# The transition state for formation of the peptide bond in the ribosome

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**Using quantum mechanics and exploiting known crystallographic coordinates of tRNA substrate located in the ribosome peptidyl transferase center around the 2-fold axis, we have investigated the mechanism for peptide-bond formation. The calculation is based on a choice of 50 atoms assumed to be important in the mechanism. We used density functional theory to optimize the geometry and energy of the transition state (TS) for peptide-bond formation. The TS is formed simultaneously with the rotatory motion enabling the translocation of the A-site tRNA 3′ end into the P site, and we estimated the magnitude of rotation angle between the A-site starting position and the place at which the TS occurs. The calculated TS activation energy, $E_a$, is 35.5 kcal (1 kcal = 4.18 kJ)/mol, and the increase in hydrogen bonding between the rotating A-site tRNA and ribosome nucleotides as the TS forms appears to stabilize it to a value qualitatively estimated to be ≈18 kcal/mol. The optimized geometry corresponds to a structure in which the peptide bond is being formed as other bonds are being broken, in such a manner as to release the P-site tRNA so that it may exit as a free molecule and be replaced by the translocating A-site tRNA. At TS formation the 2′ OH group of the P-site tRNA A76 forms a hydrogen bond with the oxygen atom of the carboxyl group of the amino acid attached to the A-site tRNA, which may be indicative of its catalytic role, consistent with recent biochemical experiments.**

quantum mechanics | ribosomal symmetry | activation energy | quantum crystallography | catalytic OH

Ribosomal crystallography has revealed the detailed structure of the ribosome, the universal cell organelle translating the genetic code into proteins. Thus, the ribosome is a ribozyme exerting substrate positioning and promoting substrate-mediated catalysis (1–5).

The ribosome, a 2.5-MDa riboprotein assembly, is composed of two unequal subunits that associate upon the initiation of the biosynthetic cycle. The mRNA is decoded at the small subunit, whereas the peptide bond is formed on the large one, within the peptidyl transferase center (PTC), which is located at the depth of a cavity built primarily of ribosomal RNA. This cavity provides the remote interactions dominating initial substrate positioning with stereochemistry suitable for the motions associated with peptide-bond formation and nascent-chain elongation (2, 4, 6, 7).

Despite the ribosome's overall asymmetric structure, a sizable 2-fold symmetry-related region, relating RNA backbone fold and nucleotide orientations, rather than nucleotide sequence identities, was revealed around the PTC in all known ribosomes structures. The symmetry-related region contains ≈180 nt and extends far beyond the PTC. It connects all functional centers involved in amino acid polymerization, including peptide-bond formation, the focus of this article (1–3). This ribosomal elaborate architectural design guides the process of peptide-bond reaction by forcing a rotational motion consistent with the 2-fold rotation axis. The bond connecting the universally conserved single-strand tRNA–3′ end with the tRNA-acceptor stem of the A-site tRNA almost coincides with the symmetry axis, indicating that A- to P-site translocation involves two synchronized mo-

tions: an overall mRNA/tRNA sideways shift and a rotation of the tRNA 3′end (1–3). Guided by PTC components, the rotatory motion facilitates peptide-bond formation and nascent-chain elongation. Furthermore, this motion places the A-site nucleophilic amine and the P-site carbonyl carbon at a distance allowing for interactions with the P-site tRNA A76 O2′ throughout a significant part of the rotatory motion (3), consistent with its suggested participation in peptide-bond formation catalysis (8). The nascent proteins are directed by the rotatory motion into the exit tunnel at extended conformation, fitting the tunnel's narrow opening. Hence, the ribosomal architecture provides all of the positional elements required for amino acid polymerization (2, 3, 9).

Although crystallography is the principal method for determination of detailed 3D structures, certain properties of ribosome function are not directly deduced by crystallographic measurement. Paramount among such properties are the energetics of the formation of the transition state (TS), which governs the formation of the peptide bond. Quantum crystallography (10) is perfectly suited to address the problem of energetics and formation of the TS. It refers to the combination of crystallographic structural information with quantum mechanical theory. The objective is to facilitate theoretical calculations and thereby add an energetic and dynamic dimension to the information that may be derived from a crystallographic experiment. The structural information may in a sense be considered a starting point, constraint, and anchor to which the quantum description of the system must conform.

In this study we applied the methods of quantum crystallography to the study of the TS for peptide-bond formation within the ribosome. Among the features of quantum crystallography is a desirable approach applicable to the ribosome in which the complication of the entire system is broken down into more manageable pieces. In that way one may describe the quantum mechanics of the individual pieces. Subsequently, this may be followed by a quantum investigation of their mutual interactions, and thus in a step-by-step manner one may rebuild the entire quantum mechanism as a whole. This approach was applied to the investigation of the peptide bond TS.

The first step in this study was choosing those atoms that seem to be most importantly involved in the mechanism of peptide-bond formation. The choice we made in our first approximation is described in *Methods*. This choice was sufficiently modest to be rigorously treatable in a fully quantum mechanical way and sufficiently aggressive to represent the essence of the TS mechanism, which leads to the formation of the peptide bond within the circumstances of the ribosome as revealed by crystallography. We kept in mind that this first choice can be successively

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**Table 1. Key geometrical parameters in the TS**
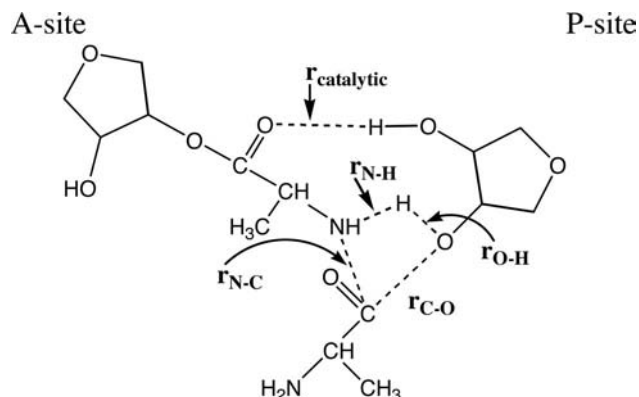


| Bond name | Bond type | Bond length, Å |
|---|---|---|
| $r_{N-C}$ | Forming | 1.577 |
| $r_{C-O}$ | Breaking | 1.912 |
| $r_{O-H}$ | Forming | 1.395 |
| $r_{N-H}$ | Breaking | 1.167 |
| $r_{catalytic}$ | Catalyzing | 1.879 |

The structure shown is a schematic representation only (see Fig. 1 for a 3D image).



**Fig. 1.** Optimized peptide bond TS in the ribosome. An initial geometry was obtained using the coordinates of ASM in D50S at the A site (Protein Data Bank ID code 1NJP) and its derived P-site tRNA. The amino acid of ASM was converted to alanine.

expanded in future investigations to bring the results ever closer to a complete quantum description of all-important factors that affect the TS.

Once the TS geometry is obtained, the angle of rotation of the A-site tRNA 3′ end within the 2-fold symmetry region that best suits its geometry can be estimated and thus the point of TS formation can be fixed. This positioning, in turn, highlights those parts of the enclosing rRNA near enough to impose putative catalyzing effect on the reaction. Such interactions would then be indicated for additional quantum mechanical calculation. Moreover, in principle, once the quantum mechanical TS is obtained its interaction with any putative ions can be incorporated as a separate quantum mechanical investigation and likewise with any putative solvent molecule. The optimal positions of any such assumed ligands interacting with the TS may be determined by geometry optimization. All of this highlights the importance of a good first approximation of the atoms that are crucial for peptide-bond formation and the subsequent quantum mechanical search for the geometry and energy of the TS.

Here we show that we have been able to define a quantum mechanical TS that is relevant to peptide-bond formation within the ribosome, characterize both its geometry and energy, and implicate these properties to events associated with peptide-bond formation and polypeptide elongations.

## Results

The key geometrical parameters of TS formation are summarized in Table 1, and Fig. 1 shows the image of the optimized TS geometry for the formation of the peptide bond in the ribosome. The optimized TS bond distances of Table 1 are labeled according to whether they are in the act of breaking or forming, to achieve the transition from reactants to products. The end result is that the peptide bond N—C is formed, which leads to elongating the nascent protein. The new O—H bond, which is formed on the P-site tRNA, saturates the open valence of the oxygen atom that would occur as the C—O bond breaks to allow release of the amino acid transferred to the nascent protein. The remaining bond that is breaking in the TS, namely, N—H, completes the release of the P-site tRNA. Hence, simultaneously with bond making and breaking, the former A-site tRNA can
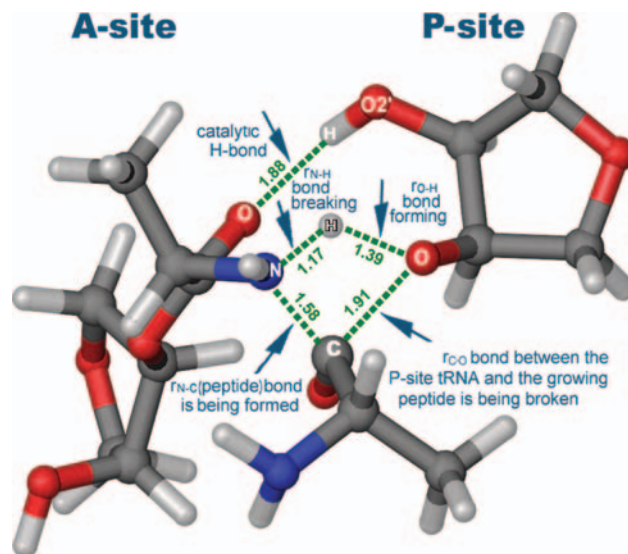
occupy the P site, which becomes available by the former P-site tRNA release.

The TS geometry of Fig. 1 shows the 2′OH of A76 of the P-site tRNA forming a hydrogen bond with the carboxyl oxygen of the amino acid bound to A-site tRNA. That hydrogen bond is formed in the TS (Table 1) having a bond length of 1.879 Å. Such hydrogen bonding, perhaps serving as an anchor holding reactants in place at the TS, is consistent with the catalytic role that has been ascribed to this 2′OH group based on recent biochemical experiments (8). A careful examination of Fig. 1, which conveys the 3D arrangements of the atoms in the TS, together with the information from Table 1, indicating which bonds are forming and breaking, allows one to perceive how the peptide bond is being formed, and how the P-site tRNA is allowed to break away after the peptide bond is made.

Notably, the TS fits perfectly into the space available for the rotating A-site 3′ end, provided by the ribosome nucleotide surroundings within the ribosomal PTC (called here the "rotatory space"), after a 45° rotation of the A-site tRNA 3′ end toward the P site (Fig. 2 b and c). We found that in the ribosome the number of hydrogen bonds, between the rotating moiety composed of the tRNA aminoacylated 3′ end (Fig. 2a) and the surrounding nucleotides of the PTC, increases as the reactants move toward the TS. A bar plot (Fig. 3) of the number of hydrogen bonds as a function of the rotation angle in the PTC shows an increase of three strong hydrogen bonds as the TS forms, resulting in a lower activation energy. Assuming, on qualitative grounds, that such hydrogen bonds might vary in strength over a range from 2 to 10 kcal (1 kcal = 4.18 kJ)/mol (11), an average value of 6 kcal/mol is adopted for each of the three newly formed hydrogen bonds. This H-bonding scheme implies a net stabilization of 18 kcal/mol, which would reduce the calculated activation energy, $E_a$, of our TS that has a value of 35.5 kcal/mol (Table 2), to a qualitatively estimated value of ≈18 kcal/mol.

The variation of the geometrical error measure, based on distances between analogous atoms of the TS, and those from the tip of the A- and P-site tRNAs, as a function of the angle of A-site aminoacylated tRNA 3′ end rotation, is shown in Fig. 4. As seen, the geometrical error measure is a minimum at the rotation angle of ≈45°. We therefore estimate that this rotation angle best
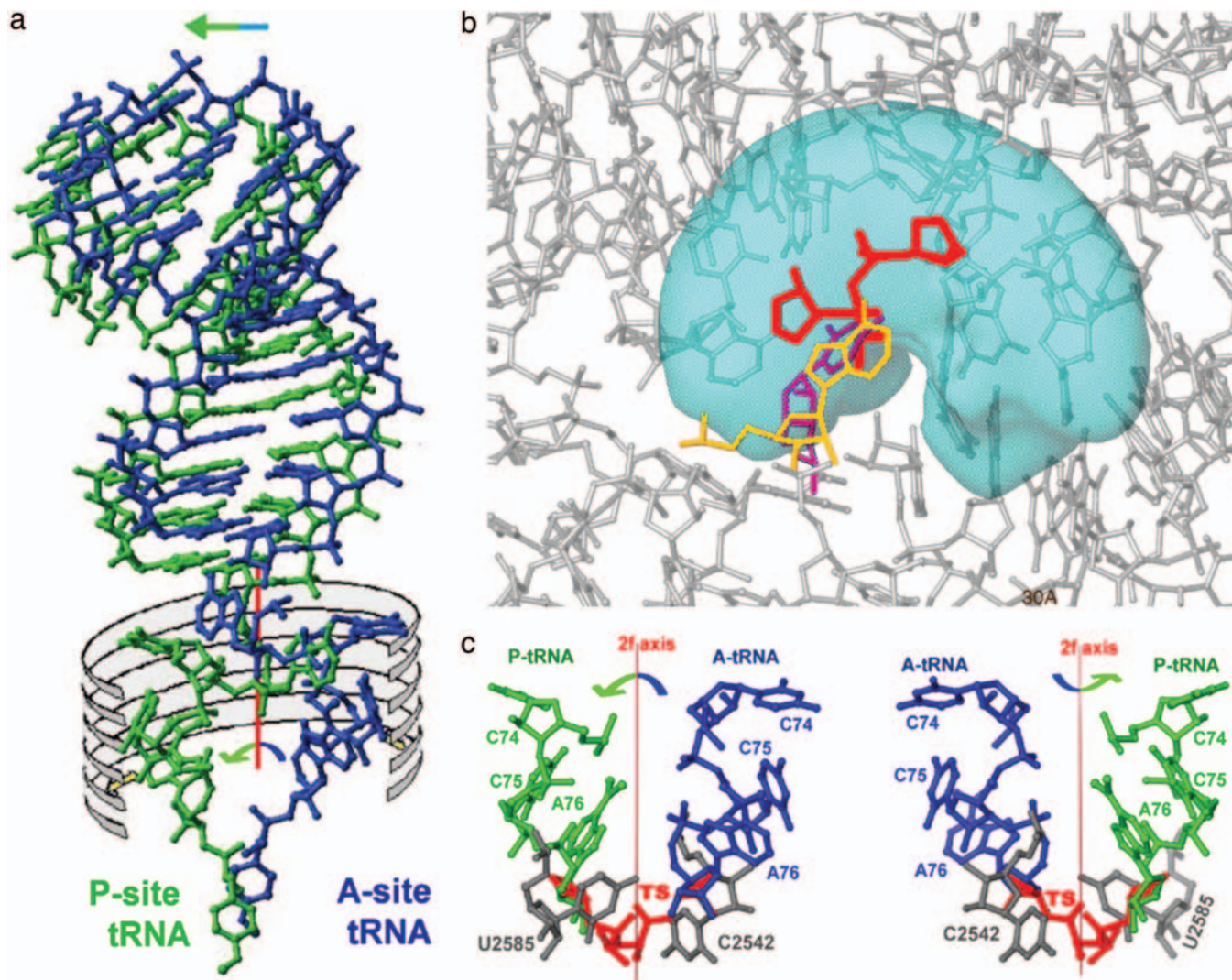
**Fig. 2.** The TS position within the volume occupied by the rotatory motion in the PTC of the ribosome. (*a*) A schematic presentation of the combined linear and rotational motions involved in the passage of the A-site tRNA from the A site to the P site. The 2-fold symmetry axis is shown in red. The apparent overlap of the two tRNA stems is a result of the specific view (diagonal toward the back of the paper plane), chosen to show best the concerted motions. (*b*) The approximately orthogonal view of the rotatory motion shown in *a*, looking approximately down the 2-fold symmetry axis, together with the TS, formed after 45° rotation (A site to P site) within the PTC of the ribosome. The transparent cyan ''cloud'' shows the entire rotatory space, as was simulated every 15° of the rotation. The ribosomal nucleotides are shown in gray. Those below the rotatory space are shown in lighter gray. The TS is shown in dark red. Nucleotides A2602 and U2585 are colored purple and yellow, respectively. Note the marked fit between the TS position and the space provided by the ribosome. (*c*) Two views perpendicular to the 2-fold rotation axis. Shown are ends of tRNAs molecules at the P site (green), the A site (blue), the 2-fold axis (red), the TS (dark red), and the nucleotides C2452 and U2585 (gray). The TS lies at its best position between the A- and P-site tRNAs. (*Left*) View from the subunit interface. (*Right*) View from the PTC rear wall.

fits with the calculated TS, as judged by the closeness of the match between the atoms of the TS sugars, and those from the tip of the A- and P-site tRNA 3′ ends that they mimic.

We have calculated the distance between the atoms of the TS and all of the nucleotides that surround it. Only nucleotides C2452 and U2585 (*Escherichia coli* numbering throughout the text) have atoms in close proximity to the TS at 45° angle of rotation. The atoms in question from C2452 do not involve bonds either ''making or breaking'' in the TS. However, a nitrogen atom in U2585 base protrudes into the space nearby where a C—O bond between a P-site tRNA and an amino acid is being broken in the TS. The proximity of U2585 and the TS (Fig. 2 *b* and *c*) may possibly allow it to play a role in facilitating the break of the P-site tRNA away from the elongating protein chain. The possible contribution of U2585 to elongation, rather than to peptide-bond formation and the remoteness of A2451 from the

TS, are in accord with recent findings that ruled out the critical catalytic contributions of these nucleotides to single peptide-bond formation performed by *in vitro*-assembled ribosomes (12). Hence, the possible involvement of U2585 in elongation remains to be investigated further.

## Discussion

Our goal was to investigate the formation of the peptide bond as it occurs within the ribosome. In particular, we studied the energy and geometry of the amino acid and the peptidyl that play a major part in peptide-bond formation while attached via ester bonds to the tRNAs at the A site and P site of the ribosome, respectively. We have chosen the 50 atoms we considered as the most important players in peptide-bond formation. Within that choice, and the quantum mechanics of density functional theory (DFT), we have computed a molecular structure and energy that
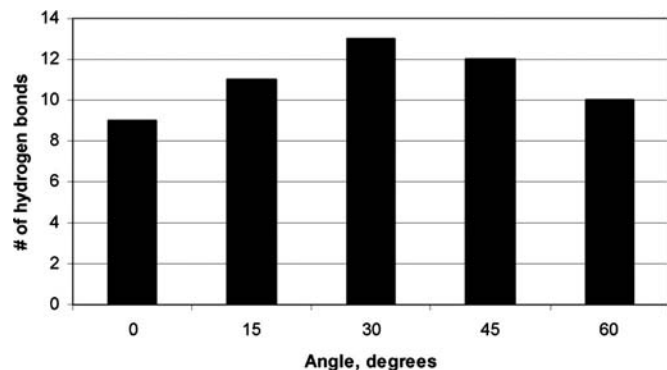
**Fig. 3.** A bar plot of the number of hydrogen bonds between the rotating moiety at the end of the A-site tRNA and the nucleotides of the ribosome PTC. The count of the number of hydrogen bonds was made with a distance criterion. The distance criterion, which considers that a hydrogen bond is being made, was based on a ''cut-off'' at 4 Å.

satisfies all mathematical criteria for a TS. In all respects, it makes good chemical sense, in terms of formation of a peptide bond, the translocation of A-site tRNA to the P site, and P-site tRNA separation from the elongated chain. The chemical sense, after the mathematical criteria, is what corroborates the TS.

One has to keep in mind the physical significance of the TS. As two molecules come together, typically the process is uphill

**Table 2. Calculated energies (using MB3LYP/6-31+G\*\* method) along the peptide bond formation pathway**



| Chemical species | Energy, a.u. | Relative (to reactants) energy, kcal/mol |
|---|---|---|
| R | −1,259.78590 | 0.0 |
| TS | −1,259.72318 | 35.5 |
| P | −1,259.79099 | −3.2 |

$\Delta E_{HB}$ represents the qualitative reduction in our calculated TS activation energy, which would be expected to occur because of increased hydrogen bonding concomitant with the reaction's progress toward the TS. An increase of three hydrogen bonds of average magnitude 6 kcal/mol would be consistent with a qualitatively estimated TS barrier of 18 kcal/mol.
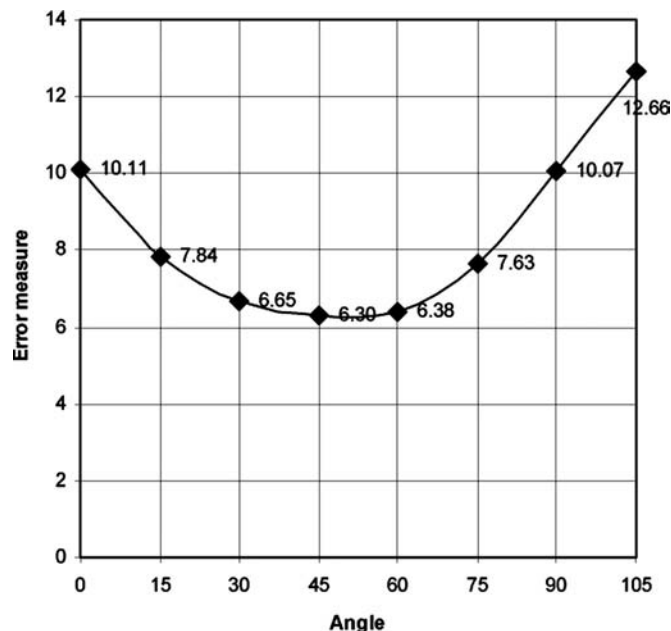
**Fig. 4.** Plot of error measure vs. angle, at average position between optimal fits of TS to the A- and P-site tRNAs. $\varepsilon = \Sigma r_i$, where $\varepsilon$ is the error measure and $r_i$ is the distance between atoms of the TS sugar moieties and those of their analog atoms at the A and P sites. The angle is measured from an origin taken to be the A-site position before rotation about the 2-fold axis of the PTC.

in energy. At the TS the molecule is at an energy maximum, for every displacement of coordinates, except for one unique displacement that corresponds to an energy minimum. Thus, the geometry of the energy surface at the TS is that of a saddle point, and physically it corresponds to the point of breaking and making of bonds that transform the reactants into the products. The TS is characterized mathematically by normal mode frequencies that are all positive, except for exactly one, which is negative, and corresponds to a vibration along the reaction coordinate sending the old reactants into the new products. As one may see (Tables 3 and 4, which are published as supporting information on the PNAS web site) from the frequency spectrum we have calculated, we have a TS characterized in just that way, i.e., all positive frequencies but one.

The calculated $E_a = 35.5$ kcal/mol for our TS applies only to the barrier associated with those 50 atoms considered in the DFT calculation. However, qualitative considerations make clear how such activation energy would be stabilized in the ribosome. During elongation the A-site tRNA carries out a "linear motion." At the same time its terminus, namely its CCA end and the amino acid attached to it, executes a rotational 2-fold motion. The combined linear and rotational motions of the full tRNA are indicated schematically in Fig. 2*a*. As may be seen from Fig. 2, the number of hydrogen bonds associated with the rotatory motion of the aminoacylated tRNA 3′ end within the PTC appears to increase, by as many as three hydrogen bonds between 0° and 45°. Adopting a reasonable average energy for such hydrogen bonds allows a qualitative estimate of the stabilization of the TS that would occur. For hydrogen bonds on the order of 6 kcal/mol, three such bonds would confer TS stabilization of 18 kcal/mol. Thus a qualitative estimate for the activation energy barrier for formation of the peptide bond in the ribosome would be ≈18 kcal/mol. This qualitative estimate for the $E_a$ may be compared with the related (but different) experimental measurement (13), which has $E_a = 17.5$ kcal/mol. Noteworthy are additional theoretical calculations (14–16), all of which, however, deal with mechanisms different from our own, as they do
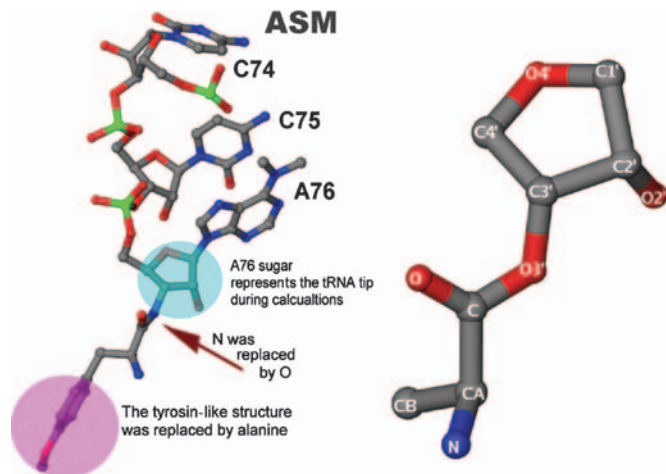
**Fig. 5.** The 3′ end of the tRNA analog. (*Left*) Shown is the tip of the tRNA ASM taken from the experimental crystal structure of its complex with D50S (Protein Data Bank ID code 1NJP), as used for the quantum mechanics calculations. The modified regions are highlighted by cyan and magenta. Hydrogen atoms are not shown. (*Right*) The sugar moiety at tip of tRNA, charged with alanine, is shown.

not include the ribosome environment and/or the rotatory motion.

Interestingly, it appears that the TS geometry is achieved after a modest rotation, which we estimate as ≈45°. It seems that at that stage the P-site A76 O2′ reaches a position allowing the formation of a hydrogen bond within the TS. Such an H bond can stabilize the TS geometry, as recently suggested based on biochemical studies (17), which means that the TS for the peptide bond is made rather early in the rotation. However, the final bonds made and broken, resulting from the TS will achieve their equilibrium values after further rotation along the guiding reaction pathway associated with the 2-fold axis of the PTC.

We conclude that it is satisfactory that the DFT quantum computations, allowing all 50 atoms to move freely, have found a mathematically, well characterized TS. Also the fact that the OH group at the P site ends up making what looks to be a catalyzing hydrogen bond, in accordance with experiments that are generally agreed to be credible, underlines again the chemical sense our TS conveys.

## Methods

The crystal structure of the 50S large ribosomal subunit from *Deinococcus radiodurans* (D50S) complexed with a tRNA acceptor stem mimic (ASM) (1) is available in the Protein Data Bank (ID code 1NJP). Fig. 5 shows a small part of this structure, the part that represents the 3′ end of the tRNA analog (ending with the highlighted sugar ring) attached via nitrogen to a tyrosine-like molecule using the nonhydrolyzable tRNA 3′ end analog, puromycin). In reality, during protein synthesis, amino acids attach to tRNA via ester-type bond, which would mean replacing N with an O at that location in Fig. 5. The highlighted region of Fig. 5 contains atoms that have been judged to be of importance to the formation of the peptide bond. There are two analogous sets of such atoms, one associated with the P position and one associated with the A position in the PTC. Both sets together constitute the 50 atoms chosen to represent the formation of the TS. All 50 atoms of the TS calculation are listed with their coordinates in Table 3.

As shown in Fig. 5, we used the sugar moiety to represent the tip of tRNA and replaced the N atom at the junction of the tRNA and the amino acid with an O atom to investigate the actual reaction and, because of computational considerations, replaced the tyrosine-like bound amino acid structure with an alanine.

The TS results from a search that, except for initial conditions, is an automatic search, which only stops at a convergence satisfying stringent mathematical criteria, showing that we have achieved a geometry that is at an energy maximum for every direction of displacement except for one, which is a displacement toward products and away from reactants. The DFT quantum computations allow all 50 atoms to move freely, until a mathematically well characterized TS is found. From a point of view of corroborating a TS, the bonds that are making and breaking must be consistent with the chemistry of the reaction.

We have used DFT to obtain the TS for the peptide-bond formation within the ribosome. Because it is not computationally feasible at present to include all atoms of the crystallographic structure mentioned in our DFT calculations, their number had to be reduced greatly. The smaller system that we have studied includes all of the atoms essential for peptide-bond formation in the ribosome, and therefore we were able to obtain results that are relevant to the problem.

Quantum mechanical calculations were carried out with the Mulliken program package (an IBM proprietary software package that implements *ab initio* quantum chemical calculations on the IBM SP/2 supercomputer, The Laboratory for Quantum Crystallography, City University of New York). The Becke three-parameter-hybrid (B3) (18) was used in conjunction with the Lee-Yang-Parr (LYP) functional (19). For all calculations, a Gaussian-type basis set, 6–31+G(d,p) was used. Thus, geometries of all reactants, products, and TSs have been optimized by using the B3LYP/6–31+G(d,p) of DFT. Vibrational frequencies have been calculated by using the same approximation for characterization of the nature of stationary points and zero-point vibrational energy corrections. All of the stationary points have been positively identified for minimum with no imaginary frequencies and the TS as a saddle point on the energy surface with one imaginary frequency. The bonds that are at the point of making and breaking in TS structure are consistent with a transformation connecting the desired reactants and products associated with peptide-bond formation. The Cartesian coordinates of all atom positions in the optimized TS and calculated values of the vibrational frequencies are provided in Tables 3 and 4.

The geometry of the TS, together with the tRNA terminus motion within the 2-fold symmetry of the PTC (1, 3), has been used to estimate the angle of rotation of the A-site tRNA at the point of peptide-bond formation. We made the estimate of rotation to the point of TS formation by using coordinates of rotations every 15° about the 2-fold axis of the PTC. Superimposing our TS sugar moiety corresponding to the A site onto the ASM sugar moiety, we let the TS ride around the 2-fold axis, looking for an angle that brought the second sugar moiety of the TS into best coincidence with its analog ring at the P site.

We assumed that the position of the tRNA at the P site is fixed, and it is the motion of the A-site tRNA in its swing about the 2-fold axis that brings the reacting amino acids into coincidence. At each 15° increment of rotation we optimized the superposition of a TS sugar moiety onto that of the A site. In an analogous way we optimized a superposition of the TS sugar moiety onto that of the P site. Because the 50 atoms of the TS have been optimized independently of the tRNAs at A and P sites, it is not possible for the TS to fit them both simultaneously. Thus, we defined a best "average" position of the TS as occurring at the midpoint along a linear transformation between the optimal superpositions on the A- and P-site tRNAs. Using an objective error measure method, shown in Fig. 4, based on the distance between analogous atoms at the average position of the TS and the A- and P-site

tRNAs, we found the best match to occur at a rotation angle of $\approx 45°$, a result indicated earlier.

Stabilization of the activation energy, as calculated and optimized by the DFT, is achieved in the ribosome by the increase in hydrogen bonds between the TS and the ribosomal components. Hydrogen bonds were considered in effect if the distances between hydrogen bond donor and acceptor atoms were <4.0 Å.

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# Corrections

**BIOCHEMISTRY.** For the article "The transition state for formation of the peptide bond in the ribosome," by Asta Gindulyte, Anat Bashan, Ilana Agmon, Lou Massa, Ada Yonath, and Jerome Karle, which appeared in issue 36, September 5, 2006, of *Proc Natl Acad Sci USA* (103:13327–13332; first published August 28, 2006; 10.1073/pnas.0606027103), the authors note that the words "minimum" and "maximum" were transposed in two instances in their article. On page 1330, right column, beginning on line 1, "At the TS the molecule is at an energy maximum, for every displacement of coordinates, except for one unique displacement that corresponds to an energy minimum" should instead read: "At the TS the molecule is at an energy minimum, for every displacement of coordinates, except for one unique displacement that corresponds to an energy maximum." On page 1331, right column, line 6, "a geometry that is at an energy maximum" should instead read: "a geometry that is at an energy minimum." These errors do not affect the conclusions of the article.

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**IMMUNOLOGY.** For the article "LPS-induced TNF-$\alpha$ factor (LITAF)-deficient mice express reduced LPS-induced cytokine: Evidence for LITAF-dependent LPS signaling pathways," by Xiaoren Tang, Daniel Metzger, Susan Leeman, and Salomon Amar, which appeared in issue 37, September 12, 2006, of *Proc Natl Acad Sci USA* (103:13777–13782; first published September 5, 2006; 10.1073/pnas.0605988103), the authors note that on page 13781, right column, in *Plasmid Constructs*, in regard to the mouse LITAF DNA, GenBank accession no. BC004063 should instead have appeared as AF230522. The online version has been corrected.

www.pnas.org/cgi/doi/10.1073/pnas.0700697104

CORRECTIONS