBr then of course react immediately to give bromine and water. The rate-determining step would seem then to be governed by the product : ion pair H^+Br^- × ion pair H^+BrO^-, which is roughly proportional to $[H^+Br^-]$ $[H^+BrO_3^-]$ or $[H^+]^2$ $[Br^-]$ $[BrO_3^-]$, giving the well known fourth order reaction commonly measured.

In a somewhat similar way the reaction between nitrite and iodide in acid solution is known to be approximately of the fourth order $[NO_2^-]$ $[I^-]$ $[H^+]^2$ which is most simply interpreted as [ion pair HNO_2] [ion pair HI]. These pairs suffer the partner-exchange type of reaction $\begin{matrix} ON - OH \\ I - H \end{matrix} = H_2O + NOI$, the NOI being unstable and breaking down at once, as would be expected from the known properties of NOCl and NOBr, to give nitric oxide and iodine.

For some purposes it would be convenient to regard salt effects on reaction velocity from this same point of view. The well-known result that reactions between like ions are accelerated by increases in the total ionic strength and those between unlike ions retarded is susceptible, as one knows, to a semi-thermodynamic treatment in terms of the activity coefficients of reactants and transition complex. From a purely kinetic point of view one can refer the effect to the greater probability of reaction between uncharged ion pairs AX and BY than between the charged ions X^- and Y^-. There are few things which would be of greater assistance in kinetics than a simple approximate and manageable theory of ion pair formation and it is to be hoped that one will some day be forthcoming.

If the theory referred to is lacking, valuable work is being done on the formation of complex ions in solutions of metallic salts. The realisation that these may often be the major participants in reactions facilitates the simple formulation of many changes. To take an example, the reaction which used to be formulated

$$2Fe^{+++} + Sn^{++} = 2Fe^{++} + Sn^{++++}$$

seems on good evidence (Weiss, *J.*, 1944, 309) to proceed by the stages

$$SnCl_2 + 2Cl^- = SnCl_4^{--}$$
$$SnCl_4^{--} + Fe^{+++} = Fe^{++} + SnCl_4^-$$
$$SnCl_4^- + Fe^{+++} = Fe^{++} + SnCl_4$$
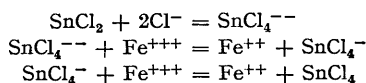
Two principles are satisfied here, namely, that reactions should preferably occur between particles which do not bear like charges, and that electron transfers occur in simple unit steps.

The kinetics of the nitration of aromatic compounds presents at first sight many complexities. These have recently been unravelled, and it now appears that they can be explained very satisfactorily by the assumption that the NO_2^+ ion is produced. This by the simplest possible exchange process replaces the proton on the negative reaction centre in the benzene ring.

In sulphonation by sulphur trioxide it seems that the molecule S_2O_6 may be involved : in the halogenation of unsaturated compounds, molecules such as Br_4 are indicated by the work of Robertson. The prior equilibria in which entities such as Br^+, Br_4, S_2O_6, NO_2^+, $Fe^{++}Cl$, $SnCl_4^{--}$, and so on participate now appear to be of the greatest interest. They present us (as do the various ion pairs referred to above) with particles by whose reaction apparently complex acts may be performed in single encounters where the entropy of activation is not impossibly low.

A new inorganic chemistry of such equilibria is now due, in which the theory of structure will become more closely linked than ever to the theory of kinetics. The latter has, so far, often taken the lead in indicating the existence of unexpected species in small concentration (for example, N_2O_2, S_2O_6, and so on) but perhaps the compliment may now be returned and a more careful study of the inorganic chemistry of unstable species may help us to predict the most probable kinetic mechanisms in examples as yet unexplored.

Other striking examples of the way the tendency to maximum simplicity operates are to be

found in the consideration of Rice and Teller and of Rice and Kossiakoff concerning the sequence of steps in chain reactions of organic compounds. These considerations help us appreciably along the road towards the prediction of the most likely sequence of changes.

To sum up certain indications from what has been said so far, I think the time is ripe for a considerable forward movement in structural inorganic chemistry, which will be brought into closer and closer relation with kinetics. The establishment of a series of workable qualitative propositions about bond strengths, and the development of a manageable approximate theory of ionic interactions, would further this work in a spectacular manner.

Time is lacking for any detailed discussion of heterogeneous reactions, but I should like just to say a word about their place in the general scheme of things. The essential thing is that the formation of chemical links between surface atoms and adsorbed atoms or radicals allows the resolution of reactions into steps of maximum simplicity with lowered energy barriers. An important character is that the active intermediates, instead of being free and transient, are preserved, as it were, in a state of suspended animation, until the appropriate reaction partners arrive. More and more progress is made in formulating the changes of heterogeneous catalysis by definite chemical equations. I will mention in passing only one example which is of a somewhat surprising kind. Eucken and Wicke (*Naturwiss.*, 1944, **32**, 161) found that, paradoxically as it at first appears, the dehydration of *iso*propyl alcohol by alumina demands the presence of water on the catalyst surface. They interpret their experimental findings by the following scheme :

$$CH_2\text{---}CH\text{---}CH_3 \qquad\qquad CH_2\text{===}CH\text{---}CH_3$$

Initial.   Final.
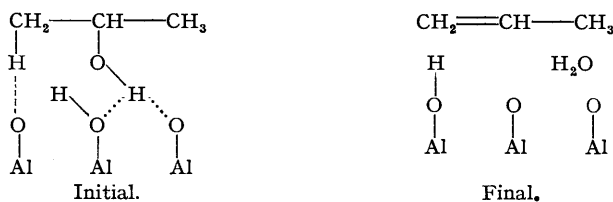
The hydrogen atom virtually migrates from one oxygen atom of the catalyst to the next : though what actually happens is that the catalyst itself contributes an atom of hydrogen to the water eliminated and receives one from the alcohol.

Much progress has been made in ordering chemical kinetics into a finished system : much remains to be done. The stages of many reactions, such as oxidation reactions of organic substances, are by no means understood; the interplay of energy and entropy factors needs further elucidation; the inorganic chemistry of ionic complexes needs elaboration; a simple and manageable approximate theory of ion pair formation is desirable; a series of qualitative propositions about the interatomic forces involved in activation phenomena needs to be formulated. Much-more information about the nature of intramolecular energy transfers may be expected to be forthcoming. All these potential advances are, however, of the nature of perfecting operations applied to an edifice the general structure of which is already evident. We think we know—though it is as well to be prepared for possible surprises—the general form of the phenomena which will be observed and of the explanations which will be provided for them. If we may appropriate from another field of scholarship the distinction of " classical " and " romantic ", then the advances to be made in the parts of the subject I have just been talking about belong essentially to the " classical " : the " romantic ", in the sense in which I am taking it, lies in the direction of those phenomena which are still mysterious and where not only the precise form but even the general character of the findings and of their explanations is largely unknown.
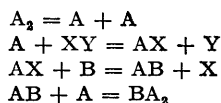
I have the feeling not only that such a region lies where chemical kinetics is applied to the living cell, but that the time is ripe for its further exploration. Some people doubt whether much progress can be made in this direction, and they may of course be right. But in many ways the transition from the kinetics of the systems we normally study to those of the cell is a quite natural one, and I do not share this negative belief.

If we consider the classification of reactions of the inorganic world we see a steady transition to those of the living cell. The resolution of a complex change into a series of simple stages is familiar; the appearance of transitory free atoms and radicals is well known; the study of polymerisation reactions has made us familiar with the continuous building up of large molecules by repeated additions to a persisting free radical; in reactions where solid products are formed we have the reproduction of basal patterns of molecules by steady additions of fresh units. In the reactions of a living cell we seem to have a combination of all these processes. And the new problem presented to kinetics is that of the mode of their interplay.

In the cell there is a highly ordered macromolecular pattern. Its order constitutes an element of low entropy—that is, it is something inherently improbable. This is reflected in an interesting way in the kinetics of denaturation of proteins. The denaturation process has a very high activation energy (which shows that the ordered structure has a considerable element of stability), but the non-exponential factor is extremely high. In other words, the entropy of activation is high, showing that the transition state is much less ordered—that is, more probable—than the initial state. The intact protein must therefore have been highly ordered, even though energetically fairly stable. This will apply to the cell material as a whole.

The process of self-synthesis proceeds in a manner which bears some analogy with crystal growth, the existing pattern guiding the new molecular units into suitably ordered positions. The entropy of activation for this synthetic process is not impossibly low, precisely because there is a persistent structure of low entropy (low probability) continuously maintained in the self-reproducing, ordered pattern. The original fluctuation which may have permitted the emergence of this order does not dissipate itself as in ordinary chain reactions, but is preserved for all time, provided that the cell mechanism continues to function. But the low entropy systems are being continually enlarged, and this is only possible if there is a steady and compensating running down of free energy. This occurs in the oxidation and other degradative reactions which accompany the autosynthetic reactions of the cell.

How one set of processes which involve increase of entropy can balance another set involving decreases is a matter which at first sight seems mysterious, but which, in principle at least, is seen to be simple when the resolution of reactions into stages is borne in mind. The following scheme shows how the coupling is in principle possible. The sequence

$$A_2 = A + A$$
$$A + XY = AX + Y$$
$$AX + B = AB + X$$
$$AB + A = BA_2$$

is equivalent to

$$(1) \quad B + A_2 = BA_2$$
$$(2) \quad XY = X + Y$$
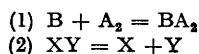
If (1) proceeds with diminution of free energy it pays the way, as it were, for (2) which can proceed with increase of free energy.

The reactions of the cell which release free energy are those such as oxidation. Oxidation reactions are almost certainly chain reactions producing free radicals. But in contrast with what happens, for example, in a mixture of hexane vapour and oxygen, these free radicals are not subject to rapid dissipation processes, because they are preserved from decay by their attachment to the more or less rigid macromolecular structure of the cell material. Cells may remain alive for a time at least without growing, and then they preserve their free radical ends in a state of mobilisation until suitable substrates are presented for them to react with. The cell, in simplest terms, consists of macromolecular polyfunctional free radical systems, constituting a region of low entropy (in virtue of its order) and low energy of activation (in virtue of its free valencies) and persistent (in virtue of its relatively rigid structure).

The system itself is thus a combination of elements with which we are already familiar in the ordinary kinetics of homogeneous and heterogeneous reactions : the mystery consists in the way in which these elements are combined so as to give rise to the phenomena of cell activity.

I should like therefore to refer briefly to the way in which one or two cell phenomena admit of discussion in terms of chemical kinetics.

One of the most remarkable manifestations of the power of the living cell is the phenomenon of adaptation. Many bacterial cells placed in presence of a new source of material, such as a new sugar for a carbon supply, are unable at first to utilise it with maximum efficiency, but learn, as it were, to do so on continued growth in the medium. Bacteria, moreover, grown in presence of an antibiotic drug at a concentration which is not completely inhibitory, often—one might even say usually—acquire a resistance to its action, and this resistance may be developed to such a degree that completely normal growth can occur in presence of concentrations a hundred times or more greater than that which would originally have stopped all growth. The most obvious explanation of these phenomena might seem at first sight to be a purely biological one, namely that the bacterial strains consist from the start of cells with different capabilities, some for example able to utilise the new substrate, others naturally resistant to the drug, and so on, and that the adaptive process consists in the selection of those cells most capable of flourishing in the new environment. Numerous detailed studies seem, however, to show that this explanation is inadequate and that there must be actual changes in the cell,

called forth by those conditions to which the adaptation occurs. These changes must consist either in the establishment of a new quantitative balance of the enzymes in the cell, or in an actual modification of the protein texture of the cell material. The adaptations show complex phenomena of reversibility or non-reversibility according to conditions, consistent with this idea, which is supported by many arguments into which I shall not enter here.

Where there is a change in the enzyme balance of the cell a direct application of kinetic ideas becomes not only possible but imperative. The synthetic reactions of the cell must consist of many stages; in the steady state of growth the rates of the different steps are so adjusted that the various parts of the cell material are built up in a standard ratio. Changed conditions may affect in unequal degrees the various synthetic reactions. This will be specially true of certain drug actions, which according to the Fildes theory are extremely specific in respect of the site of attack. When the relative rates of the different steps are changed, the proportions of the cell enzymes built up must also change, and this will lead to a calculable alteration in certain biochemical properties, such as the drug resistance. The theories which have been developed on this basis are as yet in a rough and ready state, and no doubt contain gross faults, but there can be little doubt that general propositions based upon the theory of consecutive reactions have much to say about the phenomena of cell adaptation. Thus one of the very characteristic properties of living matter comes naturally within the purview of chemical kinetics.

Not only changes in enzyme proportions, but also qualitative modifications of the protein or other macromolecular texture, must be considered and are of great importance in connexion with the theory of mutations and of adaptive processes. There seems little doubt that in the reproduction of cell material the deposition of new substance is guided by the pattern of the old in a way which is at least in part analogous to crystal growth. The possibility of forcing an initial change of pattern by the incorporation, for example, of some fresh foreign units into the macromolecular texture, will depend upon the energy and entropy of activation. These may vary greatly, and, according to their values, there may be all gradations of phenomenon between an apparently discontinuous mutation and a gradual reversible adaptation.

These matters are accessible to experiment in many ways : for example, growth in presence of one sugar may retard or even reverse the adaptation to another (Monod, " La Croissance des Cultures Bactériennes ", 1942; Postgate and Hinshelwood, *Trans. Faraday Soc.*, 1946, **42**, 45) ; growth in presence of ammonia–asparagine mixtures trains bacteria, which are initially unable to utilise ammonia alone, to perform this operation; the chief requirement for the adaptation of certain bacteria to *d*-arabinose (which they are initially unable to utilise) is the lapse of sufficient time in presence of this sugar—growth in mixtures of *l*-arabinose and *d*-arabinose being moreover no more effective than growth in mixtures of glucose and *d*-arabinose (G. A. Morrison, S. Jackson, unpublished observations). Systematic collection of observations of this kind and careful thought about their interpretation can hardly fail to contribute to our enlightenment about the nature and mode of incorporation of the molecular fragments which cells use in their synthetic operations, and about the manner of their functioning.

Another group of observations of which the interpretation constitutes a characteristically kinetic problem is that where one set of cell reactions is, in the most remarkable way, inhibited and superseded by another set. In the well-known Pasteur effect provision of oxygen inhibits the fermentation reactions by which the cell obtains its energy under anærobic conditions. Provision of oxygen in the growth of *Bact. lactis ærogenes* lessens the reduction of nitrate and nitrite; and supply of ammonia for growth inhibits the consumption of nitrite for that purpose (P. R. Lewis, unpublished observations). In all these examples it appears at first sight as though the cell knew how to select the more profitable of two alternatives : and yet such phenomena can be interpreted in terms of the rise or fall in the transient stationary concentrations of certain intermediates as the conditions of the reaction change.

There is not time for a detailed discussion of these matters, and I pass to a concluding observation. Kinetic studies (in the broadest sense of the term) have a definite contribution to make to the understanding of cell phenomena, but naturally they cannot stand by themselves. The work of Stacey and the Birmingham school on the polysaccharide components of micro-organisms (Stacey, Tilden Lecture, 1946), work on immunity, on the *X*-ray structure of proteins, on the organic chemistry of the nucleotides and so on, are in many ways more direct and more important modes of attack. And yet it is only by studying function that we can understand function, so that the kinetic aspect must be allowed to retain its place and assigned its part in the unravelling of the great mystery.