Autocatalysis

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1 Introduction

Much effort goes into devising catalysts for commercial use, and this practical work is complemented by equally extensive studies on the principles of catalysis. Not only are ordinary catalysts reasonably well understood, but progress has also been made with the complex biological catalysts, the enzymes. Their biosynthesis has been largely clarified, most of the factors which confer their catalytic power are known, equally effective analogues have been prepared, and enzymes have graduated to use in industry.

By contrast, autocatalysis is viewed as a peripheral kinetic problem of little interest. The literature contains virtually no discussion on the special conditions which bring about autocatalysis.* The research effort goes mostly into novelty items like the oscillating reactions[1] or into rather general thermodynamic studies.[2]

Indeed, by some quirk of thought or language, the autocatalytic aspects of important industrial processes are barely recognized. Combustion is seldom referred back to its underlying chemistry.[3] In the liquid phase, living cells are used to make alcohol and antibiotics and to treat sewage, being thought especially useful for these processes because they are alive. From the chemical viewpoint, they are very complex autocatalysts. If simpler autocatalysts were available, they could have considerable potential in industry.

This review has the object of bringing together those features and properties which seem most relevant to the practical task of making autocatalysts. More distantly related topics, like thermodynamics, will be left out. Also, to avoid filling the paper with qualifications and side issues, there will be no reference to kinetic changes caused by heating[4] although they may often be important in practical applications. Only a bare minimum of mathematics will be used. Rather, kinetic behaviour will be illustrated by graphs based on computer modelling.

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*Kinetic mechanisms have been offered for reaction systems like the permanganate oxidation of oxalic acid. Not only are such schemes not entirely convincing but also they do not explain the inhibition of reactions which, at first sight, seem equally likely.

[1] Faraday Division of the Chemical Society, 'Physical Chemistry of Oscillatory Phenomena, 1974, Symposium', University Press, Aberdeen, 1975.

[2] P. Glansdorff and I. Prigogine, 'Thermodynamic Theory of Structure, Stability and Fluctuations', Interscience, New York, 1971.

[3] G. J. Minkoff and C. F. H. Tipper, 'Chemistry of Combustion Reactions', Butterworths, London, 1962.

[4] D. A. Frank-Kamenetskii, 'Diffusion and Heat Transfer in Chemical Kinetics', Plenum, New York, 1969.

Because so few simple autocatalysts in solution are known, the various principles will often be exemplified from biology, treating the more primitive biological cells as complex autocatalysts.[5] This is most appropriate when considering the interactions between autocatalysts; biologists have long used a chemical kinetic approach to ecological problems.

Biological cells are notable for their chemical complexity and associated physical structure. Physical structure is an essential aspect of even the simplest autocatalysts in solution, ensuring their stability against reactions outside the catalytic cycles and enhancing their turnover rate. The kinetic characteristics of autocatalysts are such that, under some conditions, there may be feedback which alters the physical structure, building complexity.

The last two sections contain suggestions for making autocatalysts and some speculative ideas on their use.

2 Cyclic Chemistry

A. Definitions.—Reactions will be expressed as either bimolecular reactions with two products, or additions, or decompositions:

$$\mathrm{A} + \mathrm{B} \rightarrow \mathrm{C} + \mathrm{D} \tag{1}$$

$$\mathrm{A} + \mathrm{B} \rightarrow \mathrm{C} \tag{2}$$

$$\mathrm{A} \rightarrow \mathrm{C} + \mathrm{D} \tag{3}$$

The relations between reactions fall into three categories: 'competing', using the same reactant; 'alternative', yielding the same product; and 'consecutive', where a product of one reaction is reactant for another. These relations apply not only between single reactions but also between complex reaction sets or systems.

The third category, consecutive reactions, defines a larger system which is the sum of the primary reactions or systems. For example, with two reactions, equations (4a) and (4b), C1 is now an 'intermediate' species.

$$\mathrm{A1} + \mathrm{B1} \rightarrow \mathrm{C1} + \mathrm{D1} \tag{4a}$$

$$\mathrm{A2} + \mathrm{C1} \rightarrow \mathrm{D2} + \mathrm{D3} \tag{4b}$$

Cyclic reaction sets are cyclically consecutive reactions. With two reactions, involving two intermediates:

$$\begin{aligned} \mathrm{A1} + \mathrm{C2} &\rightarrow \mathrm{C1} + \mathrm{D1} \\ \mathrm{A2} + \mathrm{C1} &\rightarrow \mathrm{C2} + \mathrm{D2} \end{aligned} \tag{5}$$

When discussing complex cyclic sets, it is convenient to use the terminology for chain reactions.[4] Thus, equation (4a) gives rise to an intermediate species, so it is called a 'generating' reaction; (4b) consumes an intermediate species, so it is called a 'terminating' reaction. In equation (5), both reactions involve intermediate species but do not change the number thereof; they are 'propagating' reactions. The remaining category, 'branching' reaction, is illustrated in equation (6a):

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[5] C. N. Hinshelwood, 'Chemical Kinetics of the Bacterial Cell', Oxford University Press, London, 1946.

$$\mathrm{A1 + C2 \rightarrow C1 + C3} \tag{6a}$$

$$\mathrm{A2 + C1 \rightarrow C2 + D2} \tag{6b}$$

$$\mathrm{A3 + C3 \rightarrow D3 + D4} \tag{6c}$$

Here, both products of (6a) go further, C1 going to the propagating reaction, (6b), as in equation (5) and C3 going to a new reaction, (6c), which is terminating.

B. The Fundamental Condition.—Cyclic reaction sets are restricted sets from among the reactions which are energetically possible with the chemical species present.

It is useful to have some idea of how restricted, even though it can be only rough and general. If there are N bimolecular equations in a cyclic sequence, the number of chemical species present is proportional to N; it is $3N$ for an ordinary catalytic sequence without redundancy. On the other hand, the number of energetically possible reactions is a quadratic function of the number of chemical species, proportional to N^2. If all the chemical species have been observed to take part in some reaction of the cyclic set in a specified time interval, then on this time-scale roughly half are energetically capable of reacting with a like number; again with the ordinary catalytic sequence without redundancy, this means $9N^2/4$ reactions—call it $2N^2$. As only N reactions do occur, $2N$ times as many have been prevented.

For illustration, equation (5) is regarded as a catalysed route for the reaction

$$\mathrm{A1 + A2 \rightarrow D1 + D2.} \tag{7}$$

Certainly, (5) increases the conversion of A's into D's, but this is important only if (7) is 'slow' compared with the separate reactions of (5). Moreover, the catalysed route remains important only if the catalyst, as either C1 or C2, is not consumed by terminating reactions; these latter are 'forbidden'.

There are two kinds of reason for reactions being slow or forbidden. One is kinetic and the other relates to the physical structures of the molecules themselves. We consider them in the next section.

Although the structural reasons remain the same during the course of reaction, the effectiveness of the kinetic reasons changes. With autocatalysis, the progress of reaction alters the concentration of the catalyst, providing a feedback which is not present in the case of ordinary catalysis. In Section 6, we consider how this feedback can affect the physical structures of the autocatalysts themselves.

C. Autocatalytic Sets.—We will now deal only with 'allowed' reactions and ask what are the formal requirements for a cyclic set to be autocatalytic.

Equation (6) can readily be made autocatalytic by replacing the terminating reaction, (6c), with a propagating reaction cyclic with either (6a) or (6b). Thus, coupling back into the first reaction yields,

$$\begin{array}{l} \mathrm{A1 + C2 \rightarrow C1 + C3} \\ \mathrm{A2 + C1 \rightarrow C2 + D2} \\ \mathrm{A3 + C3 \rightarrow C2 + D3} \end{array} \tag{8}$$

This is autocatalytic, or 'reflexively catalytic', in C2, a complete cycle consuming one molecule of C2 and producing two. A further cross-coupling makes a set autocatalytic in two intermediates:

$$A1 + C2 \rightarrow C1 + C3 \qquad (9a)$$

$$A2 + C1 \rightarrow C2 + C3 \qquad (9b)$$

$$A3 + C3 \rightarrow C2 + D3 \qquad (9c)$$

This is autocatalytic in both C2 and C3, and correspondingly has two branching reactions, (9a) and (9b). For example, molecular hydrogen and oxygen combine through a sequence autocatalytic in both H and OH:

$$\begin{aligned} O_2 + H &\rightarrow O + OH \\ H_2 + O &\rightarrow H + OH \qquad (10) \\ H_2 + OH &\rightarrow H + H_2O \end{aligned}$$

Equations (8), (9), and (10) achieve autocatalysis in three reactions. It is possible to imagine a branching reaction yielding both 'daughter' molecules so that autocatalysis would minimally require two reactions. Thus, in the upper atmosphere, atomic oxygen formed by the photodissociation of molecular oxygen recombines in a sequence autocatalytic with respect to O_2:[6]

$$O + O_2 \rightarrow O_3 \qquad (11a)$$

$$O + O_3 \rightarrow O_2 + O_2 \qquad (11b)$$

This example makes the point that even unlikely looking chemicals may be autocatalysts in appropriate reaction mixtures. In practice, events in the upper atmosphere are far more complicated.[7] Reaction (11a) is exceedingly slow (see next section) and is therefore mediated by 'three-body' addition involving other atmospheric molecules. Reaction (11b) does not yield both molecules in the ground state so that a collisional deactivation is normally involved. Also at stratospheric heights, (11b) is relatively slow and is catalysed by hydroxyl, nitric oxide, or atomic chlorine. As these catalysts interact among themselves, a very complex cyclic network obtains, but it is still autocatalytic with respect to molecular oxygen.

Biochemistry furnishes examples where numerous chemical species interact in cyclic sets which are assembled into an overall autocatalytic system like the bacterial cell. Commonly, the internal cyclic sets are presented as extended catalytic sequences, usually by coupling enzyme sets through the product–reactant relationship. However, many can also be cast in an autocatalytic form. One example of this is the glyoxylate cycle, using the terminology of Mahler and Cordes,[8] (p. 446);

$$\text{NAD}^+ + \text{malate} \xrightarrow{1.1.1.37} \text{oxaloacetate} + \text{NADH} + \text{H}^+ \quad (12a)$$

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[6] S. Chapman, *Mem. Roy. Meteorol. Soc.*, 1930, **3**, 103.

[7] S. C. Wofsy and M. B. McElroy, *Canad. J. Chem.*, 1974, **52**, 1582.

[8] H. R. Mahler and E. H. Cordes, 'Biological Chemistry', Harper and Row, New York, 1966.

$$\text{Acetyl-CoA} + \text{oxaloacetate} \xrightarrow{4.1.3.7} \text{citrate} + \text{CoASH} \tag{12b}$$

$$\text{Citrate} \overset{4.2.1.3}{\rightleftharpoons} \text{iso-citrate} \tag{12c}$$

$$\text{Iso-citrate} \overset{4.1.3.1}{\rightleftharpoons} \text{succinate} + \text{glyoxylate} \tag{12d}$$

$$\text{Acetyl-CoA} + \text{glyoxylate} \xrightarrow{4.1.3.2} \text{malate} + \text{CoASH} \tag{12e}$$

$$\text{E.FAD} + \text{succinate} \overset{1.3.99.1}{\rightleftharpoons} \text{fumarate} + \text{E.FADH2} \tag{12f}$$

$$H_2O + \text{fumarate} \overset{4.2.1.2}{\rightleftharpoons} \text{malate} \tag{12g}$$

This set has one branching reaction, (12d), and the other reactions are all propagating. It is therefore autocatalytic in one intermediate, malate, which enters at (12a) and leaves at (12e) and (12g). Notice that each reaction is itself catalysed by an enzyme (the Enzyme Commission number appears on the arrow). If these are included, the cyclic sequence is indeed quite extensive.

3 Physical Requirements

Cyclic reaction sets are important when the non-cyclic, and therefore simpler, alternative paths for dissipating the chemical potential are slow or forbidden. As mentioned in the last section, the reasons for slowness can be either kinetic or structural.

A. Kinetic.—In the gas phase, straight addition reactions are unlikely; unless the colliding molecules have internal degrees of freedom which can take up much of the energy set free at reaction, energy and momentum cannot be conserved together. Especially among the simpler molecules, therefore, reaction paths are confined to those which do not include direct addition. Overall additions occur through exchanges which equally involve dissociations, the active products of which take part in further reactions. These circumstances favour cyclic reactions, both catalytic and autocatalytic. For the latter, the common examples are combustions as in equation (10). Notice that the autocatalytic intermediates, being formed during the donation of groups, are degradative products and not products of synthesis.

Even in gases, it is possible to find autocatalysts which are products of synthesis [for example, equation (11)] when an addition reaction is mediated by a 'third body'. In that example, the autocatalytic sequence is a catalysed route for the synthetic reaction, equation (13). Equation (13) is unimportant in the upper

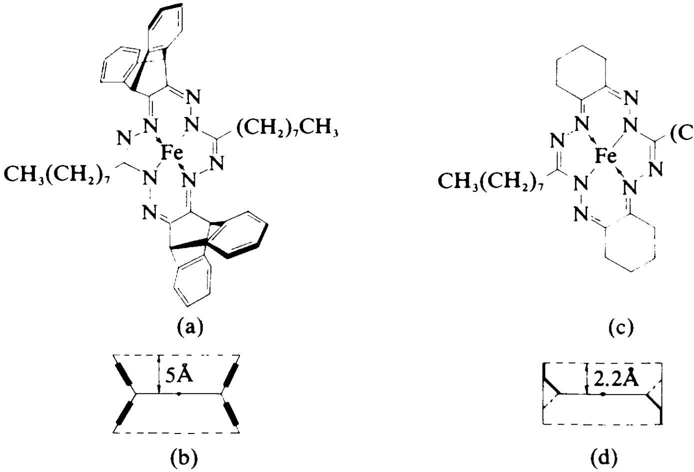
$$O + O \rightarrow O_2 \tag{13}$$

atmosphere because oxygen atoms are rare, but elaborations of equation (11) go at a reasonable rate because of the high concentration of O_2. Of course, this is a general rule—autocatalytic pathways are favoured by high relative concentrations of autocatalyst.

Now consider the liquid phase, where additions occur readily because surrounding molecules absorb the excess energy of reaction. The autocatalysts are products of synthesis (see next subsection) and among them appears another kinetic factor favouring cyclic reaction. When consecutive reactions occur on a 'particle', the local concentration of active sites is much higher than if they were uniformly dispersed through the medium. If the intermediates exchanged between the sites stay with the particle, the overall rate for consecutive reactions is greatly enhanced. Following Martell,[9] we call this the 'equilibrium effect'.

B. Physical Structure.—Because addition is easy in liquids, catalytic systems (both auto- and ordinary catalysts) are subject to terminating reactions. They persist only when the catalytic molecules possess physical structures which 'protect' active sites by ensuring specific reaction. When protection is not complete, the catalysts decay. This decay is an intrinsic property of all cyclic systems.

From the numerous examples in the literature on metal ion co-ordination catalysts, we can select only one—a 'gas carrier'. Baldwin and Huff[10] report on how ligand encumbrance affects the reversibility of oxygen binding to iron(II) complexes. According to a structural model, the complex with a 9,10-bridged-9,10-dihydroanthracene has its active site in a 5 Å cleft [Figure 1 (a) and (b)]. In toluene–pyridine solution at −78 °C, it takes up one mole of oxygen per mole. Unlike the usual binding of oxygen to iron, the attachment is very weak and can be released by freeze–thaw cycles between −196 and −78 °C. By contrast, the cyclohexane-1,2-dione complex with a cleft of only 2.2 Å [Figure 1 (c) and (d)]



(a) (c)

(b) (d)

Figure 1 *Structural diagram of an oxygen carrier* (a) *and* (b), *and of a similar compound which combines irreversibly with oxygen* (c) *and* (d)
(Reproduced by permission from *J. Amer. Chem. Soc.*, 1973, **95**, 5757)

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[9] A. E. Martell, *Pure Appl. Chem.*, 1968, **17**, 129.
[10] J. Baldwin and J. Huff, *J. Amer. Chem. Soc.*, 1973, **95**, 5757.

takes up half a mole of oxygen per mole irreversibly, oxidizing to an unspecified iron(III) complex. Even the successful oxygen carrier shows its susceptibility to decay in that, above −50 °C the uptake of oxygen is irreversible.

In a cyclic set with several stages, each intermediate must be protected, and the protection is mediated by successions of additions and substitutions. As the catalyst is regenerated after a complete cycle, the additions are only temporary and are decomposed by energy released in forming the products. For example, ethyl zinc triphenyl urea in trimeric form[11,12] assembles three phenyl isocyanate molecules into a 'pre-trimer' which is displaced as the ring compound, an isocyanurate, by excess isocyanate. This is also an example of a 'template' reaction.

With autocatalysis, the products include the autocatalyst itself. The succession of additions and substitutions then has three consequences:

(i) The autocatalyst is a product of synthesis.

(ii) It undergoes further temporary additions in its catalytic role.

(iii) Its structural complexity is related to the complexity of the process which produced it. This is in marked contrast with ordinary catalysts where there need be no such relationship.

C. Active Sites.—Now consider the consumption of active sites during the synthesis of an autocatalyst. The concept of 'active site' is indeed somewhat nebulous, but it fits in well with the terminology for chain reactions. An addition causes a termination, both on the building molecule and on the added group. If there is a further reaction, a propagation, either a new site has been generated or the added group already had an extra site, being 'polyfunctional'. In the general course of cyclic reaction sets, both options apply. Autocatalysis puts a further demand on the supply of active sites, because not only are sites used in making the product but also sites must be formed for the catalytic role of this product. It can be done either through branching reactions or through the addition of groups which are at least trifunctional. Again, it is likely that both options apply.

The autocatalytic set of reactions may contain not just one but several branching reactions, the excess supplying active sites for building the physical structure. Formally, then, a complex set may be described as being made up of sub-sets, each of which is autocatalytic because it contains a branching reaction. In Section 6F, we examine kinetic conditions which favour unions between different autocatalytic systems, so that this description may not be purely formal—complex autocatalysts may be made by joining simpler ones.

Looking at the reaction mixture rather than at the autocatalyst itself, we see that it is likely to contain poylfunctional molecules. Here is common ground between autocatalysis and polymerization, of special interest because polymers are essential components of biological cells.

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[11] J. G. Noltes and J. Boersma, *J. Organometallic Chem.*, 1967, **7**, P6.
[12] G. J. M. Van der Kerk, *Dechema Monograph.*, 1971, **68**, 75.

4 Kinetics of a Single Autocatalytic System

A. Elementary.—Take the very simplified chemical scheme for an autocatalyst, C, in a batch process,

$$R + C \xrightarrow{\beta} C + C, \qquad (14)$$

the kinetics of which obey

$$dR/dt = -\beta.R.C; \quad dC/dt = \beta.R.C \qquad (15)$$

Figure 2 shows the sigmoid curve for C (solid line), the initial rise being exponential, so-called 'autocatalytic kinetics', later tempered by the depletion of reactants. For this simple scheme, the curve for reactants, R (solid line), is the mirror image of that for C, and the whole is symmetrical about the dotted vertical line.

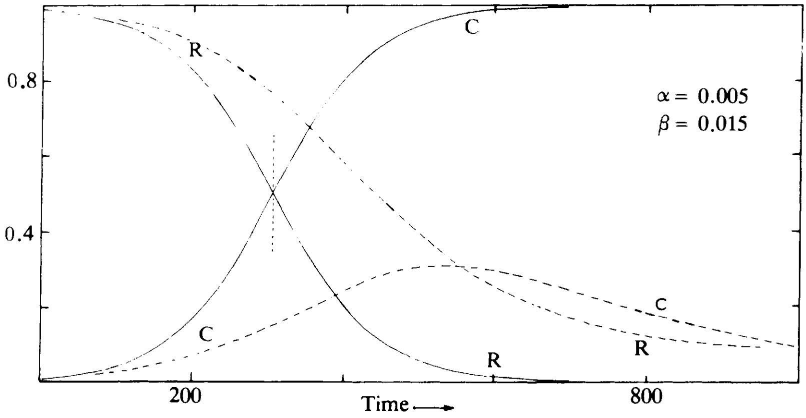

Figure 2 *Kinetic course of simple autocatalysis. Solid lines, without decay. Dashed lines, decay included*

When the intrinsic decay of an autocatalyst is included,

$$C \xrightarrow{\alpha} \text{inert products}, \qquad (16)$$

the mathematical equations become

$$dR/dt = -\beta RC; \quad dC/dt = -\alpha C + \beta RC \qquad (17)$$

where R and C also indicate the concentrations of the species R and C. The dashed lines in Figure 2 show the effect. Reactants last longer because the concentrations of autocatalyst are lower. The curve for the autocatalyst now shows the two fundamental phases of 'autocatalytic expansion' and 'decline'.

B. The Threshold Condition.—The condition for zero growth which separates the phases of expansion and decline has a prime importance [equation (18)]. Notice

$$dC/dt = 0; \quad R_0 = \alpha/\beta \tag{18}$$

especially that this threshold concentration of reactants is quite independent of the concentration of autocatalyst.

C. Replenishment.—The simplest form of replenishment is a constant supply of reactants, S, into a well-mixed vessel. Equation (17) is replaced by

$$dR/dt = -\beta RC + S; \quad dC/dt = -\alpha C + \beta RC, \tag{19}$$

which has an equilibrium solution,

$$R_e = \alpha/\beta; \quad C_e = S/\alpha \tag{20}$$

Equilibrium is approached from a non-equilibrium position by way of a heavily damped oscillation, and R settles to the threshold value given by equation (18). This kind of replenishment is not quite the same as occurs in a 'chemostat'[13] used for cultivating biological cells, where the supply and withdrawal of materials introduce dilution terms which can complicate behaviour.

D. Complex Autocatalytic System.—Complex systems still show the fundamental phases of expansion and decline separated by a threshold concentration of reactants, but there is an elaboration to these concepts. If any one step in the cyclic sequence of reactions slows through shortage of reactant, the circulation of intermediate products is retarded and the whole sequence slows. Depletion in any one reactant, then, brings on the phase of decline. The threshold is therefore determined by whichever reactant is depleted first. Similarly, the conditions reached during replenishment are governed by that reactant which is least well supplied.

Some details of the onset of depletion can be demonstrated with just a two-reaction set, in the first instance neglecting decay:

$$R1 + C1 \xrightarrow{\beta 1} C2 + P1 \tag{21a}$$

$$R2 + C2 \xrightarrow{\beta 2} C1 + C1 \tag{21b}$$

The total production of C, the sum of C1 and C2, is given by

$$dC/dt = \beta 2.R2.C2 \tag{22}$$

Instantaneously, this is independent of (21a), but that reaction supplies C2 so that the production of C depends on the 'historical' course of equation (21). Roughly speaking, R1 and R2 are used at the same rate. If they are not supplied initially in the same amount, one will be used up first. If R1 is used first, C1 accumulates; if R2 is used first, C2 accumulates (see Figure 3). C1 and C2 can be regarded as 'states' of the autocatalytic system, C, and the final stage during depletion depends on the ratio of supplied reactants.

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[13] 'Theoretical and Methodological Basis of Continuous Culture of Microorganisms', ed. I. Málek and Z. Fencl, Academic Press, New York, 1966.

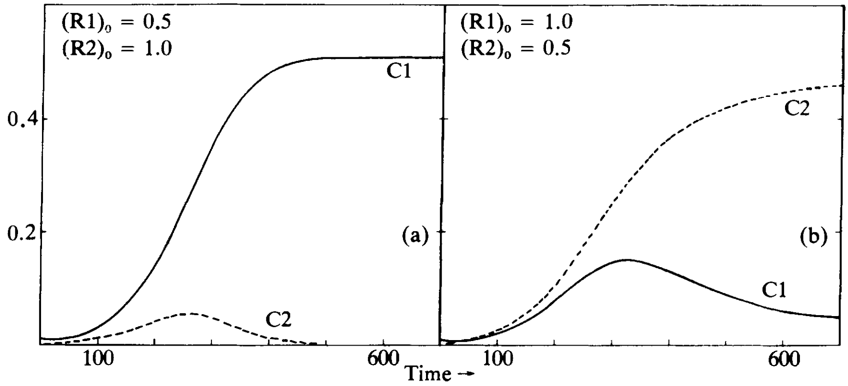

Figure 3 *Distribution among two states of an autocatalyst—no decay.* (a) R1 *in short supply.* (b) R2 *in short supply*

Now, re-introduce decay, but in moderate amount so that the behaviours of the C1 and C2 states are not severely affected when R1 and R2 are plentiful. Both reactants will still be consumed at roughly the same rate so that their ratio still will become more extreme. The reactant in shorter supply still will be depleted first, causing accumulation in the corresponding state of the autocatalyst.

We do not have space to consider the much more complicated question of widely different decay rates for the different states.

The above considerations can be extended to any cyclic sequence or network supplied by a number of reactants, *N*. It has *N* states and its final state under depletion can be determined by restricting the supply of the appropriate reactant. However, if the network can be resolved into more than *N* bimolecular reactions, the states are not all fully independent, some being intergraded by sub-states. Cultures of biological cells are an example of this. These can be regarded as very complex autocatalysts and can be 'synchronized' at selected stages in the growth cycle by starvation with respect to particular nutrients.[14]

E. Modelling.—It is useful, when modelling with a computer, to know how complexity in an autocatalytic system affects the kinetic curve. In the main, it shows as delays while the balance of states in the autocatalyst shifts, firstly when reaction is started and later when the system moves from the expansion phase into the phase of decline. However, even moderately complex systems can be approximated well by very simple equation sets like (21)—a 'growth' and a 'reproduction' condition, to borrow the biological terms. Such approximation is especially useful if the main interest is in the effects of depletion, for then the turnover rate is determined by the slow reaction which is that using the reactant in shortest supply.

The delays in a complex autocatalytic system show clearly in the batch culture

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[14] J. M. Mitchison, 'The Biology of the Cell Cycle', Cambridge University Press, London, 1971.

of bacteria. Following inoculation into fresh medium, there is a pronounced 'lag' phase. Then comes the 'logarithmic' phase in which the logarithm of population increases linearly—population increases exponentially as in autocatalytic kinetics. Between this logarithmic phase and the phase of decline is a 'stationary' phase during which the population stays fairly steady.

5 Spatial Behaviour

A. Control by Diffusion.—We now move away from the assumption of a well-mixed vessel. Take an extended region where the reactant concentration exceeds the threshold for expansion [equation (18)] and introduce autocatalyst at some point within it. The expansion phase depletes reactants locally, creating two gradients—reactants fall off towards the point of introduction and the autocatalyst falls off away from it. Diffusion acts to remove these gradients while reaction maintains them. The activity therefore moves out from the point at a speed determined by the diffusion coefficients and the rates of reaction. In the expanding zone of depletion, the autocatalyst decays. Its maximum concentration is therefore at the 'front' which is advancing into the fresh medium, the thickness of the front being determined by the speed of advance and the decay rate.

A flame propagating as a front along a tube of mixed combustible gases is an example of this. See ref. 4, Chapter VIII, for a readable mathematical account.

Bacteria spotted on to an agar disc loaded with nutrients spread as an expanding ring. Here, the autocatalytic rates are so low that a stable front forms only in a viscid medium.

B. Physical Transport.—Most often, other transport processes are faster than diffusion, so that they determine where the autocatalytic activity will occur, in a mixing zone where streams of separate reactants, including some autocatalyst, are brought together (*e.g.* combustion at a burner).

Provided the reactants exceed the threshold given by equation (18) (or the equivalent for a complex system) the autocatalytic activity will 'invade' any region accessible to the random motions of turbulence and diffusion. The speed of the invading front is therefore determined by the rates of reaction and by the effective coefficient for the mixing process; we considered only diffusion before, but more generally it will be an eddy diffusion coefficient.

The invasive property of autocatalysts requires special care in systems where they are to be controlled. Take, for example, when bacteria are commonly grown in a chemostat—a well-stirred vessel which is drip-fed, both to control the overall rate and to stop the bacteria from invading the supply of nutrients.

C. Chemical Waves.—One might be tempted to draw analogy between the progression of autocatalytic fronts and the propagation of physical wave motions like sound. However, there is a fundamental difference. Physical waves owe their existence to the conservation of energy during its exchange between alternative forms in the medium; the wave carries the energy. Chemical waves do not follow this conservation law. They require that the medium be supplied beforehand with potential energy and the wave is merely a progressive energy dissipation. There can be no constructive interference among chemical waves because, where one has passed, the medium will not support another, at least until it has been replenished.

Autocatalysis provides non-linear kinetic behaviour which potentially can cause oscillations (ref. 4, Chapter X). However, the non-linearity is in time, a history dependence, and is smoothed out in a well-mixed vessel. It follows that a single autocatalytic system will not support oscillations in a well-mixed vessel; this would require at least two interacting sources of non-linearity, and they could well be separate autocatalysts (see Section 6E). But a single autocatalytic system can propagate spatially; one can regard the propagation as a 'phase shift' wave, the different parts of the kinetic curve being spread in space so that the non-linearity is expressed.

6 Interactions between Autocatalytic Systems

Chemical kinetic techniques have been used to treat the interactions between biological species, and we can borrow the results in anticipation of the time when simpler autocatalysts are readily available. We will deduce, therefrom, a couple of very important properties. They arise from including addition reactions beyond those which normally appear in the cyclic sets for the autocatalysts. One comes from competitive interaction and the other from co-operative interaction.

A. Competition.—When two different autocatalysts use the same reactant, they compete. They might use more than one common reactant, but depletion is likely to set in with respect to just one, the controlling reactant, which then becomes the object of competition. From the simple scheme described by equations (14) and (16) [see equation (17)] the logarithmic growth rate is

$$\mathrm{d}\ln \mathrm{C}/\mathrm{d}t = -\alpha + \beta \mathrm{R} \qquad (23)$$

When reactants are plentiful, growth is controlled by β and, when they become scarce, α is controlling. There are thus two kinds of competition, one based on growth rate and one based on decay rate, illustrated for batch processes in Figures 4a and 4b respectively. Notice that, in each case, the rate coefficients differ by only 5% between the competing autocatalysts, but, because the growth rate in equation (23) is the rate for an exponential, even this difference causes a large disparity in peak concentration. The 'more successful' autocatalyst, reaching the greater peak concentration, determines the onset of depletion for both. Notice that depletion starts earlier for the less successful, as can be seen from the expression for the threshold, equation (18), which is larger in a system with smaller β or larger α.

The biologist is also interested in competition based on use of transport, but we will not pursue this difficult topic here.

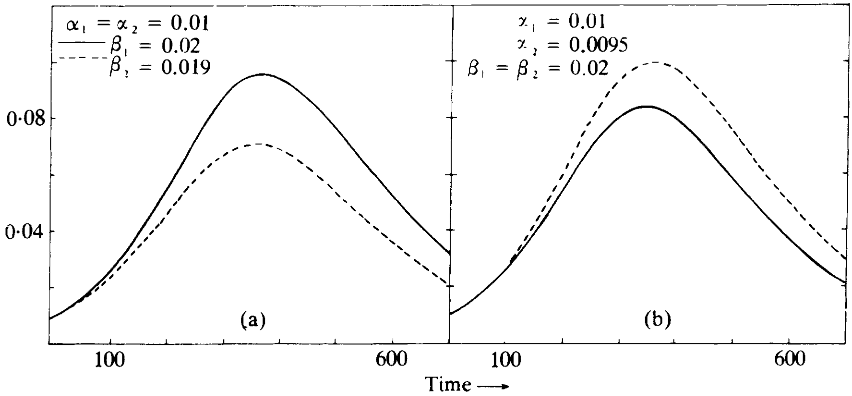

Figure 4 *Competition between autocatalysts.* (a) *With different growth rates.* (b) *With different decay rates. Notice that the solid curves in the two plots represent autocatalysts which have the same growth and decay rates, but these curves are not the same because of interaction with autocatalysts having different characteristics*

B. Competiton in Biology.—With just growth and decay, there is no distinction in principle between 'purely chemical' autocatalytic competition and that between living things over food. However, two distinct disciplines have arisen in biology related to two viewpoints on competition. Ecology treats the cases where the competing species have only one, or at most a few, nutrients (reactants) in common. This throws emphasis on the ways of supplying nutrients. Evolutionary studies, on the other hand, have the competitors sharing all, or almost all, nutrients because they are variants of the same species. This promotes interest in the causes of the variations, now attributed to mutations in DNA.

C. Particles.—We will now consider a special kind of competition, akin to the evolutionary viewpoint, where the variants arise not from mutation but from differences in physical structure. Compare two variants, one where all the cyclic reactions take place within a single kind of 'particle', and the other where the same cyclic reactions are distributed between two kinds of particle. Section 3 described how physical structure affects the chemistry, protecting active sites and promoting the turnover rate through the equilibrium effect. In both respects, the single particle has a great advantage over the two-particle (or any multi-particle) variant. Provided even slow addition reactions are available to build the single particle structure, its competitive advantages ensure that the cyclic reactions of an autocatalytic set are 'packaged' in this way. This is the first of the two properties dependent on addition reactions mentioned at the beginning of this section.

Here is a conspicuous difference between an autocatalyst and an ordinary catalyst. Both benefit equally, in terms of turnover rate and resistance to decay, from advantageous physical arrangements. But only the autocatalyst has the kinetic feedback to select the most effective structure, generally speaking, the single particle. The biological individuals, like bacteria, are examples of very complex autocatalytic particles.

D. Co-operative Interaction.—Different autocatalytic systems interact 'co-operatively' when their reactions are consecutive—a product of one is reactant for the other. Autocatalysts introduce a distinction into consecutive reactions which was not obvious in Section 2:

(i) One autocatalyst is itself a reactant for the second, being consumed or at least disrupted.

(ii) Another product of the first autocatalyst is a reactant for the second.

The latter class is important for describing the ecological interactions between biological species. Its detailed behaviour depends very much on how the whole system is replenished and on the relative growth and decay rates of the separate species. We will not pursue it here.

E. The Predator–Prey Scheme.—The first class of consecutive autocatalytic schemes, (i) above, is famous in biology as the predator–prey scheme, described by the Lotka–Volterra equations. Goel *et al.*[15] discuss and illustrate the temporal oscillations in detail (see Figure 5 for an example).

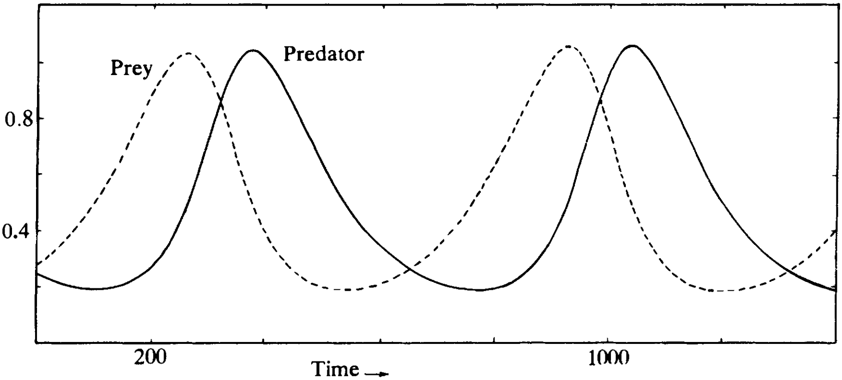

Figure 5 *Predator–prey oscillations. Solid line, predator. Dashed line, prey. In the general case, the predator and prey do not show the same amplitudes of oscillation*

This system has the unusual feature of neutral stability, such that oscillations continue with a fixed amplitude determined by the starting conditions; different starting conditions give a different amplitude. Naturally (see Section 5C), the system also oscillates in space, and it has been invoked to explain patchiness in marine plankton.[16]

F. Mutual Exchange.—This bears the same relation to autocatalysis as a catalytic

[15] N. S. Goel, S. C. Maitra, and E. W. Montroll, *Rev. Mod. Phys.*, 1971, **43**, 231.

[16] D. M. Dubois, *Ecological Modelling*, 1975, **1**, 67.

pair does to simple reactions [equation (5)]; a product of one is reactant for the second and a product of the second is reactant for the first. The mutual exchange creates a cyclic set which includes those of the separate autocatalysts. The inclusive cyclic set is therefore autocatalytic in two intermediates—the primary autocatalysts.

We can now apply the ideas in Sub-section C on the advantages of particle structure. If the primary autocatalysts are in single-particle form, addition reactions between their members creates a new particle, a 'union', which contains all the reactions of the inclusive cyclic set. The union gains a competitive advantage over the primary species because of the equilibrium effect over the exchanged materials and, if these materials are not supplied with the other reactants, this advantage is decisive. Figure 6 shows the time course of the union in batch process for two different values, ω, of the rate coefficient for the addition reactions (dashed curves, A and B). Indeed, ω merely determines the time required to build up the union to a point where autocatalytic regeneration predominates; smaller ω means a longer delay, but the final 'bloom' is the same. The primary autocatalysts are depleted of the exchanged materials and their course is the inconspicuous solid line labelled 'A and B'.

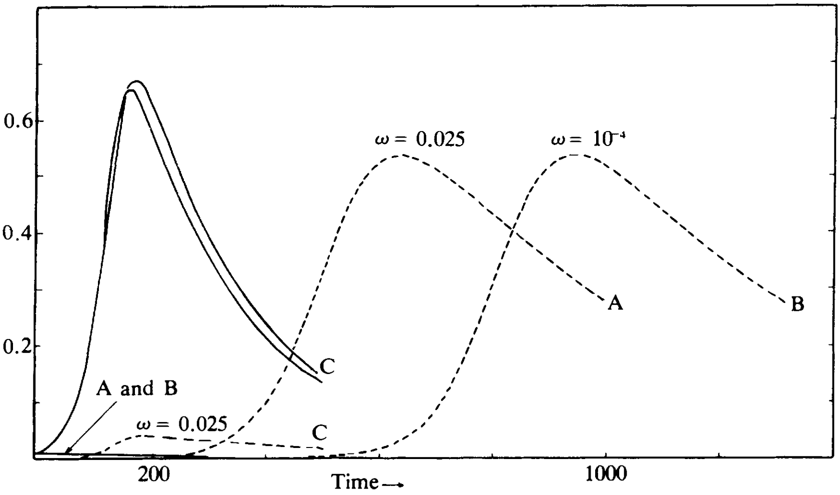

Figure 6 *Kinetic course for two primary species (solid lines) and the species formed by their union (dashed lines). See text for labelling*

On the other hand, if the exchanged materials are well supplied initially, a different situation holds. The primary autocatalysts are now well supplied and can expand. Consider the turnover time for a complete cycle of the union; it is at least as long as the longer turnover time for the primary particles and probably approaches the sum of their times. With quicker turnover, the primary particles now have the competitive advantage. The pair of solid lines, C, in Figure 6 show their time course while that of the union, even for the high value of ω, is given by the dashed line, C.

There are thus two regimes for this system, one favouring union and the other favouring separate primary particles, depending on the initial supply of exchanged materials. If ω is small, the transition from one regime to the other occurs abruptly.

In biology, the regime of separate primary species is called 'mutual association through nutrition' or 'disjunctive symbiosis', while the union is a 'conjunctive symbiosis'.

7 Making Autocatalysts

A. General Strategy.—The foregoing sections have set out various properties of autocatalysts which should be borne in mind when trying to make them: (i) The reaction sets are cyclic. (ii) In solution, physical structure is needed to restrict reaction to the cyclic sets. (iii) Autocatalysts suffer intrinsic decay, so that a phase of expansion is inevitably followed by a phase of decline. (iv) There is a threshold concentration of reactants below which they will not support a phase of expansion. (v) All reactants must be present: if any one falls below the threshold, the system is in decline. (vi) The reaction mixture may contain polyfunctional molecules. (vii) Because the autocatalyst and its parent mixture are all reactive species, foreign materials should be strictly excluded.

Careful consideration of these points indicates that it may be very difficult to specify reactants which together will yield 'autocatalytic kinetics'. On the other hand, it may be relatively easy to make a mixture which contains an autocatalyst in steady state with its reactants, making it by irradiating a complex degenerate mixture.

So long as a mixture contains absorbing molecules, radiant energy promotes cyclic action, though much of it may be merely physical cycling of energy.[17] Chemical cycling is encouraged by the presence of 'scavengers', compounds which react with the primary photoproducts with low activation energies. These in turn act as energy stores for other cyclic or non-cyclic chemical action. Non-cyclic chemistry causes material to be withdrawn so that, after irradiation for some time, only materials remain chemically active which are capable of supporting cyclic sets on this time-scale.

A reaction mixture which supplies an autocatalyst can, in principle, form it by an uncatalysed route. In batch process, the likelihood is low because competing reactions consume the mixture, the more so with increasing autocatalytic complexity. However, in an irradiated mixture supporting cyclic sets, the competing reactions are routes for recycling the reactants for the autocatalyst. Even very low rates for uncatalysed formation can, given time, accumulate the autocatalyst. An autocatalyst differs from the other cyclic sets in such a mixture by its ability to regenerate itself. All the ordinary catalysts are subject to decay, whereas the auto-

[17] V. Balzani and V. Carassiti, 'Photochemistry of Co-ordination Compounds', Academic Press, London, 1970.

catalyst, through regeneration, maintains its concentration so long as the supply of reactants is maintained. In the long run, therefore, the autocatalyst predominates.

B. Simplified Analysis.—Let us relate the concentration of autocatalyst to the threshold concentration of reactants, using the simple autocatalytic set,

$$\begin{aligned} R + C &\xrightarrow{\beta} C + C \\ C &\xrightarrow{\alpha} P \\ P &\xrightarrow{\rho} R \\ R + R &\xrightarrow{\gamma} C + C \end{aligned} \tag{24}$$

Here, ρ is the rate for converting spent products, P, back into reactants, R and is therefore proportional to the incident radiation. This set does not include competition with decaying ordinary catalytic cycles and is thus appropriate only for the late stages of the process described above. It is useful for the final equilibrium condition and for clarifying the role of γ, the rate coefficient for uncatalysed production of the autocatalyst.

At equilibrium,

$$dC/dt = -\alpha C + \beta RC + \gamma R^2 = 0 \tag{25}$$

giving

$$C = (\gamma/\alpha)R^2/(1 - R/R_0)\,, \tag{26}$$

where R_0 is again the threshold value, α/β. Notice that γR^2 stays together, so that the assumption of second order production does not restrict the generality. Equation (26) is easily plotted as a function of total reactants, R + C + P, by assigning values of R (necessarily less than R_0), deducing C and then P from its recycling condition,

$$P = C\alpha/\rho \tag{27}$$

For concentrations of total reactants below the threshold (see Figure 7), they are nearly all in the form of active reactants for the autocatalytic process, R. At higher concentrations, excess reactants appear as autocatalyst and spent products in a ratio determined by the intensity of radiation.

The role of uncatalysed production can be seen by plotting the kinetic course for different values of γ (Figure 8). In this figure, the total reactants have the value, 1.0, twice the threshold. At relatively large γ, 0.005, uncatalysed production depresses R and raises C. At small γ, the final values of R and C are invariable but they are achieved after a time delay which is longer for smaller γ.

The recipe for making autocatalysts is thus to irradiate a complex mixture for a long time, detecting success from the constant final concentration of some reactant regardless of the total concentration of them all.

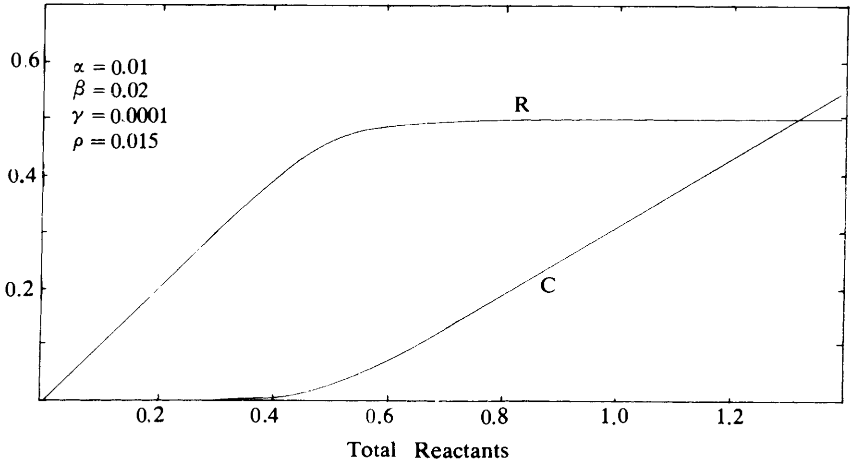

Figure 7 *Irradiated mixture. The equilibrium concentrations of active reactants,* R, *and autocatalyst,* C, *as functions of total reactants*

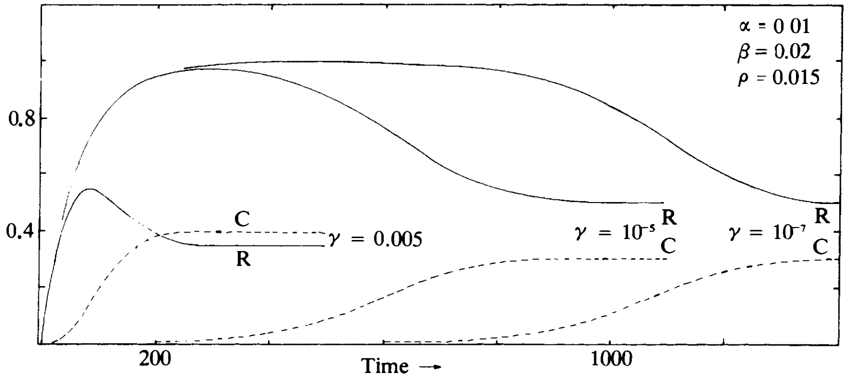

Figure 8 *Kinetic course of irradiated mixture for three different values of* γ, *the coefficient for uncatalysed production of autocatalyst*

C. Suitable Materials.—Cyclic chemical action is most readily achieved among those classes of compounds which exhibit a relatively wide range of binding strengths, the co-ordination compounds of metal ions,[18] hydrogen-bonded compounds,[19] and heterocyclic organics like the biological co-enzymes (ref. 8, Chapter

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[18] S. F. A. Kettle, 'Co-ordination Compounds', Nelson, London, 1969.

[19] G. C. Pimentel and A. L. McClellan, 'The Hydrogen Bond', W. H. Freeman, San Francisco, 1960.

8). Indeed, the literature on catalysis by co-ordination compounds and the organometallics is now very extensive.[9,12,20–26] Their photochemistry is also an active field of research,[17,27,28] and Wrighton *et al.*[29] have explored some aspects of the photoformation of catalysts. These materials provide a good starting point.

8 Uses for Autocatalysts

The expansion phase of the kinetic curve distinguishes autocatalysts from ordinary catalysts, and it provides automatic replenishment of catalyst when the reactants to a system are replenished. This makes it possible to think in terms of very complex catalysts, difficult to make initially and perhaps with high rates of decay, yet available so long as they are kept in use. Indeed, the living cells employed for treating sewage cannot be made initially, but they are used because the process is self-regulating. The other motive for using complex catalysts is to get complex products at high yield, the manufacture of antibiotics being a good example. Synthetic autocatalysts offer the same prospect. However, we should note that they are likely to be homogeneous catalysts with the attendant problem of separating the catalyst from the desired product. Some solutions to this problem are already available[30] and could well be applied to autocatalysts, also.

Gaseous autocatalysis is widely used, in the form of flames and explosions, to release stored energy in a controlled manner. The internal combustion engine is an elegant coupling of autocatalysis and mechanical processes. Autocatalysis in the liquid phase is unlikely to be used thus, but it does raise the possibility of much more sophisticated chemical amplifiers and control devices. It may be possible to use switching between autocatalytic states according to the supply of reactants and interaction with the environment by spatial propagation. Under what circumstances would it be advantageous to have such a chemical device rather than a mechanical or electrical one?

Although we have stressed the necessity for physical structure in order that autocatalysts may function, we have not considered the more detailed physical changes which occur during the cyclic chemical action. Conceivably, cyclic additions and decompositions could be arranged to cause physical movement. Indeed, biological examples are commonplace, from the threading of m-RNA through ribosomes to the movement of amoebae and the operation of muscle.

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[20] M. M. Jones and W. A. Connor, *Ind. and Eng. Chem.*, 1963, **55**, 14.

[21] J. Chatt, *Science*, 1968, **160**, 723.

[22] 'Homogeneous Catalysis', Advances in Chemistry Series No. 70, American Chemical Society, Washington, 1968.

[23] J. Halpern, *Pure Appl. Chem.*. 1969, **20**, 59.

[24] D. R. Eaton, Chapter 9 of 'Bio-Inorganic Chemistry', Advances in Chemistry Series No. 100, American Chemical Society, Washington, 1971.

[25] F. G. A. Stone, *Nature*, 1971, **232**, 534.

[26] C. A. Tolman, *Chem. Soc. Rev.*, 1972, **1**, 337.

[27] W. L. Waltz and R. G. Sutherland, *Chem. Soc. Rev.*, 1972, **1**, 241.

[28] M. Wrighton, *Chem. Rev.*, 1974, **74**, 401.

[29] M. S. Wrighton, D. S. Ginley, M. A. Schroeder, and D. L. Morse, *Pure Appl. Chem.*, 1975, **41**, 671.

[30] D. Commereuc and G. Martino, *Rev. Inst. Français du Pètrole*, 1975, **30**, 89.

However, the disparity between the size of everyday mechanical devices and the size of molecules makes it difficult to achieve a practical chemical motor. Living matter solves the problem by stacking layers of autocatalytic particles through their own growth until the free space is filled. It is at least interesting to speculate about copying this principle.

More immediately realizable is the storage of photochemical energy. Basically, it waits only on the successful generation of autocatalysts according to the scheme suggested in the last section. Both energy storage and cyclic chemical action call for physical structure to restrict reaction to a specific route. Storage may be achieved in a complex ordinary catalyst[31] or by the physical separation of products.[32] But again, autocatalysis offers the advantage of a self-regulating process. Nature does it autocatalytically when growing trees for us to burn.

We have drawn amply on biology for examples of autocatalysis and, likewise, some of the ideas in this review may be useful in biology. To some extent, they have already been applied to the questions of the origin of life[33] and the evolution of prokaryotic cells.[34]

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[31] D. V. Stynes, *J. Amer. Chem. Soc.*, 1974, **96**, 5942.

[32] S.-N. Chen, N. N. Lichtin, and G. Stein, *Science*, 1975, **190**, 879.

[33] G. A. M. King, *Origins of Life*, 1977, **8**, 39.

[34] G. A. M. King, *BioSystems*, 1977, **9**, 35.