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Counterion-Induced Condensation of Deoxyribonucleic Acid. A Light-Scattering Study†

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ABSTRACT: The addition of the trivalent or tetravalent cations spermidine or spermine to a solution of T7 DNA in aqueous solution causes an alteration of the DNA from its extended coil form to a condensed form. If performed at low DNA concentration and at low ionic strengths, this transformation results in a monomolecular collapse to form a particle with a hydrodynamic radius of about 500 Å. We have monitored this change using quasielastic and total intensity light scattering. In a solution of 50% methanol in water, the divalent cations Mg^{2+} and putrescine also can cause the condensation of DNA. Using Manning's (1978) counterion condensation theory, we calculate a striking unity among these disparate ions: the collapse occurs in each case when from 89 to 90% of the DNA phosphate charges are neutralized by condensed counterions.

The majority of DNA in all living organisms is present in a compact form. In higher organisms the histones are responsible for maintaining this packaging, and the interaction between DNA and the histones is the subject of a great deal of current research. In viruses, several different molecules have been implicated in the maintenance of a condensed form of DNA. These include internal proteins (Laemmli, 1975) and the polyamines such as putrescine, spermidine, and spermine (Ames & Dubin, 1960). Several studies have demonstrated the efficacy of these compounds in collapsing DNA in vitro. Collapse has been observed by using electron microscopy (Chattoraj et al., 1978; Laemmli, 1975) and inferred from turbidity, circular dichroism, and hydrodynamic measurements (Gosule & Schellman, 1976, 1978). Collapse has also been induced by using neutral polymers such as poly(ethylene oxide) in the presence of high NaCl concentrations (Lerman, 1973).

We are interested in the packaging of DNA into viruses and therefore wished to investigate the condition under which cations can cause the self-association of DNA and to characterize the particles which result from its monomolecular collapse. We have attempted to study the collapse of DNA under conditions which favor intrachain interactions over intermolecular association. A very sensitive photon counting laser light-scattering instrument enables the rapid determination of the conditions required for DNA condensation even at the very low concentrations used to avoid intermolecular association. Since this is a quasielastic light-scattering apparatus, we have the additional ability to obtain diffusion coefficients for the collapsed particles.

In order to study the effects of cation concentration and valence on the DNA condensation, we have added various combinations of Na^+, Mg^{2+}, spermidine^{3+}, and spermine^{4+} to solutions of the DNA from T7 bacteriophage. The results are discussed in terms of the counterion condensation theory developed by Manning (1978).

Materials and Methods

(*a*) *DNA.* The T7 bacteriophage DNA was obtained by gentle phenol extraction of a phage suspension which had been prepared by using a version of the method of Studier (1969). The DNA fraction was exhaustively dialyzed against a phosphate buffer containing 0.094 M Na^+ and 5×10^{-4} M

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EDTA (pH 7.0) and stored at 4 °C.

(*b*) *Polyamines.* Spermine tetrahydrochloride, spermidine trihydrochloride, and putrescine dihydrochloride were all purchased from Sigma and used without further purification.

(*c*) *Buffers.* All experiments were performed in a buffer containing equal molar amounts of sodium chloride and sodium cacodylate (pH 7.0–8.0). Sodium cacodylate was used rather than more standard buffers to avoid possible interaction of the polyamines with PO_4^{2-} or citrate (Hirschman et al., 1967).

(*d*) *Sample Preparation.* All buffers except those containing methanol were filtered through 0.22-μm type GS Millipore filters. The methanol was filtered through 1.0-μm type FA Millipore filters. Samples were prepared by rapidly mixing 1 mL of a solution containing T7 DNA in the appropriate buffer with small volumes of a solution containing the higher valence cation. The mixing was done in the test tubes which are used as light-scattering cells. After mixture, the tubes were centrifuged at 2000*g* for about 10 min. The combination of filtration and centrifugation effectively reduces the scattering from dust and impurities.

(*e*) *Light-Scattering Instrument.* The instrument used for this study is an assembly of several components arranged in a standard configuration for quasielastic light scattering (Bloomfield & Lim, 1978). Incident light is supplied by a Lexel Model 95-2 argon ion laser operating at 514.5 nm. This light is focused to a diameter of about 0.1 mm on the center of the scattering cell, a Pyrex 9820 test tube. The scattered light is detected by an I.T.T. FW-130 photomultiplier mounted on a goniometer arm. The photopulses are amplified by an Ortec Model 9301 fast preamplifier and a L.R.S. Model 133B linear amplifier. The amplified photopulses are discriminated and shaped by a Canberra Model 1433 discriminator. In later studies the amplification and discrimination were performed by a Products For Research Model ADH 1400-120 photon counting amplifier–discriminator module.

The amplified photopulses may be treated in two ways. The total intensity of scattered light is measured by a pulse counting Canberra Model 1480 linear rate meter. For quasielastic light-scattering measurements autocorrelation functions are measured by using a Langley-Ford digital correlator. A PDP-8 minicomputer is interfaced to the correlator and is used for data reduction and analysis. The cumulant method, as described by Koppel (1972), is used for this analysis.

(*f*) *Light-Scattering Analysis.* The intensity of light scattered at a given angle by a suspension of large macromolecules is proportional to their concentration, molecular weight, and a form factor, S, which depends on the size and shape of the scatterers and on the scattering angle. The form factor arises from the destructive interference of the scattered light and is equal to 1 or less. For a Gaussian chain (a suitable model for high molecular weight DNA)

$$S = 2[\exp(-q^2R_G^2) - 1 + q^2R_G^2]q^{-4}R_G^{-4} \qquad (1)$$

(Berne & Pecora, 1976). Here R_G is the radius of gyration and q is the scattering vector

$$q = \frac{4\pi n \sin(\theta/2)}{\lambda}$$

where θ is the scattering angle, n is the refractive index of the solution, and λ is the wavelength of laser light in vacuo. For a sphere of radius R

$$S = [3(\sin qR - qR\cos qR)qR^{-3}]^2 \qquad (2)$$

(Berne & Pecora, 1976).

Quasielastic light scattering gives additional information regarding the dynamic properties of the scatterers. The homodyne photocurrent autocorrelation function measured with our instrument is

$$C(t) = e\langle i\rangle\delta(t) + \langle i\rangle^2 + \langle i\rangle^2|g^{(1)}(t)|^2 \qquad (3)$$

The first and second terms represent shot noise and the square of the average photocurrent, respectively. The third term contains the dynamic information. For a monodisperse system of spherical scatterers

$$g^{(1)}(t) = \exp(-q^2D_Tt) \qquad (4)$$

where D_T is the translational diffusion coefficient of the particle.

Counterion Condensation Theory

The theory discussed here is basically that developed by Manning (1978). This theoretical approach to counterion condensation was first developed for the limiting case of infinite dilution. It now appears that it may be appropriate at much higher counterion concentrations (Manning, 1977). It is based on the concept that counterions will condense on a polyelectrolyte to lower its linear charge density to a limiting value. For a solution containing the polyelectrolyte and only one species of counterions with charge Z, the linear charge density of the polymer will be reduced by a factor of

$$r = 1 - (|Z|\zeta)^{-1} \qquad (5)$$

where $\zeta = q_p^2/\epsilon kTb$ and q_p is the charge of a proton, ϵ is the bulk dielectric constant, and b is the average linear charge spacing of the polyelectrolyte in the absence of any associated ions. For DNA in aqueous solution, $b = 1.7$ Å and $\zeta = 4.2$. Therefore, for example, the linear charge density of DNA in solution with Na^+ ions will be reduced by 76% from the bare phosphate charge.

For a mixture of counterions with different valences, the situation is more complicated. In this case, there will be competition between ions for condensation, and the charge density will be determined not only by the valences but also by the concentrations of the counterions.

We shall address the problem of a solution containing a linear polyanion in the presence of an excess of two types of simple cations of charges Z_1 and Z_2. Electrical neutrality is maintained by simple monovalent co-ions. This system has been treated by Manning (1978) with his two-variable theory in which the free energy of the system is minimized with respect to the number of bound counterions of each kind. We have slightly altered his equations to allow for cation 1 to have a valence higher than 1 and also to allow the two ions to have different values of the volumes in which they are assumed bound, V_{P1} and V_{P2}. After minimizing the expression for the free energy, with respect to the fraction of bound ions, θ_1 and θ_2, we arrive at two equations

$$1 + \ln\frac{10^3\theta_1}{c_1V_{P1}} = -2Z_1\zeta(1 - Z_1\theta_1 - Z_2\theta_2)\ln(1 - e^{-\kappa b}) \qquad (6)$$

and

$$\ln\frac{\theta_2}{c_2} = \ln\frac{V_{P2}}{10^3e} + \frac{Z_2}{Z_1}\ln\frac{10^3\theta_1 e}{c_1V_{P1}} \qquad (7)$$

where c_1 and c_2 are the concentrations of the counterions and κ is the Debye screening parameter. These two equations are equivalent to eq 53 and 54 in Manning (1978).

The bound volumes V_{P1} and V_{P2} are assumed constant and equal to their limiting values: that is, those values which give the proper reduced charge densities for the DNA when the

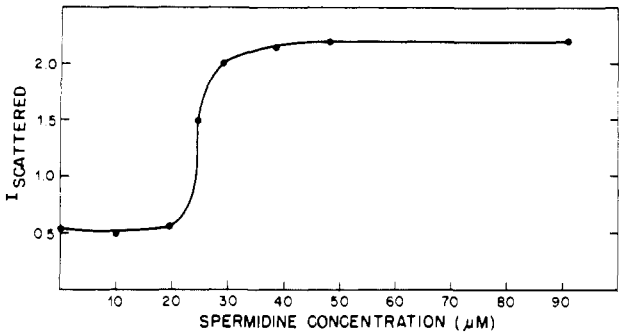

FIGURE 1: A plot of the intensity of scattered light at 60 °C vs. the concentration of spermidine. The solution contains 2.8 μM DNA phosphate, 1.0 mM NaCl, and 1.0 mM sodium cacodylate. T = 20 °C. $q = 1.62 \times 10^5$ cm^{-1}.

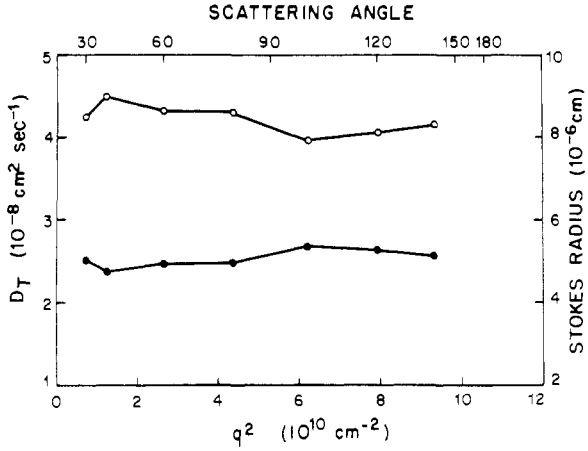

FIGURE 2: A plot of the hydrodynamic radius (●) and diffusion coefficient (○), determined by using quasielastic light scattering, as a function of scattering angle for a particle formed by the collapse of T7 DNA by spermidine.

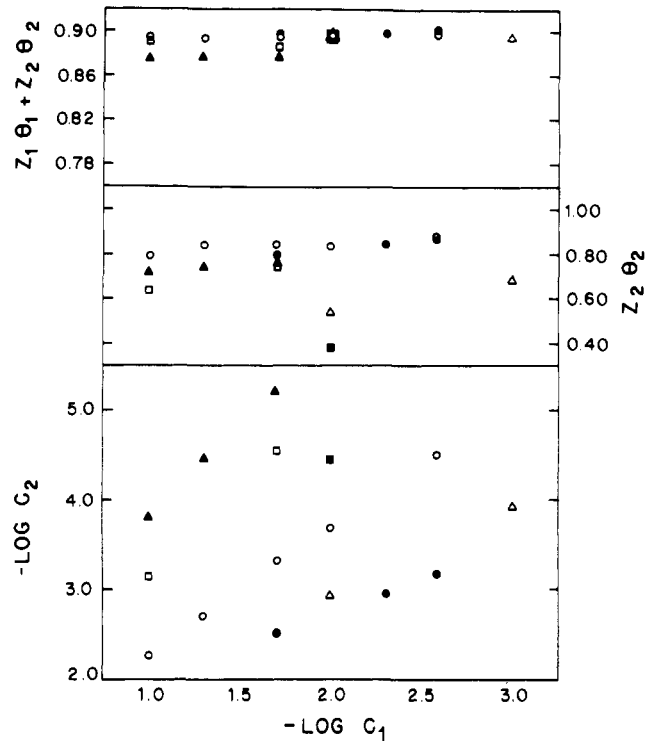

FIGURE 3: A graphical summary of the counterion concentrations which result in DNA collapse. Species 1 and 2 are the lower and higher valence counterions, respectively. Also plotted are calculated values of the total fraction of phosphate charges neutralized, $Z_1\theta_1 + Z_2\theta_2$, and the fraction neutralized by the higher valence counterion, $Z_2\theta_2$, corresponding to each pair of collapse concentrations. (○) c_1 = [Na^+], c_2 = [spermidine]; (△) c_1 = [Mg^{2+}], c_2 = [spermidine]; (▲) c_1 = [Na^+], c_2 = [spermine]; (■) c_1 = [Mg^{2+}], c_2 = [spermine]. All of these experiments were performed in H_2O at 20 °C. (□) c_1 = [Na^+], c_2 = [spermidine]; (●) c_1 = [Na^+], c_2 = [Mg^{2+}]. All of these experiments were performed in 50% methanol at 20 °C.

cations are at infinite dilution (Manning, 1977). κ is calculated from the total ionic strength. We compute values of θ_1 and θ_2 as functions of c_1 and c_2 using eq 6 and 7 and an iterative FORTRAN computer program. The total fraction of DNA phosphate charges neutralized is given by $r = Z_1\theta_1 + Z_2\theta_2$.

Results

When increasing amounts of spermidine are added to T7 bacteriophage DNA in a buffered solution containing 1 mM NaCl and 1 mM sodium cacodylate, an abrupt increase in the light-scattering intensity is noted at a critical concentration of 20–24 μM (Figure 1). This critical spermidine concentration is very near that required for the spermidine-induced collapse of DNA discussed by Gosule & Schellman (1978) and Chattoraj et al. (1978). They have shown, using flow linear dichroism and electron microscopy, that spermidine causes a transformation of DNA from its random-coil form to a condensed particle. From the hydrodynamic measurements they infer that the particle is roughly spherical in shape in solution. The electron microscopy studies revealed toroidal particles and spheroids, with the exact structure depending on the method of preparation.

Such a change in form is expected to cause a large change in light-scattering intensity. The form factor calculated by using eq 1 and a radius of gyration for T7 DNA of about 5300 Å yields a value of $S_{RC} = 2.7 \times 10^{-2}$ for $q = 1.62 \times 10^5$ cm^{-1} (θ = 60°). For a sphere with a radius of 500 Å (roughly the size of the particles seen with electron microscopy), S_S = 0.88, a 33-fold increase over the random-coil form. We are unable to measure the excess scattering intensity over background of the DNA before collapse. However, a 30-fold increase in excess scattering upon collapse is consistent with our data.

In Figure 2 are shown the results of quasielastic light-scattering measurements on the collapsed particle. The diffusion constants are calculated by using eq 3 and 4 and the radius from the Stokes–Einstein equation, $R = kT/6\pi\eta D$. The invariance of these values with the angle at which they are measured is an indication of a monodisperse sample. We obtain an average for D_T of 4.2×10^{-8} cm^2 s^{-1} corresponding to a Stokes radius of approximately 500 Å.

As the concentration of added Na^+ is increased, the concentration of spermidine required for the DNA to collapse also increases. In Figure 3 are plotted the critical concentrations of spermidine needed for collapse vs. the concentration of added Na^+. Also plotted are the calculated values of the fraction of the DNA phosphate charges neutralized by spermidine, $Z_2\theta_2$, and the total fraction of charges neutralized, $Z_1\theta_1 + Z_2\theta_2$, at the concentration of ions needed for collapse.

The addition of Mg^{2+} ions also increases the concentration of spermidine required for collapse, as shown in Figure 3. The fraction of phosphate charges neutralized by spermidine at the collapse concentration in the presence of Mg^{2+} is lower than that in the presence of Na^+. However, the total fraction of phosphate charges neutralized at collapse is approximately the same in all cases. This indicates that the ratio of bound spermidine to DNA phosphate is not important in governing collapse but that collapse is simply the result of neutralizing 89–90% of the total phosphate charges.

Support for this viewpoint can be gained from experiments performed in solutions containing 50% methanol by volume

in water. The charge density parameter, ζ, is a function of the dielectric constant. As a consequence, the fraction of charge which can be neutralized by an ion of given valence will differ in different solvents. The dielectric constant of water at 20 °C is 80 while that of a mixture of 50% methanol in water is 60 (Travers & Douzou, 1970). Therefore, according to the ion condensation theory, a divalent ion can neutralize only a maximum of 88% of the DNA charges in water but can neutralize up to 91% in a 50% methanol solution.

Gosule and co-workers (Gosule & Schellman, 1978) were unable to detect any evidence of DNA collapse using either of the divalent ions, Mg^{2+} or putrescine, in water. By using solutions containing 50% methanol, we have been able to induce DNA collapse with both of these cations. In Figure 3 are plotted the critical concentration of Mg^{2+} needed for collapse vs. Na^+ concentration. Again, it can be seen that collapse occurs at calculated values of 89–90% neutralization of the phosphate charges.

A more direct comparison can be made between the results of spermidine-induced collapse in water and in 50% methanol. The concentration of spermidine needed to cause collapse at a given Na^+ concentration is reduced on going from water to the methanol system (see Figure 3). This reduction is also expected if it is assumed that a 89–90% decrease in charge density will cause collapse of the DNA. That is, the reduction in the dielectric constant has caused a decrease in the concentration of the higher valence ions needed to reach a given degree of neutralization.

In this discussion we have neglected to mention many factors which could affect the collapse of DNA and the calculation of the fraction of charge neutralization. The counterion condensation theory is approximate in many respects. It distinguishes between ions only on the basis of charge, and thus all ions are treated as simple point charges. We have therefore neglected any specific ion effects such as size, degree of hydration, and geometric complexity. In fact, specific ion effects are evident in our experiments. Putrescine is somewhat less effective in causing DNA collapse in methanolic solution than is Mg^{2+}. In a 0.002 M Na^+ solution about 2 times as much putrescine as Mg^{2+} is required to induce collapse. Riemer & Bloomfield (1979) found that Mg^{2+} is more effective than putrescine at lowering the binding affinity of proflavin to DNA. They took this as an indication that Mg^{2+} binds to DNA more tightly than putrescine.

Spermine, with a +4 charge, is expected to have a larger binding constant and hence collapse DNA at a lower concentration than spermidine. This is demonstrated in Figure 3, in which are plotted the concentrations of spermine required for DNA collapse as a function of the concentration of Na^+ or Mg^{2+}. We calculate that 88% of the phosphate charges are neutralized at the collapse concentrations of spermine and Na^+ and that 90% are neutralized at collapse with spermine and Mg^{2+}. The difference between these two percentages and between the first and the 89–90% neutralization found with the other systems may reflect real differences between collapsed complexes and the mechanism of collapse or may merely represent inadequacies in our calculations.

It was hoped that only intramolecular collapse would be observed at the low DNA concentrations used in this study. We have, however, noticed a tendency for aggregation under many of the conditions employed. Aggregation was monitored by noting increases, with time, in the total intensity of the scattered light and accompanying decreases in the average diffusion constant as measured by using quasielastic light scattering. Aggregation was favored by higher concentrations of the DNA and by higher ionic strengths. At the lowest concentration of DNA that could be conveniently used for quasielastic light scattering (1 μg/mL), we observed aggregation at ionic strengths higher than 0.01.

Discussion

The data from this study, when analyzed by using Manning's counterion condensation theory, are consistent with the premise that the self-association of DNA in solution occurs when the linear charge density of the polymer is reduced approximately 89–90% by counterions.

At low DNA concentrations and at low ionic strengths this self-association results in monomolecular condensates with hydrodynamic diameters of about 1000 Å. These structures, when viewed by using electron microscopy, are seen most commonly as toroids but occasionally as spheres (Chattoraj et al., 1978). It is interesting that the toroidal form for condensates of DNA has been widely observed. It has been seen when collapse was caused by polyamines, poly(ethylene oxide), and Na^+ (Evdokinov et al., 1972), polylysine (Laemmli, 1975), and nuclear histones (Olins & Olins, 1971). It is not clear if this structure also represents the solution form or is the result of the preparation of the sample for electron microscopy.

Our experiments indicate that, if the solution form is a torus, there is a significant decrease in size in going from solution to the electron microscope grid. If we assume a torus with a diameter equal to 3 times its thickness, which is roughly what has been seen in electron micrographs, we calculate that a diameter of 1400 Å is needed to give the observed diffusion constant (Garcia de la Torre & Bloomfield, 1978). This is a factor of 1.7 times larger than the value of around 800 Å observed (Chattoraj el al., 1978). (Our own much more limited electron microscopy studies give results similar to these.) Assumption of an oblate ellipsoidal shape with an axial ratio of 3 gives the similar result that a diameter of 1300 Å is required to give the measured diffusion constant.

Our quasielastic light-scattering measurements are in better agreement with the structures seen by Chattoraj et al. (1978) when they did not use a heavy metal stain in preparing their samples for electron microscopy. For samples prepared in this way they reported spheroidal particles with diameters averaging from 944 to 1021 Å. This compares with a value of 1000 Å from our diffusion measurements.

Any mechanism that is proposed to explain the condensation of DNA into the compact structures must result in an overall favorable free energy for the process. There are several free energy factors which oppose this process. These include the loss of entropy by the DNA on going from the random-coil to the condensed form, the energy needed to bend the stiff helix or needed to cause local melting or kinking, and the electrostatic repulsion of the charged chains. These unfavorable energetic factors must be compensated by favorable ones. Reimer & Bloomfield (1978) have discussed the similar problem of balancing the energetic factors involved in the packaging of DNA in the head of a virus. They concluded that electrostatic repulsion dominates the unfavorable interactions and that in bacteriophage it is counteracted by favorable interactions between polyamines and the DNA. Oosawa (1971) has demonstrated that such favorable interactions can result when the electrostatic repulsion of a polyelectrolyte is reduced by counterion condensation and a net attraction between segments results from the correlation in the motion of these loosely associated ions.

In discussing the energetics of the collapse process we have omitted any mention of a change in the solvation state of the

DNA. In fact, it is not clear if any change takes place. The volume of the collapsed particles is quite large, indicating extensive hydration. There is no change in the circular dichroism spectrum of DNA on its collapse with polyamines. Therefore, structural changes, such as B form to A or C form, which result from changes in hydration, are absent. When circular dichroism changes have been observed, such as with the poly(ethylene oxide)–Na^+ induced collapse of DNA, they have been attributed to the formation of long-range, ordered states rather than to changes in secondary structure (Lerman, 1973). It therefore appears that while subtle hydration changes may be present, evidence for them is lacking.

We have not offered a mechanism for DNA collapse largely because information on the detailed structure of the collapsed particles is not available. In particular, the interstrand separation and the mode of bending are very much needed. In fact, there may well be a range of structures, with different cations promoting slightly different conformations for the collapsed DNA. There is some support for this point of view from circular dichroism measurements made on collapsed particles. These spectra seem to be strongly dependent on the cations used to cause collapse as well as on the treatment of the sample. For example, Damaschun et al. (1978) reported that the complexes of spermine and calf thymus DNA, when formed at high DNA concentrations, gave two entirely different circular dichroism spectra when dissolved in 0.075 to 0.15 M NaCl. When using T7 DNA and spermine at low DNA concentrations, we find no change in the circular dichroism spectra on collapse just as Gosule & Schellman (1978) found no change on collapse with spermidine. There are numerous similar examples of anomalous circular dichroism spectra obtained on DNA collapsed by basic amino acids, histones, or high molecular weight neutral polymers and Na^+.

The theory we used to arrive at the degree of DNA phosphate charge neutralization does not recognize the possibility of site binding of the cations. All ions are treated as if no change in their hydration occurs on binding and as if they are totally free to move within the bound volume. It therefore neglects the possibility that the more complex polyamines may bridge between phosphates on the same or different chains. Such specific ion effects may be important in the binding of counterions and the subsequent collapse of DNA. This sort of detailed analysis is beyond the simple counterion condensation theory. It is probable that the 89–90% charge neutralization discussed here represents a minimum requirement for condensation of the DNA and that processes such as bridging by ions fine tune the resultant structures and are responsible for the many different forms of collapsed particles that have been studied.

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