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Shape of Protein L11 from the 50S Ribosomal Subunit of *Escherichia coli*†

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ABSTRACT: Protein L11 from the 50S ribosomal subunit of *Escherichia coli* A19 was purified by a method using nondenaturing conditions. Its shape in solution was studied by hydrodynamic and low-angle x-ray scattering experiments. The results from both methods are in good agreement. In buffers similar to the ribosomal reconstitution buffer, the protein is monomeric at concentrations up to 3 mg/mL and has a molecular weight of 16 000–17 000. The protein molecule resembles a prolate ellipsoid with an axial ratio of 5-6:1, a radius of gyration of 34 Å, and a maximal length of 150 Å. From the low-angle x-ray diffraction data, a more refined model of the protein molecule has been constructed consisting of two ellipsoids joined by their long axes.

The topographical studies of ribosomal components performed by immune electron microscopy and neutron scattering experiments (reviewed by Brimacombe et al., 1978) have given some preliminary evidence about the shape of ribosomal proteins.

More directly, hydrodynamic studies and low-angle x-ray scattering experiments on proteins S1 (Laughrea & Moore, 1977; Giri & Subramanian, 1977), S3, S4, S5, S7, and S20 (Rohde et al., 1975; Paradies & Franz, 1976; Österberg et al., 1976a,b), S8 (Giri et al., 1977) as well as on L6 (Giri et al., 1977), L7/L12 (Wong & Paradies, 1974; Österberg et al., 1976b), L7/L12-L10 (Österberg et al., 1977a), and L18 and L25 (Österberg et al., 1976a) have shown that both globular and elongated shapes occur in the *E. coli* ribosome.

Protein L11 from the 50S subunit has been shown to play an important role in the function of the *E. coli* ribosome. It is involved in the binding of chloramphenicol (Dietrich et al., 1974), thereby establishing its presence at the A site of the 50S subunit and its proximity to protein L16. Partial reconstitution experiments have shown that L11 is involved in the peptidyl transferase activity of the 50S subunit (Nierhaus & Montejo, 1973). Protein L11 has further been identified by photoaffinity labeling as one of proteins involved in EF-G-dependent GDP binding (Maassen & Möller, 1974). It has been cross-linked to the functionally important proteins L7/L12 and L10 (Expert-Bezançon et al., 1975, 1976). Recently, it was reported that protein L11, prepared under nondenaturing conditions, binds specifically to 23S ribosomal RNA (Littlechild et al., 1977). By immune electron microscopy two antibody binding sites on the 50S subunit were found for L11 (Tischendorf et al., 1975). These authors suggested that protein L11 might therefore have an elongated shape in situ.

We have studied the shape of protein L11 which was prepared by a nondenaturing purification procedure. Protein L11 was found to have an elongated shape resembling a prolate ellipsoid with an axial ratio of 5-6:1 and a maximum length of 150 Å. Refinement of the model suggested the possibility of two separate structural domains in the molecule.

Experimental Procedures

Protein Preparation. Protein L11 was obtained from *Escherichia coli* strain A19 by a nondenaturing purification method (Dijk, J., & Ackermann, I., submitted for publication). Briefly, this was accomplished by extracting the 50S subunits with 1 M or 2 M LiCl in the presence of 0.01 M Hepes,[1] pH

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[1] Abbreviations used: Hepes, *N*-2-hydroxyethylpiperazine-*N'*-2-ethanesulfonic acid; CM, carboxymethyl; $NaDodSO_4$, sodium dodecyl sulfate.

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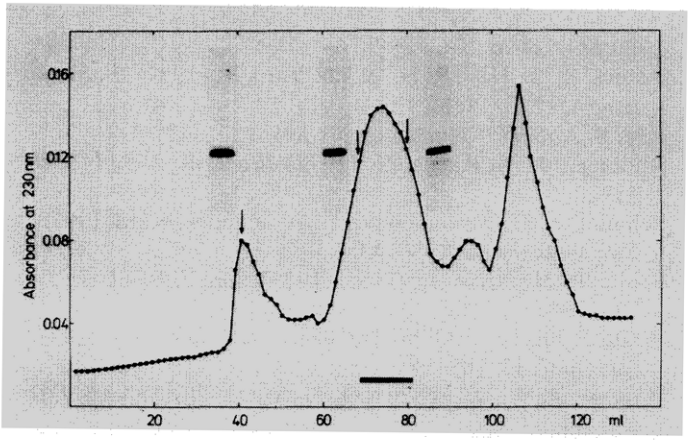

FIGURE 1: Gel filtration of protein L11 on Sephadex G-100. Ten milligrams of L11 in 2 mL of buffer A obtained by CM-Sephadex C-25 chromatography was applied to a Sephadex G-100 column (1 × 148 cm). The column was equilibrated with buffer B and eluted at a rate of 5 mL/h. Fractions of 1.4 mL were collected and samples analyzed by $NaDodSO_4$ slab gel electrophoresis. The inserts show the gel tracks of the fractions which were analyzed as indicated by arrows. The samples were precipitated with 5% (w/v) trichloroacetic acid in the presence of 100 μg of sodium deoxycholate; approximately 2 μg of protein was applied on each gel. The direction of migration was from top to bottom. The third and fourth peaks contained no protein; the latter is probably caused by the oxidized form of 2-mercaptoethanol present in the protein sample. The fractions indicated by the solid horizontal bar were pooled, concentrated by dialysis against dry Sephadex G-150, and used for experiments.

7.0, 0.01 M $MgCl_2$ and separating the proteins on a CM-Sephadex C-25 column with a gradient of LiCl and further purification by gel filtration on Sephadex G-100, equilibrated with 0.5 M LiCl in 5 mM Hepes, pH 7.0. The protein solution was concentrated in Spectrapor 3 or 6 dialysis tubing (Spectrum Medical Industries Inc., Los Angeles; mol wt cut off of 3500 and 2000) embedded in dry Sephadex G-150. The protein was stored at −80 °C at a concentration of 3 mg/mL. All purification steps were performed at 0–4 °C; the buffers contained 6 mM 2-mercaptoethanol as well as the protease inhibitors phenylmethanesulfonyl fluoride (5×10^{-5} M) and benzamidine (1×10^{-4} M). L11 was identified and checked for purity by two-dimensional gel electrophoresis (Kaltschmidt & Wittmann, 1970) and $NaDodSO_4$ slab gel electrophoresis (Laemmli & Favre, 1973). Protein concentrations were determined by either nitrogen assays (Jaenicke, 1974), using the nitrogen content (16.3%, w/w) obtained from amino acid sequence data (M. Dognin, personal communication) to calculate the concentration, or by amino acid analysis. For the experiments the protein solution was dialyzed to equilibrium in Spectrapor 3 or 6 dialysis tubing. Both protein solution and buffer were filtered through Uni-Pore membrane filters (Bio-Rad, pore size 1.0 μm). Two buffers were used: (A) 0.35 M KCl, 0.010 M Hepes (titrated with 1 N KOH to pH 7.0), 0.020 M $MgCl_2$; (B) 0.35 M KCl, 0.05 M potassium phosphate (pH 7.0). Both buffers contained in addition 0.001 M dithioerythritol, 5×10^{-5} M phenylmethanesulfonyl fluoride and 1×10^{-4} M benzamidine.

Hydrodynamic Studies. All sedimentation velocity and equilibrium experiments were carried out on a Beckman Model E ultracentrifuge. In sedimentation velocity studies either schlieren optics or photoelectric scanner were used. With the former method a capillary type single sector centerpiece was used to generate a synthetic boundary. The second moment position (r_z) was determined (Schachman, 1959) to calculate the weight average sedimentation coefficient at several protein concentrations.

Molecular weights were determined by conventional sedimentation equilibrium method using the UV photoelectric scanner exclusively. The apparent weight average molecular weights were determined from a least-squares fit of ln c vs. r^2, at several protein concentrations.

In order to obtain the partial specific volume, $\bar{v}$, the apparent specific volume, ϕ, was determined from density data at several protein concentrations. The limiting value of ϕ as $c \rightarrow 0$ was considered to be equivalent to the $\bar{v}$ value (Creeth & Pain, 1967).

Diffusion coefficients were measured in a capillary-type synthetic boundary single sector centerpiece in the An H rotor of the Beckman Model E ultracentrifuge using schlieren optics. The peak area was obtained by numerical integration.

Viscosity experiments were carried out with an Ostwald type microcapillary viscometer coupled to an automatic viscosity measuring system (AVS/G, Schott Glass Co., Mainz, West Germany) at 20 ± 0.01 °C. The viscometer had a flow rate for water of 100 s and required a 2 mL volume. Dilutions of the protein solution were made in the viscometer by removing 0.6 mL and adding 0.6 mL of buffer. No correction for shear gradient was made.

Low-Angle X-Ray Scattering Experiments. These were made with a Kratky camera. The L11 solutions were placed in Mark capillaries and kept at constant temperature of 4 °C during irradiation through the use of a cooling cuvette (Anton Paar KG, Graz). The scattered intensities were recorded by a scintillation counter with pulse height discrimination set to receive the Cu lines Kα and Kβ. Scattering data have been obtained at 79 different scattering angles ranging from 2.25×10^{-4} to 1.2×10^{-1} rad, set by an electronically programmed step-scanning device (Elektrotechnische Fabrikations- und Grosshandels-Gesellschaft, Berlin). A minimum of 10^5 pulses was taken at each angle in order to get the relative statistical error down to 0.3%.

A series of concentrations was measured ranging from 7.5 to 1.9 mg/mL in buffer A and 3.5 to 1.75 mg/mL in buffer B. The absolute intensities were determined via a Lupolen sample (Kratky et al., 1966) that had been calibrated previously at the Graz Institut für Physikalische Chemie.

Evaluation of the scattering data was done using several computer programs. Examination of statistical reliability of the data and subtraction of background scattering was carried out by a program written by Zipper (1972). Corrections for collimating effects caused by the line-shaped primary beam and the presence of Cu Kβ radiation were made using a method developed by Glatter (1974).

The experimental data were compared with theoretical curves for various models of uniform electron density using tabulated values for simple triaxial bodies and two computer programs which handle models composed of an arrangement of several spheres according to the formula of Debye (1915) and models built up from a series of surfaces of second degree using a fast Fourier transform algorithm (Labischinski & Bradaczek, 1978).

Results

Initially, protein L11 preparations were used after the first CM-Sephadex chromatography since they were essentially pure as determined by two-dimensional electrophoresis. However, on $NaDodSO_4$ slab gels one major band and two minor slower bands were observed (Figure 1). The slowest band was found to be due to a contamination by L10 which did not show up on the two-dimensional gels because of its very low concentration. Since L10 showed strong aggregation in solution, the contamination could be removed by gel filtration on

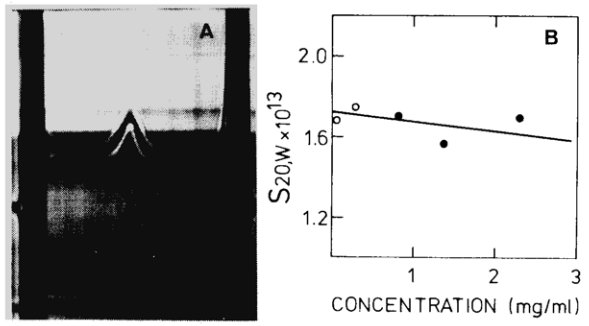

FIGURE 2: (A) Schlieren pattern of protein L11 in buffer A. A capillary type synthetic boundary centerpiece was used at a speed of 52 000 rev/min at 20 °C. This picture was taken 20 min after the rotor reached speed. (B) A graph of $s_{20,w}$ vs. concentration of protein L11. Open and filled circles represent UV scanner and schlieren experiments, respectively.

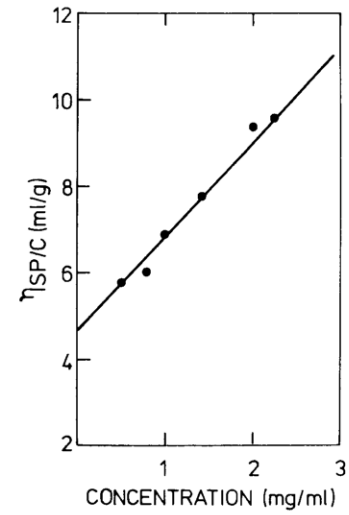

FIGURE 3: A graph of reduced viscosity vs. concentration of protein L11 in buffer B.

Sephadex G-100, at the same time some L11 aggregates were removed (Figure 1). The L11 protein sample obtained in this way was used for most of the experiments. It still showed two bands in $NaDodSO_4$ slab gels. No explanation for this heterogeneity has been found yet; an artifact of the purification procedure is unlikely since L11, prepared by another method using 6 M urea (Hindennach et al., 1971), also showed two similar bands. The slow band mainly appeared in the leading part of the monomer peak (see gel inserts, Figure 1) indicating a higher apparent molecular weight. From the gel filtration profile of the Sephadex G-100 column, which was calibrated with proteins of known Stokes radius (Tanford et al., 1974), a Stokes radius of 24 ± 2 Å was estimated for protein L11. From the $NaDodSO_4$ slab gels, also calibrated with marker proteins, a molecular weight of 15 700 for the major band and of 16 000 for the minor band was obtained.

Sedimentation equilibrium experiments were performed at protein concentrations ranging from 0.5 to 1.5 mg/mL. A linear plot of ln c vs. r^2 was obtained suggesting a homogeneous protein preparation. The apparent weight average molecular weight varied from 16 000 to 17 500. A weight average molecular weight of 16 000 was obtained by extrapolation of the apparent molecular weight to infinite dilution.

Molecular weights were also determined using Svedberg & Pedersson (1940) and Scheraga & Mandelkern (1953) equations which gave values of 20 600 and 17 660, respectively.

Results from sedimentation velocity experiments are shown in Figure 2. A symmetrical single peak was always observed, indicating a homogeneous protein solution (Figure 2A). The sedimentation coefficient was slightly dependent on protein concentration (Figure 2B). The $s^0_{20,w}$ value obtained by extrapolation was 1.70 S.

Diffusion coefficients obtained by synthetic boundary experiments were independent of protein concentration. Since the experimental error in this parameter was relatively large the data were averaged and a $D^0_{20,w}$ value of 7.4×10^{-7} cm^2 s^{-1} was obtained.

The reduced viscosity of protein L11 was found to be strongly concentration dependent (Figure 3). By extrapolation to infinite dilution an intrinsic viscosity value of 4.7 mL/g was obtained which is somewhat higher than values commonly reported for globular proteins (Tanford, 1961).

For the determination of shape factors, a hydration of 0.35 g of water per g of protein was estimated from the amino acid composition (Kuntz, 1971). Using this hydration and the intrinsic viscosity value a shape factor of 4.8 was obtained from the equation (van Holde, 1971): $[\eta] = \nu(\bar{v} + \bar{v}_0\delta)$, where ν is the shape factor, $\bar{v}_0$ is the partial specific volume of water and δ is the hydration.

A Stokes radius of 23.5 Å and a frictional coefficient of 1.40 were calculated from the experimentally determined $s^0_{20,w}$, molecular weight and $\bar{v}$ values using the following equations (Tanford, 1974; Rohde et al., 1975):

$$s = \frac{M(1 - \bar{v}\rho_0)}{6\pi\eta_0 NR}$$

$$f/f_{min} = \frac{(4/3)^{1/3}}{6\eta_0(\pi N)^{2/3}}\left(\frac{1 - \bar{v}\rho_0}{\bar{v}^{1/3}}\right)\frac{M^{2/3}}{s}.$$

A similar value of f/f_{min} was calculated from the Stokes radius.

A shape factor of 4.8 (calculated from viscosity) and an f/f_{min} value of 1.40 would correspond to an axial ratio of 5:1 for both prolate and oblate ellipsoids. It is difficult to choose prolate or oblate model with certainty at this stage.

Nevertheless, if one assumes a prolate ellipsoidal shape then the total length ($2a$) of the molecule can be estimated to be 100–120 Å by combining molecular weight and intrinsic viscosity data according to the equation (Yang, 1961):

$$L(2a) = 6.82 \times 10^{-8}([\eta]M)^{1/3}(p^2/\nu)^{1/3}$$

where $(p^2)^{1/3}$ is the shape factor for the calculation of length. Using a length of 120 Å an approximate radius of gyration of 33 Å is obtained from the equation (Tanford, 1961):

$$R_G{}^2 = \int_{r=0}^{L/2} r^2 dr \Big/ \int_{r=0}^{L/2} dr = L^2/12$$

A similar value (34 Å) is obtained for the radius of gyration from the equation (Tanford, 1961):

$$s^0 = \frac{M(1 - \bar{v}\rho_0)}{6\pi\eta_0 N\xi R_G}$$

where ξ is a coefficient whose value is given as 0.665.

The low-angle x-ray scattering results showed that L11 in buffer A was aggregated at concentrations higher than 2.5 mg/mL. However, in buffer B (containing phosphate buffer) it was monomeric even at 3.5 mg/mL, as indicated by the Guinier plot (Figure 4). No obvious concentration dependence could be observed. The values of the radii of gyration were 32.5 Å, 36 Å, and 34 Å at concentrations of 3.5, 2.5, and 1.75 mg/mL, respectively. Therefore the scattering curve (Figure 5) was extrapolated from different slit corrected curves to a

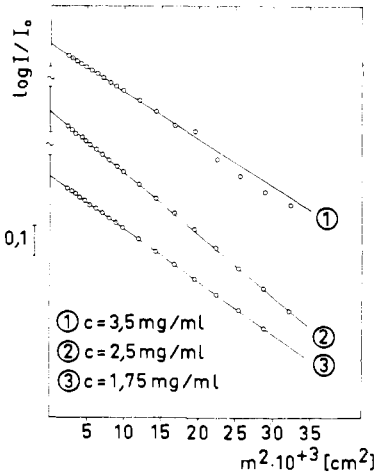

FIGURE 4: Guinier plots of log I vs. m^2 ($m = 2a\theta$; 2θ = scattering angle; a = distance of protein sample to detector) of the innermost portion of the scattering curves of protein L11. The protein concentrations were as stated in the figure.

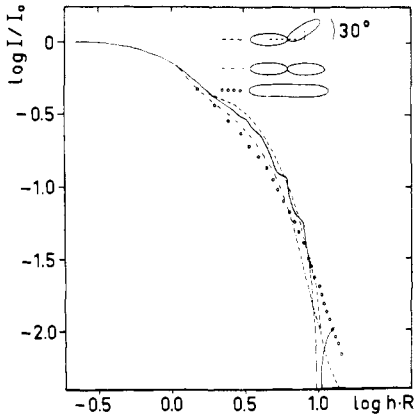

FIGURE 5: Experimental and calculated x-ray scattering curves of protein L11. Experimentally observed scattering curve after elimination of the collimation effect (—). Scattering curves were calculated for several models (as indicated in the figure) consisting of either one ellipsoid with an axial ratio of 6:1:0.5 or two ellipsoids with axial ratios of 4.5:1.5:1.

radius of gyration of 34 ± 2 Å. Furthermore, a cross-section radius of gyration of 7 ± 0.5 Å could be obtained. The molecular weight was determined to be 16 000.

Because the scattering curve shows an increase in its outer part no true h^{-4} dependence ($h = 4\pi \sin\theta/\lambda$; 2θ = scattering angle; λ = wavelength) could be detected. This increase could arise from significant deviations of homogeneous electron density inside the protein. It should be borne in mind, however, that the experimental errors in the distal part of the curve are as a rule relatively high, especially when it is necessary to use as low concentrations as in this study. Under these conditions a reliable value for the volume cannot be expected; therefore this parameter was not calculated. The scattering curve can be approximated by an ellipsoid with an axial ratio of 6:1:0.5; the longest semiaxis has a value of 75 Å.

Discussion

Proteins prepared by the nondenaturing method are soluble in salt-containing buffer (e.g., reconstitution buffer) at protein concentrations sufficiently high for physical studies, viz., in the range of 1–5 mg/mL. In contrast, proteins prepared under denaturing conditions in the presence of urea are only partially soluble at high ionic strength and aggregate at concentrations

TABLE I: Physical Properties of Protein L11.

A. Hydrodynamic Data	
$s^0_{20,w}$	1.7×10^{-13} s
$D^0_{20,w}$	7.4×10^{-7} cm² s⁻¹
$[\eta]$	4.7 mL g⁻¹
$\bar{v}$	0.717 mL g⁻¹
Mol wt	
From sedimentation equilibrium	16 600
From S and D	20 600
From S and $[\eta]$	17 660
Stokes radius (R_s)	23.49 Å
f/f_{min}	1.40
f/f_0	1.23
Axial ratio from $[\eta]$	
Prolate	4:1
Oblate	5:1
Length ($2a$)	
Prolate	110–120 Å
Radius of gyration (R_G)	33 Å
B. Low Angle X-Ray Scattering Data	
Mol wt[a]	16 000
Radius of gyration[b] (R_G)	34 ± 2 Å
Axial ratio	6:1:0.5
Length	150 Å
Internal hydration	0.24–0.26 g of H_2O/g of protein

[a] Calculated according to Kratky et al. (1950). [b] Guinier (1937).

above 1 mg/mL (Giri et al., 1977; Morrison et al., 1977a). In addition to the difference in solubility several lines of evidence suggest that the protein L11 prepared under nondenaturing conditions has retained more of its "native" structure in contrast to protein L11 isolated in the presence of urea. It binds, in contrast to protein L11 isolated in the presence of urea, specifically to 23S RNA (Littlechild et al., 1977). Proton magnetic resonance experiments also show that it contains an appreciable amount of tertiary structure (Morrison et al., 1977b). By treatment of protein L11 with proteases at low temperature ("limited proteolysis"), a stable fragment is obtained, comprising approximately one-half of the molecule while the remainder is digested to small products (Dijk, J., 1977, manuscript in preparation). This strongly suggests the existence of two separate structural domains in the protein molecule.

Under reconstitution conditions protein L11 behaves as a monomeric protein molecule with a molecular weight of 16 000–17 000, a value slightly higher than that obtained from amino acid sequence, namely, 14 800 (M. Dognin, personal communication). From the hydrodynamic studies it can be concluded that the molecule is moderately elongated. A globular protein with the same molecular weight can be expected to have an $s^0_{20,w}$ value of approximately 2.2 S, while L11 has 1.70 S. Also, the frictional coefficient ratio, f/f_{min} for globular proteins is in the range of 1.15–1.35 (Tanford et al., 1974); therefore, the value for L11, 1.40, is the uppermost limit of this range and suggests a moderately elongated molecule. At this point it should be emphasized that the observed f/f_{min} depends not only on asymmetry but also on hydration. Although the high concentration dependency of the reduced viscosity of L11 is not well understood, the intrinsic viscosity value of 4.8 mL/g found here also indicates an elongated shape. From these data the L11 molecule can be approximated as a prolate ellipsoid with an axial ratio of 5:1, a length of 120 Å, and a radius of gyration of 33 Å.

The results from low-angle x-ray scattering are in good

agreement with those from the hydrodynamic studies (Table I). They suggest also a prolate ellipsoid with axial ratios of 6:1:0.5, a length of 150 Å, and a radius of gyration of 34 Å.

When the theoretical scattering curve of such a model is compared with the experimental one, there remain significant deviations. These deviations are slightly larger than the errors in the curve. Also, the form of the calculated scattering curve is slightly different from that of the experimental one. Since there is some evidence that L11 may consist of two structural domains also, more complicated models, composed of two ellipsoids, were tested. A better fit is obtained using a model composed of two ellipsoids (axial ratio 4:1.5:1) linked together with their long axes making an angle between 0 and 30° (Figure 5). The total length of such a model is about 120–125 Å. The length of the models presented here is compatible with the distance between the two antibody binding sites on the 50S subunit, observed for L11 (Stöffler & Wittmann, 1977). Protein L11 belongs to a group of elongated ribosomal proteins which are represented by very elongated proteins like S1 and S4 (Laughrea & Moore, 1977; Giri & Subramanian, 1977; Paradies & Franz, 1976; Österberg et al., 1977b) and moderately elongated proteins such as L6 (Giri et al., 1977).

At this stage it seems appropriate to consider the relationship between the shape of protein L11 in solution, as determined by the two experimental procedures, and its conformation in the ribosome. The protein has been prepared by a new procedure which purposely avoids denaturing conditions and is therefore called "nondenaturing". The protein, prepared in this manner, clearly has properties quite different from those of the protein prepared by denaturing procedures. However, it cannot be excluded that the removal of protein L11 from its ribosomal environment leads to a conformational change. Therefore, at the moment every comparison between the shape of L11 in solution and in the ribosome is tentative.

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