PAR AVION

LETTRE

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May 26, 1992

Dear Dr. Bahadur:

I am sure this letter finds you in the best of health and high spirit. The 21st May issue of Nature has a write up in its news and views section entitled, "Life in a test tube." Reading this echoed my life back almost half a century ago at Allahabad chemistry department. There are many aspects which are described here which may interest you and I am sure you will find at home reading this piece and references cited there in. I am enclosing one of these references. But most pertinent reference seems to be Ref. No: 2, which unfortunately is yet to arrive at my library. The volume is misprinted. It is 'Science' Vol. 256.

Life at my end is extremely busy on the research front. A number of new and challenging ideas to experiment with. The focus of my current research is directed towards the understanding of the mechanism of signal transduction at the level of cell nuclei. We have documented that

two key molecules of cellular Signal transducing System are located in the nucleus i.e. protein kinase C and inositol 1, 4, 5- trisphosphate receptor. We are investigating how protein kinase C regulates IP_3- receptor in the nucleus. This will explain the mechanism of movement of calcium in and out of nucleus. We are also studying the phosphorylation of retinoblastoma tumor suppressor gene product in a cell cycle dependent manner. I have a band of young people working with me who are keen to learn more and more.

On the home front I have two daughters named Natasha ~~[redacted]~~ ($3\frac{1}{2}$ yrs) and Chetna ($2\frac{1}{2}$ yr). Natasha visited with me Allahabad last year. I could not visit you during my sojourn there due to ~~traffic~~ emanating from Ram Temple issue.

I understand that Kalyan Singh Govt. in U.P. is trying to tone up administration. I do not know how far Kalyan Singh understands Indian bureucracy. The greatest bottlenecks in Indian System is a self defeating bureucracy and IAS or PCS corrupt to

the core. ~~Does~~ ~~Do~~ During the past several decades Indian bureucracy has amazed privileges reminiscent of old ~~shahs~~ and until and unless these privileges are not withdrawn nothing will come out. Does Kalyan Singh have the mental calibre or moral courage to deprive bureucracy the unquestioned privileges they have secured for themselves? I have my doubts because I have found Kalyan Singh when he was Health Minister. Let us hope for the best, for the poor man walking on the streets.

Please convey my regards to Mrs. Bahadur & compliments to all your grown ups and grand children.

With kind regards &
Cordial greetings.

Sincerely yours

A. N. Mathuriya

the seemingly abrupt appearance in the early Early Cretaceous (Neocomian) of sustained powered flight and endothermic physiology in the first habitually arboreal birds.

5) *Reassessment of early avian phylogeny and ecology*. The advanced flight apparatus and opposable hallux in *Sinornis* and the Spanish bird (*6*) suggest that sustained powered flight and perching capability are primitive for Ornithurae and can no longer be used to unite Ichthyornithiformes and Neornithes to the exclusion of Hesperornithiformes (*18*). These synapomorphies must have been reduced or lost during the evolution of diving habits in Hesperornithiformes. The interrelationships among Late Cretaceous birds are correspondingly less secure, although several additional features maintain a close relationship between Ichthyornithiformes and Neornithes (Fig. 5). Nearly all Mesozoic birds known from reasonably complete remains have been discovered in quiet near-shore marine or marginal lagoon sediments, and this taphonomic bias has colored our view of early avian evolution. The discovery of *Sinornis* in freshwater lake deposits highlights the important, yet largely unknown, role that inland wooded habitats must have played in the early evolution of birds.

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21. Supported by the National Geographic Society (4262-90 to P.C.S.) and the David and Lucile Packard Foundation (to P.C.S.). We thank J. Ostrom for allowing access to fossil materials in his care, W. Simpson for preparation and casting of the skeleton, and C. Abraczinskas for execution of the finished illustrations. We also thank L. Chiappe, J. Cracraft, A. Feduccia, J. Ostrom, and L. Witmer for comments on the manuscript.

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Competition, Cooperation, and Mutation: Improving a Synthetic Replicator by Light Irradiation

JONG-IN HONG, QING FENG, VINCENT ROTELLO, JULIUS REBEK, JR.*

Replication and mutation are necessary elements of evolution, and some properties of self-replicating molecules (replicators) can be explored with synthetic structures. Selection and evolution at the molecular level require systems capable of competition and inheritable change. These phenomena have now been observed with synthetic molecules. Two such molecules were prepared having sufficient structural similarity that they catalyzed each other's formation as well as their own. One of the replicators bears a photochemically active function that is cleaved on irradiation. The resulting species is more effective at replication than the original and rapidly takes over the system's resources.

SELF-REPLICATING MOLECULES CAN be synthesized by covalent linkage of two complementary subunits to give a self-complementary structure (*1*). Complementarity in this context refers to sizes, shapes, and the weak intermolecular forces involved in molecular recognition between the two subunits. Behavior such as autocatalysis and sigmoidal product growth can be expressed by these synthetic replicators as well as by nucleic acid derivatives (*2–5*). For the system to evolve, replicators are expected to make "mistakes," or respond to environmental stresses that favor new and more (or less) competitive species (*6*). Accordingly, we have synthesized structures capable of cooperation and mutation and report here their properties.

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Coupling of the imide ester **1** (Eq. 1) with amines bearing adenine nuclei **2** in $CHCl_3$ yields the respective amides **3** (*7*). The self-complementarity of these products leads to their extensive dimerization through hydrogen bonding to **4** and is the key to their replicative behavior (*1*).

All three products are replicators: They catalyze their own formation. Specifically, adding 20% of a product to its respective reaction mixture enhances the initial coupling rate by 60% for **3a** and by ~30% for **3b** and **3c** (Figs. 1 and 2). The autocatalysis results from the template effects that gather the two reacting components on the product surface as suggested in Eq. 2. The unsubstituted **3a** can replicate both through Hoogsteen base pairing as shown in **5** and through Watson-Crick pairing as shown in **6**. The urethane-protected **3b** and **3c** are disadvantaged in this respect; the nitrogen substituent hinders base pairing in the Wat-

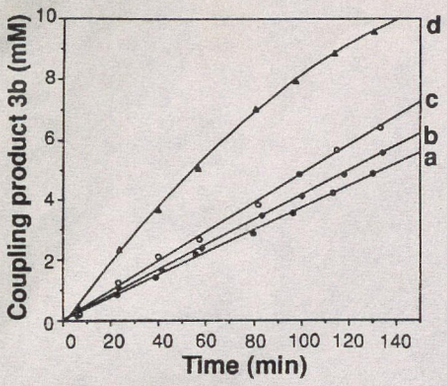


Fig. 1. Product **3b** appearance as a function of time for the reaction of **2b** + **1** at 50 mM each in $CHCl_3$: (a) no additive; (b) 20% **3c** added; (c) 20% **3b** added; and (d) 20% **3a** added.

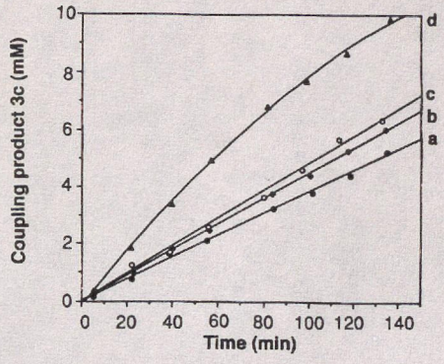


Fig. 2. Product **3c** appearance as a function of time for the reaction of **2c** + **1** at 50 mM each in $CHCl_3$: (a) no additive; (b) 20% **3b** added; (c) 20% **3c** added; and (d) 20% **3a** added.

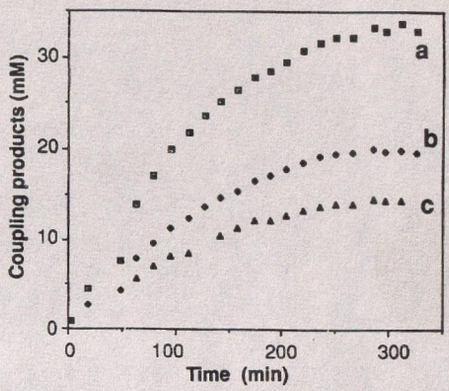
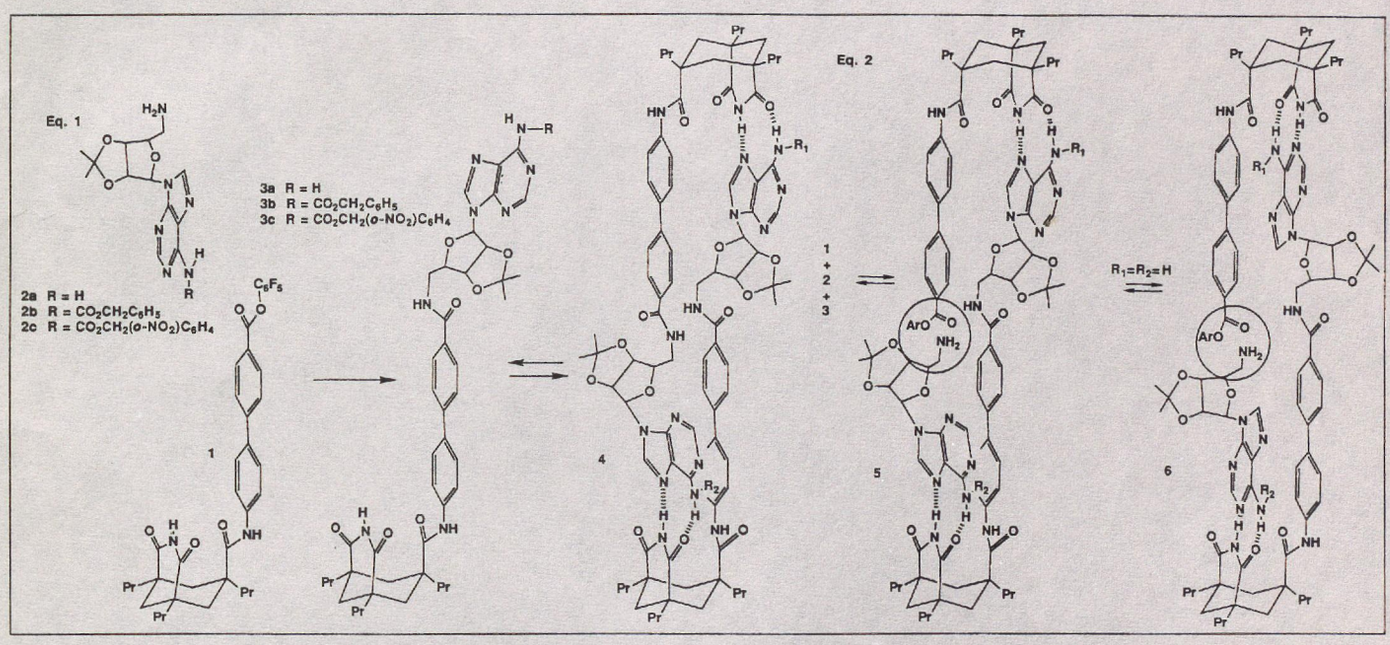


Fig. 3. Product appearance as a function of time for the reaction of **2a** + **2b** + **2c** + **1** (42 mM each) in $CHCl_3$: (a) **3a**; (b) **3b**; and (c) **3c**.

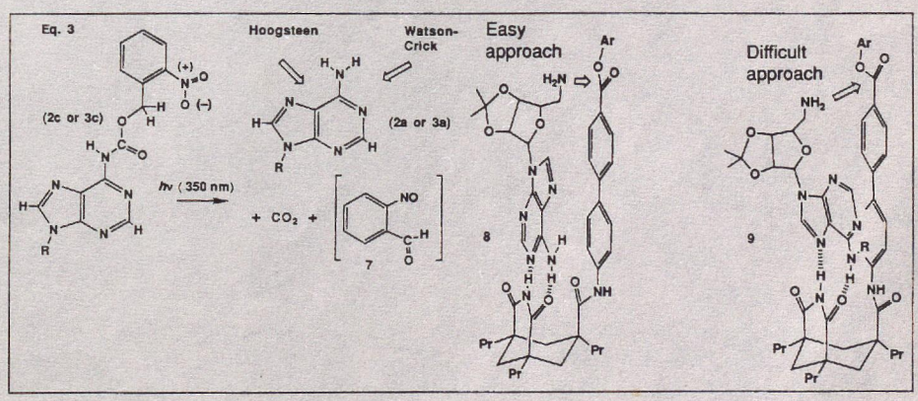


Equations 1 and 2.

son-Crick modes (*8*) and limits it largely to the Hoogsteen modes shown in **5**.

The products do make mistakes: They catalyze the formation of the other replicators. For example, the presence of 20% **3b** during the coupling of **1** with **2c** increases the rate of appearance of **3c** by 18% and the presence of 20% **3c** during the coupling of **1** with **2b** increases the rate of appearance of **3b** by 10%. The cooperative and reciprocal behavior is understandable because the structural similarity of **3b** and **3c** is high; the NO_2 versus H difference between the two molecules is at a site remote from their recognition surfaces. In chemical terms, the structures show low selectivity. As a result, the heterogeneous (mixed) termolecular species **5** or **6** ($R_1 \neq R_2$, Eq. 2) and product dimers **4** ($R_1 \neq R_2$, Eq. 1) are as likely to form as the homogeneous ones ($R_1 = R_2$).

The nitrated derivatives are irreversibly mutated by light. Compounds **2c** and **3c** bear photolabile blocking groups (*9*) that can be removed by irradiation at 350 nm (Eq. 3). For example, in $CDCl_3$ a solution of **3c** in a cuvette irradiated for 30 min (Rayonet reactor) is cleanly converted to **3a**; likewise **2c** can be converted to **2a** (*10*). The resulting deblocked system is a more efficient replicator: Direct competition of the three amines **2a**, **2b**, and **2c** for a limited



Equation 3 and structures **8** and **9**.

quantity of the ester **1** results in rapid formation of the efficient replicator **3a** as the dominant product (Fig. 3).

The superiority of **3a** as a replicator is due to its ability to base pair in both senses (**5** and **6**, $R_1 = R_2 = H$) or even a combination of the two. In addition, rapid initial reaction of **2a** with the ester **1** can take place through the Watson-Crick base pair **8** where aryl stacking interactions (*11*) position the reacting functions near each other. In contrast, initial reaction of **2b** or **2c** occurs through **9** where the functions are farther apart. Despite its efficiency, the mutant **3a** is not selfish; it provides effective catalysis for the formation of its competitors, **3b** and **3c**. The presence of 20% **3a** enhances the coupling rates of either of these more than twofold (Figs. 1 and 2).

In the present case adenine-imide base pairing in $CHCl_3$ provides the molecular recognition that leads to self-replication. Other weak intermolecular forces between other host-guest pairs in other solvents could also be used. For example, the solvophobic forces involved in cyclophane-arene complexation in water (*12*) could give rise to a synthetic replicator by way of a covalent linkage between host and guest. The variety of suitable recognition vehicles is vast. Replicating molecules are at the boundary of chemistry with biology, and such synthetic structures can be used to further model evolution at the molecular level.

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12 September 1991; accepted 18 December 1991

Gating of the Cardiac Ca^{2+} Release Channel: The Role of Na^+ Current and Na^+-Ca^{2+} Exchange

JAMES S. K. SHAM, LARS CLEEMANN, MARTIN MORAD*

In cardiac myocytes, calcium influx through the calcium channel is the primary pathway for triggering calcium release. Recently it has been suggested that the calcium-induced calcium release mechanism can also be activated indirectly by the sodium current, which elevates the sodium concentration under the cell membrane, thereby favoring the entry of "trigger" calcium via the sodium-calcium exchanger. To test this hypothesis, sodium current was suppressed by reducing the external sodium concentration or applying tetrodotoxin. At potentials positive to −30 millivolts, calcium release was unaffected. A small calcium release at more negative potentials could be attributed to partial activation of calcium channels, because it was unaltered by replacement of sodium with lithium and was blocked by cadmium. Thus, sodium influx or its accumulation does not initiate calcium release. In addition, sodium-calcium exchange–related calcium release at potentials positive to +80 millivolts has slower kinetics than calcium channel–induced release. Therefore, only the calcium channel gates the fast release of calcium from the sarcoplasmic reticulum in the range of the action potential.

IN MAMMALIAN CARDIAC MYOCYTES, the release of Ca^{2+} from the sarcoplasmic reticulum (SR) is controlled by Ca^{2+} influx through the Ca^{2+} channel (*1–3*) by Ca^{2+}-induced Ca^{2+} release (*4*). This mechanism is specific to Ca^{2+} because Ca^{2+} can be released by rapid elevation of Ca^{2+} in skinned (*4*) or intact cardiac myocytes (*5*), and neither Na^+ nor Ba^{2+} can substitute for Ca^{2+} in the release process when they are the charge carrier through the Ca^{2+} channel (*2*). As an extension of this scheme, it has been reported that the Na^+ current can also trigger Ca^{2+} release (*6*) through subsarcolemmal accumulation of Na^+ in quantities sufficient to reverse the Na^+-Ca^{2+} exchanger and allow Ca^{2+} to enter the cell and trigger Ca^{2+} release (*6*, 7). This could provide a theoretical basis for a beat-to-beat regulation of Ca^{2+} release and contraction by the Na^+ current via the Na^+-Ca^{2+} exchanger. In this report, we examine the role of the Na^+ channel and Na^+ accumulation in the subsarcolemmal space in Ca^{2+} release.

Rat ventricular myocytes were enzymatically isolated (*8*) and whole-cell voltage-clamped (*9*). Intracellular fura-2 (120 to 200 μM) was used to monitor the intracellular Ca^{2+} activity. Fura-2 was excited at 335 and 410 nm, and intracellular Ca^{2+} activity was determined from the ratio of the two fluorescence intensities, measured at 520 nm (*3*). The external solution bathing the experimental cell was exchanged rapidly (20 to 100 ms) for short periods (usually 1 to 5 s) with a concentration-clamp system, allowing minimal steady-state alteration of the cytosolic Na^+ and Ca^{2+} concentrations.

To examine the role of the Na^+ current (I_{Na}) in the release of Ca^{2+}, we suppressed or abolished I_{Na} by rapidly reducing extracellular Na^+ from 142 to 10 mM (for about 2 s) repeatedly at different potentials and analyzed the voltage dependence of intracellular Ca^{2+} transients in myocytes with an intracellular Na^+ concentration of 10 mM (Fig. 1). We chose 10 mM external Na^+ to set the equilibrium potential of Na^+ (E_{Na}) at about 0 mV during the experimental run. In a control solution (142 mM Na^+), depolarization of the myocyte from −80 to 0 mV activated both the Na^+ and Ca^{2+} currents and a maximal Ca^{2+} release. Reduction of the Na^+ concentration to 10 mM 0.5 to 1 s before the depolarization of the cell to 0 mV (E_{Na} in test solution) completely suppressed I_{Na} but had no effect on the rate or magnitude of Ca^{2+} release (Fig. 1, A and C). On the other hand, the smaller Ca^{2+} release in the control solution, triggered by depolarization of the myocyte to −50 mV, was abolished by the reduction of the Na^+ concentration to 10 mM (Fig. 1, A and C).

The effects of rapid reduction of Na^+ were also examined at other membrane potentials, ranging from −50 to +60 mV (Fig. 1, B and D). Despite considerable suppression of the Na^+ current, there was no significant difference in Ca^{2+} transients in high- and low-concentration Na^+ solutions except at potentials between −50 and −30 mV, suggesting a very limited range of potential for the Na^+ current–induced effect. The results were highly reproducible (n = 7 cells) with only minor variations in the degree of suppression of the inward current

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Crossover Reactions Between Synthetic Replicators Yield Active and Inactive Recombinants

Qing Feng, Tae Kyo Park, Julius Rebek, Jr.

Self-replicating molecules can be synthesized through the covalent linkage of two complementary subunits to give a self-complementary structure. Complementarity refers to sizes, shapes, and the weak intermolecular forces involved in molecular recognition between the two subunits. In order to provide a model system for evolution at the molecular level, "crossover" or recombination experiments were staged with synthetic replicators. These reactions gave rise to new structural types. The ability (or inability) of the new recombinants to catalyze their own formation is shown to be a consequence of their molecular shapes.

Self-replicating molecules (replicators) lie at the interface of chemistry with biology. Synthetic replicators provide a means by which evolutionary phenomena such as competition, reciprocity, and mutation can be expressed at the molecular level (*1*). We describe new self-replicating structures arising from recombination of other replicators. Two such recombinations were synthesized. One forms hydrogen-bonded dimers readily and shows autocatalytic behavior, whereas the other features mismatched binding surfaces that diverge; it is unable to act as a template for its own formation.

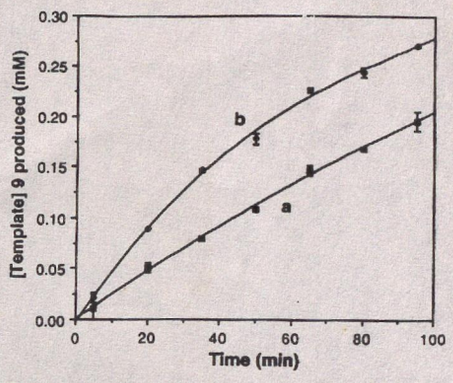
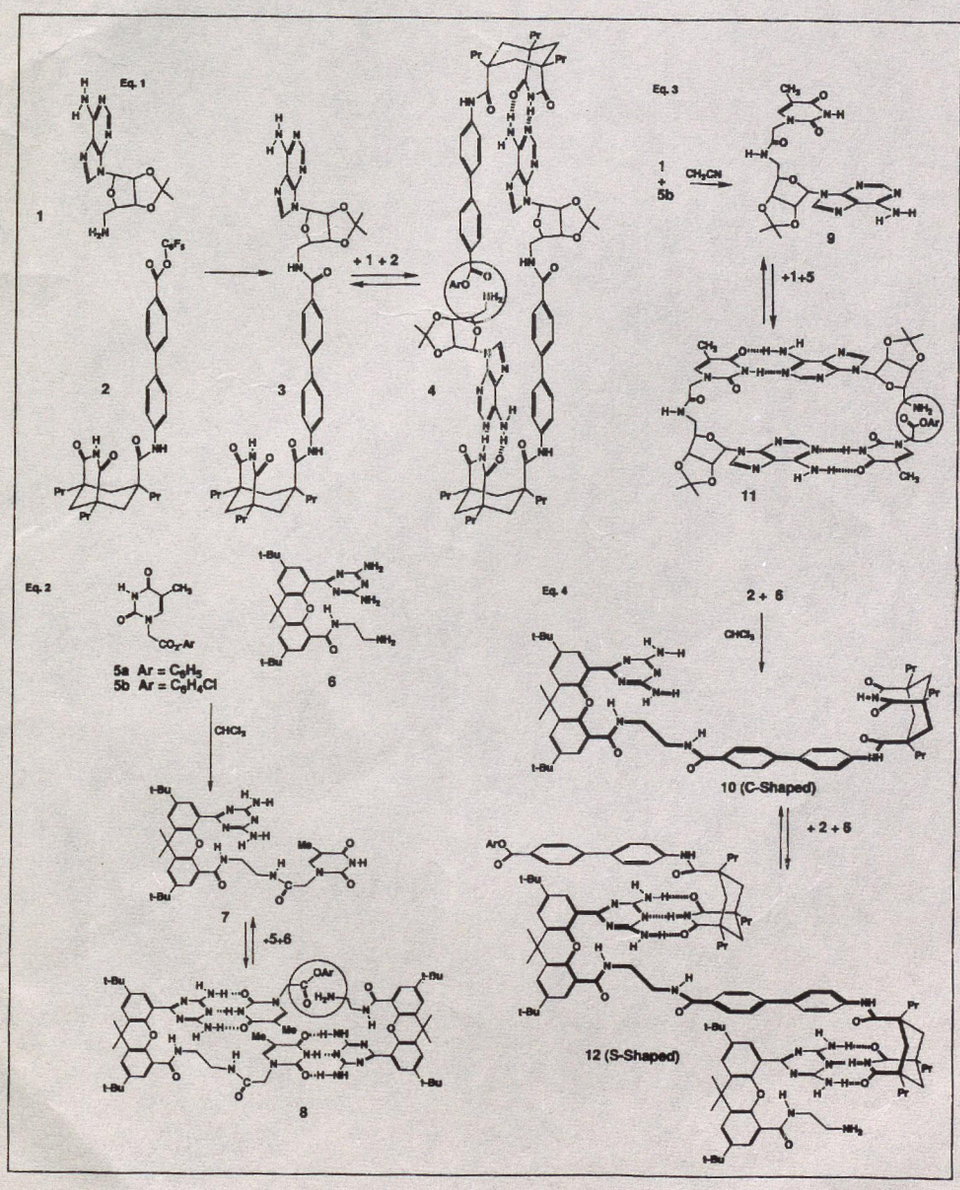


Fig. 1. Appearance of **9** as a function of time. Initial concentrations are [**1**] = [**5b**] = 3.0 mM in CH_3CN. Triethylamine (18 equivalents) was present in all of the reaction solutions. Error bars represent standard deviations of multiple independent runs. (a) Reaction of **1** and **5b** without additive. (b) Reaction of **1** and **5b** with 0.07 equivalent of **9** added.



The structural requirement for replicators is self-complementarity (*2*), and earlier we described two such minimalist systems. The first involved adenine-imide hydrogen bonding (*3*) and aryl stacking as the intermolecular forces that lead to molecular self-recognition (Eq. 1). The second features thymine-diaminotriazine hydrogen bonding (*4*) (Eq. 2) in the coupling reaction of **5a** with **6**. Both reaction products **3** and **7** are replicators: they catalyze their own formation through the template effects depicted in structures **4** and **8**.

A competition experiment was carried out in which recombination (crossover) products could be produced. Specifically, coupling of the adenine **1** with the thymine *o*-chloro-phenylester **5b** gave the dinucleotide analog **9** with an amide linkage (*5*) (Eq. 3), whereas the corresponding reaction of **2** with **6** gave **10** (Eq. 4).

At first glance, both recombinants might be expected to replicate. They bear self-complementary recognition surfaces and can gather their respective reaction components in termolecular complexes. In fact, the adenine-thymine hybrid **9** does act as such a template. Addition of **9** to mixtures of **1** and **5b** in CH_3CN led to the increased coupling rates (Fig. 1) characteristic of autocatalytic systems (*6*). It is a riotously fertile hybrid. Compared with previous synthetic replicators, it shows the largest autocatalytic effects observed to date (*7*). The situation is quite different for the recombinant **10**. No increase in initial coupling rate for **2** with **6** was

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June 2, 1992

Dear Dr. Baharden!

This is the article which has been quoted in the Nature's news & views section, a copy of which I have sent you. I thought it may be intellectually stimulating for you since there is an echo of what you were aiming almost 25 years ago.

With kind regards. Sincerely yours

A. N. Mathiya

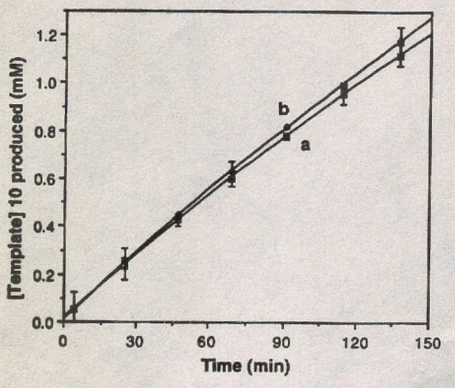

Fig. 2. Appearance of **10** as a function of time. Initial concentrations are [**2**] = [**6**] = 8.0 mM in $CHCl_3$. Triethylamine (12 equivalents) was present in all of the reaction solutions. Error bars represent standard deviations of multiple independent runs. (a) Reaction of **2** and **6** without additive. (b) Reaction of **2** and **6** with 0.28 equivalent of **10** added.

observed on adding 0.28 equivalent of the product **10** (Fig. 2). It is an inactive recombinant.

The differences in reactivity of **9** and **10** can be related to the orientations of their respective recognition surfaces. In **9** these can achieve a parallel arrangement. The molecule behaves as a template and can attract **1** and **5** in a productive termolecular complex **11**, poised for intramolecular coupling (Eq. 3). The initial reaction product is the hydrogen-bonded cyclic dimer of **9**. Dissociation of this dimer then results in the increasing concentrations of template that provide the autocatalytic effect.

The hybrid **10** is composed of two U-shaped modules—the Kemp triacid (*8*) and the xanthene diacid (*9*). Its overall configuration is either C-shaped, in which its recognition surfaces converge (**10**, Eq. 4), or S-shaped, in which its recognition surfaces diverge (as in **12**). Neither case allows a productive termolecular complex to be assembled. Nor can the molecule form a hydrogen-bonded cyclic dimer; instead, its self-complementarity is expressed by forming chains.

Self-complementarity is also a common feature of macromolecules, and the orientation of the recognition surfaces within these structures determines the nature of the assemblies that are formed. When these surfaces permit the formation of a dimer, replication is possible (*2*). Even dynamic systems such as micelles are capable of self-assembly and replication (*10*). With carefully fixed recognition elements, the assembly of synthetic self-complementary structures into predictable, closed surfaces that encapsulate molecules—or reaction events—of an appropriate scale should be possible (*11*).

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Reproducible Imaging and Dissection of Plasmid DNA Under Liquid with the Atomic Force Microscope

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Reproducible images of uncoated DNA in the atomic force microscope (AFM) have been obtained by imaging plasmid DNA on mica in *n*-propanol. Specially sharpened AFM tips give images with reproducible features several nanometers in size along the DNA. Plasmids can be dissected in propanol by increasing the force applied by the AFM tip at selected locations.

Scanning probe microscopes such as the AFM (*1*, *2*) can be used at near-ambient conditions and can yield even atomic resolution on some surfaces (*3*). If this high resolution can be obtained on DNA there could be many benefits, including the potential for sequencing DNA. Until now, however, high-resolution AFM images of DNA have been difficult to reproduce.

Recently Vesenka *et al.* (*4*) and Bustamante *et al.* (*5*) developed a method for anchoring and imaging plasmids that gives reproducible images with mean apparent plasmid widths on the order of 10 to 15 nm. We report here an improvement of this technique that shows reproducible structure along the DNA strands and can resolve detail that is in some cases the size of the double helix. This method may have applications in diverse fields ranging from protein–nucleic acid interactions to chromosome mapping.

Double-stranded plasmids [BlueScript II from Stratagene, La Jolla, California and pSK 31, a gift from W. Rees at the University of Oregon, Eugene, Oregon (*5*)] were attached to mica treated with magnesium acetate. This method (*6*) builds on earlier methods for imaging DNA on mica in the electron microscope (*7*, *8*). DNA on mica was stored over desiccant and then imaged under *n*-propanol in a Nanoscope II AFM (*9*) at constant force mode by using narrow (120- or 200-μm) silicon nitride cantilevers with integrated tips (*10*). The scan speed was typically 9 Hz, or 1 min per image. Good DNA images were easily obtained, although it was sometimes a challenge to get a plasmid distribution over the sample that was neither too sparse nor too dense.

Imaging plasmids under propanol (Fig. 1, A to E) gives better resolution of detail along the strands and narrower apparent widths than imaging in air (Fig. 1F). Propanol was chosen as a medium for imaging based on previous results in air and ethanol. Imaging forces in air are typically on the order of ten times greater than imaging forces in liquids such as ethanol (*11*, *12*). Therefore it is desirable to image DNA under liquid to obtain images under the most gentle conditions. Ethanol had been

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are turning up a number of wide binaries in regions of star formation (H. Zinnecker, University of Wurzburg). It is, however, the use of interferometric methods, sensitive to binaries of intermediate separations, that has so vastly expanded the roster of pre-main sequence binaries, particularly through near infrared-speckle and lunar-occultation techniques. (The use of the near infrared passband allows the detection of companions that are not yet optically visible, being still shrouded in their natal gas and dust). It is among these systems, with separations in the range ten to several hundred astronomical units (the Earth's orbit has a radius of one astronomical unit), that there would appear to be an excess of binaries compared with main-sequence counts, according to reports from three independent groups (A. Ghez, California Institute of Technology; C. Leinert, University of Heidelberg; M. Simon, State University of New York at Stony Brook). With the present sample sizes this result is significant only at the two sigma level. But if it persists in larger samples it poses a number of questions: either a large number of systems are being missed in main-sequence surveys or else many binaries in this separation range are somehow destroyed during their main-sequence lifetimes.

Whatever the outcome of this particular controversy, the discovery of so many pre-main-sequence binaries provides a welcome dataset against which theorists can test their pictures of binary star formation. For instead of having only to produce a correctly finished product, such models have now also to be checked against the appearance of binaries that are still in the late stages of formation — in which, for example, the remnant gas around the young binary can provide a clue as to the initial formation process. Thus numerical models, such as those of A. Boss (Carnegie Institute: see *Nature* **351,** 274; 298–300; 1991) and I. Bonnell (University of Montreal) have now to pass more stringent observational tests than ever before. And this can only hasten the arrival of a consensus about binary formation — and thus, implicitly, about all star formation. □

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EVOLUTIONARY CHEMISTRY

Life in a test tube

Laurence D. Hurst and Richard Dawkins

How many lifes are there? How many lifes could there be? Not lives, lifes. We have experience of only one life, the one on this planet based on DNA as replicator and protein as executor. Is DNA the only molecule with the necessary qualifications? Are there others but vanishingly rare, such that the origin of a life in the Universe is a prodigiously lucky event? Or is there a profusion of alternative biochemistries waiting to be discovered? Work by a group led by Julius Rebek, described in a forthcoming paper[1] and in this week's *Science*[2], suggests that not only can relatively small molecules act as replicators but that it is quite realistic to consider whole other-worlds of chemical replicators.

Rebek's first test-tube replicator had two basic components[3] — an imide ester (which we will call molecule A) and an adenine-containing amine (molecule B). In a solvent the two molecules pair to form a third molecule (molecule C). It is this third molecule that acts as a replicator. Molecule C not only acts as a template on which A and B are guided by hydrogen bonds to line up, but also catalyses the covalent union between A and B. Two identical C molecules then become available to carry on the autocatalysis. Just as a laboratory population of bacteria exponentially grows until it runs out of resources, so growth of the population of C molecules describes the classic sigmoidal form.

As it stands, however, selection (and hence evolution) in this system is impossible as there are no variants. By the incorporation of a variety of B-type molecules which differ only in single side groups, the system can be modified to take account of this[4]. The resulting different C-type molecules have both differing replicating (autocatalytic) capabilities, as well as differing capabilities to catalyse the formation of non-like C-type molecules. A population of two rival variants of C molecules now exists in a state of competition. This variation had to be artificially created, but one of the new B types made the C molecules sensitive to ultraviolet radiation. Exposure to ultraviolet cleaves off part of the B subunit of C, producing a new C-type molecule. This new molecule not only replicates, it actually outcompetes the unmutated molecule and rapidly takes over the system's resources[4]. This then is a replicating system in which new variants are spontaneously generated, albeit in a rather limited fashion.

In their paper in press with *Journal of the American Chemical Society*[1], Rebek *et al.* describe a wholly different chemical replicator. This too has two subunits, D and E, which pair to form a new molecule, F. Like C, F can catalyse the synthesis of more F from D and E. Mutation in this system has yet to be described.

The next move was to attempt to make hybrids[2] and to investigate whether A with D or B with E would make a replicator. The team comment that "at first glance both recombinants might be expected to replicate. They both bear self-complementary recognition surfaces, and can gather their respective reaction components in termolecular complexes". Duly, one of the hybrids did replicate, and in no insignificant terms. It was in fact the most efficient replicator found to date. Conversely, the other was sterile. The difference between the two was simply a question of the orientations of the respective recognition surfaces. The successful hybrid had the recognition surfaces in parallel whereas the other hybrid was either C shaped or S shaped. In neither the C nor S form could the stable intermediate structure be formed.

What does this elegant system tell us about evolution and the origin of life? At the very least it shows that DNA and RNA are not the only possible replicators. However, Rebek's work might have another importance. Short of travelling the Galaxy, it is hard for us to know which features of life are particular, which general. We can surmise that some form of darwinian selection is universal for all lifes[5] but beyond that we cannot say what chemical properties would be necessary. Rebek's work allows us to approach the question of which chemical and structural aspects of replicators are necessary, and which are details. We can for instance start to ask whether some types of structures are inherently more or less likely to become replicators, and whether there are general properties of all of the chemical structures which can replicate. The new studies show that replicators need not be particularly large molecules and that simple replicators could have the potential to mutate. Life could have relatively modest beginnings. Similarly, the fact that the C- and S-form hybrid molecules were sterile is significant in that it goes some way to defining necessary structural characteristics which replicators must have. Furthermore, Rebek's chemicals and DNA share a number of properties: they are organic, use hydrogen bonding as structural information and covalent bonds to maintain structural integrity. But until we have a larger compendium of replicators we will not know if these are necessary characteristics or simply characteristics which happen to be shared by these two systems.

Although Rebek's system is unique in employing synthetic chemicals, analogous systems of replicating molecules have been set up using biological chemicals[6]. Whereas these biological replicators can be seen as attempts to understand what actually occurred at the origin of life, Rebek's system, like Thomas Ray's replicatory computer world[7,8], can be seen as a different, but parallel, replicating kingdom. Ray's work might best be thought of as being complementary to that of Rebek. Where Rebek's programme attempts to investigate the conditions necessary for the initial evolution of a life, Ray's replicating 'information sets' are defined with the ability to replicate and hence permit study of the consequences of mutation and selection in a population of simple replicators. The revealing aspect of Ray's work is that a diverse population can evolve from such an initial population of simple replicators. For instance, the tendency for parasites (replicators which use another's replicatory machinery) to invade and persist means that parasitism might be an unavoidable aspect of all lifes.

There might however be a fruitful connection between the two approaches. Just as we can ask whether particular types of 'information sets' differ in their evolutionary potential, so we can now ask whether different systems of chemical replicators differ in their capacity to evolve, and if so why. Where Rebek's system (and probably protein replicators[9,10] as well) falls short is that these replicators, unlike DNA, do not encode much information. This must surely limit their evolutionary potential. But it is probable that in early evolution DNA (or whatever the early replicator was) didn't encode much information either. Could strings of Rebek-type chemicals evolve to encode more than their own replication? If so, would we want to think of this as a life in a test tube? □

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ELECTRONICS

Single atoms as transistors

Sean Washburn

As the drive to gigabit computer memory chips accelerates, requiring smaller and smaller transistors, one might ask what the limits are to making transistors smaller. Recent experiments indicate that the limit might be reached only at the level of single atoms. Three independent groups of researchers now show[1–3] that electrical current can be controlled by the configuration of an individual atom's quantum-mechanical state and that the state itself can be switched on and off.

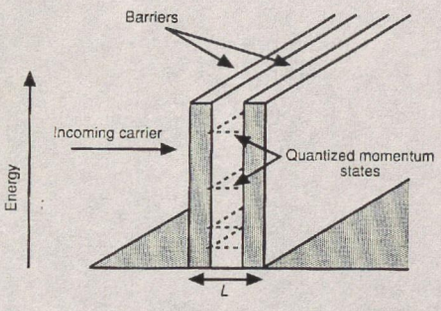

FIG. 1 Resonance tunnelling: a pair of barriers separate off a slice of semiconductor, a quantum well, inside which only discrete momentum states (broken lines) are possible. Charge carriers impinging from the left will be reflected unless their momentum is aligned with one of the allowed states in the well. Carriers in the well are free to move parallel to the plane.

The transistor of Dellow *et al.*[1], from the Universities of Nottingham and Glasgow, is based on the process of resonant tunnelling, which has been used for many years[4], but never on so small a scale. Current through such a device is controlled by the existence of discrete quantum levels in a thin confined layer through which it must pass, whose energies can be adjusted externally (Fig. 1). Charge carriers entering from one side of the device cannot be transported across the barriers unless one of these levels in the quantum is tuned into resonance with the carriers' energy. To attain the quantum-well states, it is not necessary to restrict the charge-carriers' motion in all three directions. It is sufficient for the barriers to confine the motion along only the current direction on a scale of length which is short compared with the carriers' characteristic lengths, such as the wavelengths of their wavefunctions (a few nanometres in the GaAs semiconductor used by Dellow *et al.*[1]).

So earlier work on resonant tunnelling concentrated on planar systems with motion free in the plane but confined across it[5], or on tunnelling through localized carrier states in disordered insulators[6]. If the motion is confined along other directions, the quantum effects can be more dramatic[7]. This drama occurs when the size w of the tunnelling region (Fig. 2*a*) is also comparable with the important characteristic length. Dellow *et al.* have used a constricting ring to squeeze the tunnelling area down to less than 0.1 μm^2, inside which only a few donor atoms are active. The conduction region is schematically drawn in Fig. 2*a*, which shows that the carriers are confined to flow from the top through a small port of dimension w containing the two tunnel barriers to the bottom. Depending on the voltage settings on the transistor, most of the carriers are funnelled through only a single donor. By changing the voltage settings, the authors can cause the carriers to flow through one or another of the donors or study the voltage dependence of the donors' states. As the donors move through the resonance, peaks appear in the transistor's current–voltage curve. The peaks mark the energy spectrum of the donors.

Gregory, of Bellcore, has also studied tunnelling of electrons through a single atom between two wires that nearly touch[2]. His ingenious technique is to bring the two thin tungsten wires very close to each other magnetically, by passing a current through one in an applied field, and to cement them in place with the van der Waals forces between helium atoms adsorbed onto their surfaces. In such a configuration, the electrons tunnel from wire to wire preferentially through the nearest two points (as the tunnelling probability is exponentially smaller elsewhere). Again, a single impurity atom can be the funnel point, just as a particular donor was in the device of Dellow *et al.* (Fig. 2*b*).

Gregory used this technique to study tunnelling through magnetic impurities. Sometimes there is a magnetic inclusion in the asperity where tunnelling occurs. This leaves a specific signature in the current–voltage curve, and, because the interaction with the carriers is magnetic, the signature can be altered by a magnetic field. The signature is a 'zero-bias-anomaly' similar to those studied for several decades[8,9]. Tunnelling experi-

Correction

It has been pointed out that increased error estimates, mentioned in a Résumé item (*Nature* **356**, 288; 1992) on the latest γ-ray burster statistics from the Compton Gamma Ray Observatory, are attributable to the inclusion of an estimate of the positional uncertainty in burst locations, and do not indicate deteriorating results.