ON THE UNWINDING OF DNA

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There have been a number of discussions of the problem of the mechanism of the unwinding of the two strands of the double helix structure of DNA during replication. In particular, these efforts have been directed toward finding ways in which the two strands can become separated without requiring rotation of the whole molecule through a large number of turns. Rotation has been considered to be a serious difficulty because it has been visualized as a motion involving some kind of lateral translation of the strands through the fluid, that is, a whipping or flailing motion of the parting strands. Such whipping motion would (a) produce a great amount of tangling which would tend to inhibit the motion and (b) use an excessive amount of energy in viscous drag. Several alternate mechanisms have been put forward\(^1\) which offer possible ways around the above difficulties and which are topologically workable. In all cases, however, some essential departure from the simple picture of replication originally advanced by Watson and Crick\(^2\) is involved, and in general the complexity is increased. The discussion to be presented here should not be considered as necessarily supporting the Watson-Crick mechanism, in which synthesis is concomitant to unwinding, as against the variations that have been proposed. It will, however, show that the unwinding problem, at least, does not give rise to a valid objection to this mechanism.

In line with the Watson-Crick model, let us visualize a \(Y\) in which the vertical part is the parent helix and in which the two arms are the growing progeny. The crotch of the \(Y\) represents the point at which the two parallel threads of the parent helix separate. We assume that the new and complementary structure forms on each of the old threads as the separation progresses. By an appropriate combination of rotations of the vertical part and the arms, \textit{each on its own axis}, all the requirements of the unwinding of the parent and the coiling of the progeny can be satisfied without the \(Y\) changing its orientation in space. All that will happen to the \(Y\) will be gradual shortening of the vertical part and lengthening of the arms, together with a spinning of all three branches, in the way in which a speedometer cable spins. By a little experimentation with a crude model, one can easily satisfy himself that the foregoing model is workable topologically. There are, however, several questions of a more quantitative nature that have to be considered.
1. Is the energy required to produce the rotation, against viscous drag, small enough compared to the energy of formation of the bonds so that it will be supplied easily as a by-product of the replication process?

2. Does a comparison of the viscous drags for the various possible kinds of rotational motion dictate that the particular one we have postulated will predominate?

3. Is the mechanical strength of the helix sufficient to withstand the necessary torque without seriously stretching the bonds?

The calculations which follow will give some of the answers we require.

If one treats the DNA particle as a cylinder rotating about its axis, one can calculate the energy required, per revolution, to overcome the viscous drag. This energy is

$$E_a = \frac{16\pi^2 n^2 \eta p r^2}{T},$$  \hspace{1cm} (1)

where $n$ is the number of turns in the molecule, $p$ the pitch of the helix, $r$ the radius, $\eta$ the viscosity coefficient for the medium, and $T$ the time required for the replication. As approximate values applying to our case, we insert in the formula $n = 6,000$, $p = 34 \, \text{A}$, $r = 10 \, \text{A}$, $\eta = 1 \, \text{centipoise}$, and $T = 100 \, \text{seconds}$. The result is $E_a = 6 \times 10^{-15} \, \text{ergs per revolution}$, or $1.2 \times 10^{-22} \, \text{calories per revolution}$. One revolution corresponds to the formation of about 20 phosphate bonds. On the basis of a value of 10 kilocalories per mole for the energy of formation of the bonds, the formation of 20 bonds will require $3.3 \times 10^{-19} \, \text{calories}$. Thus, the energy required for the viscous drag is only about one one-thousandth as much as that required for the formation of the phosphate bonds, and it therefore increases the total energy requirement only insignificantly. The energy is presumably supplied in some form of high-energy bonds in the immediate precursors. This calculation is not significantly altered by the fact that the molecule is not straight but randomly curved, as long as we assume sufficient rigidity so that at no point is the radius of curvature less than several hundred angstroms. However, the calculation does assume that the rotation will take place about the axis of the molecule.

The hydrodynamics problem is somewhat more complicated if we want to calculate the torque required to make such a structure rotate about an axis which is not coincident with that of the helix. If the distance $R$ from the molecular axis to the axis of rotation is small compared to $r$, then the torque will vary as $(r/R)^2$. If $R$ is large compared to $r$, we can treat the problem as though the cylinder of length $L$ were moving linearly in a viscous fluid. To calculate the frictional drag per unit length of such a cylinder moving with a velocity $v$, either we can use the theoretical expression

$$F = \frac{4\pi \eta}{\log (L/r) + 0.5},$$

or we can estimate the frictional drag from the sedimentation constant of DNA. These two methods give approximately the same answer, and the ratio of the torque for rotation about an axis away from the molecule to that for rotation on the axis is $R^2/T r^2$. One expects that, when a torque is applied at one end of a flexible thread having negligible inertial forces compared to viscous forces, the kind of ro-
tation having the least "drag" will predominate. The result of the foregoing calculation shows that in the case of our molecular helix the "easy" kind of rotation is the speedometer cable type. This type will, then, be the principal kind of motion, while the off-axis rotation will be suppressed because of the far greater magnitude of the torque that is required to produce it.

We consider, finally, the question of the stretching of the bonds due to the torque applied at the end of the helix. The tangential force in the helix is computed easily by dividing by $2\pi r$ in equation (1). It is
\[ F_t = \frac{8\pi^2 n \eta p r}{T} = 10^{-3} \text{ dynes.} \]

A reasonable value for the force constant in the phosphate bond is $5 \times 10^4$ dynes/cm. Thus the stretching will be $2 \times 10^{-4} \text{ A}$, which is extremely small compared to the inter-atomic distances.

The results of the above calculations show that the kind of motion postulated for the $\gamma$, namely, a rotation of each branch on its own axis, $(a)$ involves requirements of mechanical strength and energy production which are well within those available and $(b)$ is the favored type of motion from the standpoint of the viscous drag.

The foregoing discussion was made relative to a rather specific model in which the one branch of the $\gamma$ "unzips" as the other two branches build into double helices, that is, a model in which the neighborhood of the crotch of the $\gamma$ is the scene of the replication process. It should be pointed out, however, that the conclusions are more generally applicable. For example, they would apply to any of the variations in mechanism cited earlier, which involve in any way the spinning of a helix on its axis. As a further possible variation in which they would apply, let us imagine that the $\gamma$, instead of being free in the liquid, is attached at its crotch to, say, an enzyme on a surface, which plays a part in the unzipping and building process. Here one of the kinds of motion which were considered, namely, rotation of the whole $\gamma$, would no longer be a possibility, but the speedometer cable motion would still be topologically possible and would be as feasible, energetically, as it was found to be in the case which was used for the calculation.

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