Interactions between HIV-1 gp41 Core and Detergents and Their Implications for Membrane Fusion*

Weish Shu, Hong Ji, and Min Lu‡

From the Department of Biochemistry, Weill Medical College of Cornell University, New York, New York, 10021

The gp41 envelope protein mediates entry of human immunodeficiency virus type 1 (HIV-1) into the cell by promoting membrane fusion. The crystal structure of a gp41 ectodomain core in its fusion-active state is a six-helix bundle in which a N-terminal trimeric coiled coil is surrounded by three C-terminal outer helices in an antiparallel orientation. Here we demonstrate that the N34(L6)C28 model of the gp41 core is stabilized by interaction with the ionic detergent sodium dodecyl sulfate (SDS) or the nonionic detergent n-octyl-β-D-glucopyranoside (βOG). The high resolution x-ray structures of N34(L6)C28 crystallized from two different detergent micellar media reveal a six-helix bundle conformation very similar to that of the molecule in water. Moreover, N34(L6)C28 adopts a highly α-helical conformation in lipid vesicles. Taken together, these results suggest that the six-helix bundle of the gp41 core displays substantial affinity for lipid bilayers rather than unfolding in the membrane environment. This characteristic may be important for formation of the fusion-active gp41 core structure and close apposition of the viral and cellular membranes for fusion.

Enveloped viruses enter cells by a viral envelope protein-promoted membrane fusion process that mediates penetration of the viral genome into host cells. The mechanism of viral membrane fusion is best understood for the hemagglutinin (HA)1 protein of influenza virus. The labile native (nonfusogenic) structure of HA is transformed, in a “spring-loaded” manner, by acidic pH to an energetically more stable, fusion-active (fusogenic) conformation (1–7). This conformational change leads to insertion of the hydrophobic fusion domain termed fusion peptide at the N terminus of the transmembrane subunit HA, into the target membrane and ultimately results in fusion of the viral and cellular membranes and infection of the cell (1, 2, 5–9).

* This work was supported by National Institutes of Health Grant AI42382. The costs of publication of this article were defrayed in part by the payment of page charges. This article must therefore be hereby marked “advertisement” in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.

† To whom correspondence should be addressed: Dept. of Biochemistry, Weill Medical College of Cornell University, 1300 York Ave., New York, NY 10021. Tel.: 212-746-6562; Fax: 212-746-8875; E-mail: mlu@mail.med.cornell.edu.

‡ The abbreviations used are: HA, hemagglutinin; HIV-1, human immunodeficiency virus type 1; SDS, sodium dodecyl sulfate; βOG, n-octyl-β-D-glucopyranoside; [θ]222, molar ellipticity at 222 nm; CD, circular dichroism; HPLC, high performance liquid chromatography; Tm, midpoint of thermal denaturation; PBS, neutral pH phosphate-buffered saline; DMPG, dimyristoylphosphatidylglycerol; POPE, 1-palmitoyl, 1,2-oleyl phosphatidylethanolamine.

The human immunodeficiency virus type 1 (HIV-1) envelope glycoprotein mediates the early binding and entry steps in viral infection. The envelope glycoprotein consists of a complex of the surface subunit gp120 and the transmembrane subunit gp41 (10, 11). gp120 determines viral tropism by binding to both CD4 and one of several chemokine coreceptor molecules at the T-cell surface (Refs. 12 and 13; see also Ref. 14). These protein-protein interactions induce structural changes in the envelope protein and exposure of the hydrophobic fusion peptide of the gp41 subunit, which then mediates fusion of the apposed virus and cell membranes. Significant advances have been made in recent years in elucidating the molecular basis of gp41-mediated membrane fusion (reviewed in Ref. 15). Protein dissection studies revealed that two 4,3 hydrophobic (heptad) repeat regions within the gp41 ectodomain form a soluble, α-helical complex consisting of a trimer of antiparallel heterodimers (Fig. 1) (16–18). X-ray crystallographic analyses confirmed that this gp41 core is a six-helix bundle (19–21). Three N-terminal helices form a central, three-stranded coiled coil, while three C-terminal helices pack in the antiparallel manner into conserved hydrophobic grooves on the surface of the coiled-coil trimer. On the basis of these findings and a number of recent studies, it was proposed that this six-helix bundle structure represents the core of fusion-active gp41 (16, 19–24). Consistent with this view, a monoclonal antibody specifically recognizing the gp41 core binds to the surface of HIV-1 infected cells only after interaction of the envelope protein complex with soluble CD4 (25).

The structure of the gp41 core resembles the proposed fusion-active conformations of the transmembrane envelope protein from influenza virus and Moloney murine leukemia virus (2, 19–21, 26). The core of each of the three structures consists of a trimeric coiled coil adjacent to the N-terminal fusion peptide, with three α-helices packed in an antiparallel orientation against the coiled coil. This conserved structure suggests a common theme for viral membrane fusion, notably that formation of the helical-hairpin structure leads to juxtaposition of the virus and cell membranes for fusion (20, 23, 27). According to this theory, the helical-bundle molecule, a protein, is required to break the energy barrier for fusion of two membranes, which is energetically unfavorable. This model implies that the helical structure interacts with lipid membranes. This notion is supported by electron paramagnetic resonance spectroscopic experiments that indicate that the coiled-coil region adjacent to the fusion peptide region of HA interacts with lipid bilayers only in the fusion-active state (28). Again, using electron paramagnetic resonance, a peptide corresponding to the N-terminal heptad-repeat region within the gp41 ectodomain of HIV-1 shows membrane binding (29). These lipid-binding phenomena are postulated to facilitate membrane fusion (28).

The surface of the gp41 core is highly grooved and possesses distinct hydrophilic and hydrophobic regions, features that may be essential for the binding of lipid membranes. Here we
show that the N34/L6/C28 model of the gp41 core is stabilized by interaction with the anionic detergent sodium dodecyl sulfate (SDS) or the nonionic detergent n-octyl-β-d-glucopyranoside (βOOG). The x-ray structures of N34/L6/C28 crystals grown from these detergent micellar media at resolutions of 2.7 (SDS) and 1.45 Å (βOOG) reveal a six-helix bundle conformation that is very similar to that of the molecule in water. Moreover, N34/L6/C28 folds into a fully helical conformation in lipid vesicles. Our results suggest that the six-helix bundle structure can interact with lipid bilayers. This membrane binding may play a role in facilitating both the gp41 conformational change during fusion activation and local apposition of the viral and cellular membranes for fusion.

**EXPERIMENTAL PROCEDURES**

**Protein Production**—The recombinant N34/L6/C28 model was expressed in *Escherichia coli* BL21(DE3)pLysS using the T7 expression system (30) and purified to homogeneity by reverse-phase high performance liquid chromatography (HPLC) as described previously (17). Protein identity was confirmed by mass spectrometry. Protein concentrations were determined by absorbance at 280 nm in 6 M guanidinium hydrochloride, with an extinction coefficient calculated based on tryptophan and tyrosine (31).

**Circular Dichroism Spectroscopy**—CD spectra were acquired in 50 mM sodium phosphate, pH 7.0, and 150 mM sodium chloride (PBS) with an Aviv 62 DS spectrometer as described previously (32). The same buffer was also used to prepare micellar solutions of βOOG and SDS. The wavelength dependence of molar ellipticity, [θ], was monitored at 20 °C as the average of five scans, using a five-second integration time at a 1.0-nm wavelength increments. Spectra were baseline-corrected against the cuvette with buffer alone. Helix content was estimated from the CD signal by dividing the mean residue ellipticity at 222 nm by the value expected for 100% helix formation by helices of comparable size, −33,000 degrees cm² dmol⁻¹(33). Thermal stability was determined by monitoring the change in CD signal at 222 nm as a function of temperature, and thermal melts were performed in 2-degree intervals with a 2-min equilibration at the desired temperature and an integration time of 30 s. The thermal melts were not reversible, and the protein precipitated after thermal denaturation. The midpoint of the thermal unfolding transition (apparent melting temperature, Tm) was determined from the maximum of the first derivative, with respect to the reciprocal of the temperature, of the [θ]zzz values (34). The error in estimation of Tm is ±1 °C.

**Equilibrium Ultracentrifugation**—Sedimentation equilibrium analysis was performed on a Beckman XL-A analytical ultracentrifuge as described previously (32). Protein solutions were dialyzed overnight against PBS containing SDS or βOOG, loaded at initial concentrations of 10, 40, and 150 μM, and analyzed at rotor speeds of 22 and 25 k rpm at 20 °C. Data sets were fitted to single-species models. Protein partial specific volume and solvent density were calculated with constants from Laue et al. (35). Molecular weights were all within 10% of those calculated for an ideal trimer, with no systematic deviation of the residuals.

**Vesicle Preparation**—Small unilamellar vesicles of dimonosterylphosphatidylglycerol (DMPG) (Sigma) and 1-palmitoyl, 1-oleyl phosphatidylcholine (POPE) (Avanti Polar Lipids, Birmingham, AL) were prepared by nitrogen stream evaporation of a 5 mg/ml chloroform solution of the lipid followed by redispersion in PBS (pH 7.0) and sonication in a bath sonicator at 4 °C for 45 min.

**Crystallization and Data Collection**—N34/L6/C28 was crystallized at room temperature by vapor diffusion. A stock of HPLC-purified N34/L6/C28 was dissolved in water, and its final protein concentration was adjusted to 10 mg/ml. Initial crystallization conditions were found by using the hanging-drop method with sparse matrix crystallization kits (Crystal Screen 1 and II, Hampton Research, Riverside, CA) and then optimized. Centered cubic crystals with the symmetry of space group P2₁2₁2₁ were obtained from 0.1 mM sodium HEPES, pH 7.5, 0.8 mM potassium sodium tartrate, and 10 mM SDS. Data to 2.7 Å resolution on the cubic crystals were collected at room temperature at the X-ray Crystallography Facility at the Weill Medical College of Cornell University using an R-axis IV image plate detector mounted on a Rigaku RU200 rotating anode x-ray generator. Primitive rhombohedral crystals with the symmetry of space group R3 were obtained from 0.1 mM sodium citrate, pH 5.6, 1.0 M ammonium dihydrogen phosphate, and 35 mM βOOG. The crystals were transferred to a cryoprotectant solution containing 25%/v/v glycerol in the corresponding mother liquor. Cryo-protected crystals were frozen in propane before data collection. Data to 1.45 Å resolution were collected at 95 K using a Mar research image plate scanner at the X12B beamline of the National Synchrotron Light Source. All diffraction intensities were integrated and scaled with the HKL suite (36).

**Structure Determination and Refinement**—The structures of N34/L6/C28 crystallized in the presence of detergent were determined by molecular replacement by using the program AMoRe (37). The 2.4 Å structure of N34/L6/C28 (Protein Data Bank code 1DFZ) was used in a combined rotation-translation search (using 8.0–3.5 Å data) to yield a solution for N34/L6/C28/SDS (correlation coefficient, 60.9%; R-factor, 45.1%). Density interpretation and model building were done with the program O (38). Crystallographic refinement of the structure was done with the program X-PLOR (39). Prior to refinement, 5% of the diffraction data were set aside for cross-validation (free R-factor calculation). Noncrystallographic symmetry restraints were not used in the final refinement. Despite the relatively high mean B-factor 42 Å², the model is generally well defined in the electron density (see Fig. 5A). The final refined model (Rfree = 18.3%; R = 31.5%) includes 162 of 204 residues in the N34/L6/C28 trimer. No ordered density was observed for SDS. The following regions do not have clear electron density and are presumed to be disordered: residues 548–550 and 653–655 of gp41 and the linker region. All ϕ and ψ angles are in allowed regions of the Ramachandran plot.

Cross-rotation and cross-translation functions (using 10.0–3.0 Å data) by using the 2.4 Å structure of N34/L6/C28 as a search model yielded a solution for N34/L6/C28/βOOG (correlation coefficient, 58.2%; R-factor, 43.8%). The model was subjected to rigid body refinement (8.0–2.5 Å) of the whole molecule by using the program X-PLOR (39). This procedure was followed by least squares minimization of the atomic positions with the program O (38). The resulting map was subjected to rounds of automatic tracing and model building by using the program Arp-Warp 5.0 (40) and the program REFMAC from the CCP4 program suite (41). The refinement was monitored by using the free R-factor. At this stage, the model yielded higher quality of the 2Fobs – F and Fobs – F electron density maps compared with the starting maps. Noncrystallographic symmetry restraints were not used in the refinement. Crystallographic refinement of the structure was done with the program X-PLOR (39). The final refined model (Rfree = 20.9%; R = 24.5%) contains residues 548–578 and 628–651 of gp41, Gly-5 and Gly-6 of the linker, and 90 water molecules. No ordered density was observed for βOOG. Residues 546, 547, 579, and 662–655 of gp41 and Ser-1, Gly-2, Gly-3, and Arg-4 of the linker are not seen in the electron density, and the side chains of Glu-550 and Glu-647, as well as Met-629, are disordered and were thus modeled as serine and alanine, respectively. All ϕ and ψ angles are within allowed regions. The atomic coordinates have been deposited in the Protein Data Bank (codes 1DF4 and 1DF6).
Interactions between gp41 Core and Detergents

**RESULTS**

**N34(L6)C28 Conformation in Lipid Vesicles**—We have previously shown that the recombinant N34(L6)C28 model of the HIV-1 gp41 core forms a six-helix-bundle structure in solution and in crystals and shows a cooperative thermal unfolding transition (18, 21). To analyze the conformation of N34(L6)C28 in the hydrophobic environment of the lipid bilayer, we first characterized the physicochemical properties of N34(L6)C28 in the presence of the ionic detergent SDS. SDS micellar system (the critical micellar concentration is 8.2 mM) has been widely used to study peptide-lipid and protein-lipid interactions (42–48). On the basis of CD measurements at a 10 µM protein concentration in PBS at 20 °C in the presence of 2 and 10 mM SDS, N34(L6)C28 displays a ∼75% α-helical structure, with characteristic double minima in CD spectra at 222 and 208 nm (Fig. 2A). Under these conditions, N34(L6)C28 exhibits a cooperative thermal melt with an apparent melting temperature (T_m) of 88 °C in 2 mM SDS, in contrast to that of 70 °C in aqueous buffer (Fig. 2B; Table I). Remarkably, N34(L6)C28 has a thermal stability that exceeds 100 °C in 10 mM SDS micelles (Fig. 2B). Because N34(L6)C28 denatures irreversibly with temperature in all cases, T_m values measured by CD spectroscopy are useful as only a qualitative guide to stability. Moreover, sedimentation equilibrium measurements indicate that N34(L6)C28 sediments as a clean trimer in 10 mM SDS micelles (Fig. 2C; Table I).

Taken together, these results indicate that N34(L6)C28 can form a highly stable six-helix bundle in SDS micelles. The lower helicity of N34(L6)C28 in the presence of SDS compared with PBS may be due to the partially unfolded region in the molecule (see below). It is extremely unusual for a small protein motif, in SDS solution that is in excess of its critical micellar concentration, to fold into a stable structure that is similar to that found under native conditions. By extension, the six-helix bundle of the gp41 core likely interacts preferentially with SDS micelles.

To determine the general feature of the gp41 core-detergent interaction, we analyzed the conformation of N34(L6)C28 in βOG micelles. βOG is a nonionic detergent with a critical micellar concentration of 25.3 mM. In PBS at a 10 mM protein concentration in the presence of 35 mM βOG, CD experiments indicate that the folded N34(L6)C28 molecule appears to be ∼90% helical at 20 °C and ∼45% helical at 90 °C (Fig. 3A; Table I). In addition, sedimentation equilibrium experiments indicate that N34(L6)C28 is trimeric in 35 mM βOG micelles (Fig. 3B; Table I). Thus, N34(L6)C28 folds into a stable six-helix bundle structure in βOG micelles. These results strongly suggest that the fusion-active gp41 core displays substantial affinity for detergents.

**N34(L6)C28 Conformation in Lipid Vesicles**—To further investigate the gp41 core-membrane interaction, we examined the conformation of N34(L6)C28 in DMPG and POPE bilayer vesicles, systems that imitate more closely the structural features of physiologically relevant bilayer membranes (e.g., 49, 50). CD measurements at 10 µM protein and 4 mM lipid concentrations in PBS (pH 7.0) at 20 °C indicate that N34(L6)C28 folds into α-helical structures in both DMPG and POPE vesicles (Fig. 4). Because up to 2-fold reductions in ellipticity have been observed in the spectra of membrane-bound proteins (51, 52), it is striking that N34(L6)C28 appears to be more helical in lipid environments than that in aqueous solution; the ellipticities of N34(L6)C28 at 222 nm are 30,000, 34,000, and 39,000 degrees cm^2/dmol in water, DMPG, and POPE, respectively (Fig. 4). In the light of recent evidence that helix formation for...
The overall topologies of N34/L6/C28 crystallized from the detergent media are the same as that of the molecule in water. In all cases, three hairpin-like molecules pack together on the crystallographic 3-fold symmetry axis to form a six-helix bundle. Three N34 helices within the bundle form a central, parallel trimeric coiled coil with a left-handed superhelical pitch, whereas three C28 helices pack, in an antiparallel orientation, into three hydrophobic grooves on the surface of the N34 coiled coil (Fig. 6A). The root mean square deviations between Cα atoms of N34/L6/C28 in the aqueous and detergent structures are 0.55 Å for SDS and 0.58 Å for βOG (Fig. 6B). Thus, the N34/L6/C28 model of the gp41 core forms extremely stable, well structured six-helix bundles in SDS and βOG micellar media. However, the N and C termini of both the structures do not have clear electron density and are presumed to be unfolded, consistent with the lower helicity of the N34/L6/C28 molecule in detergent micelles by CD measurements (Figs. 2 and 3).
As was observed with the crystal structures of the gp41 core, the N-terminal coiled-coil trimer surface is highly grooved and possesses three conserved hydrophobic cavities that provide binding pockets for three C-terminal helices (19–21, 53). The predominantly hydrophobic interactions between the N- and C-terminal helices are the key determinants of the six-helix bundle fold and may play a role in the gp41 core-lipid interaction. A comparison of the hydrophobic cavity in the N34(L6)C28 structures in water and detergent media reveals that the two key residues (Trp-571 and Trp-631) involved in forming the cavity show different rotamers (Fig. 7). Whereas the side chains of the surface residues in the vicinity of the conserved cavity deviate substantially in the three structures, the interior core residues in the coiled-coil heptad positions have similar packing geometries (Fig. 7). In all three structures, Thr 569 at a heptad position in the N34 coiled coil, for example, has its hydroxyl group hydrogen-bonded to the carbonyl oxygen of Leu-565 and still uses its hydrophobic methyl group pointing toward the center of the trimeric coiled coil. Although we cannot exclude the possibility that the exterior side chain packing discrepancies among the three structures of N34(L6)C28 may be due to differences in crystallization media, crystal packing contacts, and the use of different crystal forms, these surface residues are likely to be involved in the six-helix bundle-lipid interaction. In addition, the SDS and βOG molecules are not detected in the high resolution crystal structures of N34(L6)C28, probably because they do not often form ordered arrays due to thermal motion (43, 44). It is also possible that the gp41 core binds to lipid membranes through nonspecific interactions.

DISCUSSION

Emerging structural and biochemical work reveals conservation of a core structure between HIV-1 gp41 and the transmembrane subunits of the influenza virus and Moloney murine leukemia virus envelope proteins (2, 19–21, 26). The core structure reveals a three-stranded, α-helical coiled coil adjacent to the N-terminal fusion peptide that is known, at least in the case of HA2, to insert into the host bilayer at an initial step of membrane fusion (8, 9). Moreover, the polypeptide chain reverses direction at the end of the N-terminal coiled coil and forms an α-helix that proceeds toward the N terminus of the molecule. The overall fusion mechanism of viral envelope proteins is thought to involve the refolding of α-helical coiled coils that underlies activation of membrane fusion (for a recent review, see Ref. 54). It is striking that this mechanism is likely to be shared by the SNARE proteins that mediate cellular membrane fusion processes (54).

Numerous studies have led to the proposal that viral membrane fusion proteins can exist in two major conformations: the native structure on the surface of the virion is metastable and thus has the potential to transform to a stable and fusogenic conformation during the membrane fusion step of HIV-1 infection (1, 3, 4). The native state of the influenza HA protein, for example, is trapped in a metastable conformation that, upon destabilization, converts into an energetically more stable and...
fused-active structure (1, 3, 4, 55). This strategy might well be shared by the HIV-1 envelope glycoprotein (4). Therefore, understanding the factors that determine the conformational specificity and stability of the native and fusogenic folds is required for addressing essential structural and mechanistic questions about the mechanism of viral entry into cells.

The native state of the HIV-1 envelope protein complex is also thought to be metastable and readily undergoes a receptor-activated conformational change to a fusogenic structure (reviewed in Ref. 14). Recent evidence indicates that the six-helix bundle structure of the gp41 ectodomain core represents the fusogenic state of the HIV-1 envelope, similar to the low pH-induced conformation of influenza virus HA (16, 19–25). This finding and the structural and biophysical studies of the gp41 core (16–21) suggest that upon binding of gp120 to CD4 and its subsequent interaction with a chemokine coreceptor, the gp41 ectodomain orchestrates a complex series of protein-protein interactions and structural changes that results in the colocalization of the virus and cell membranes (20, 23, 27). According to this suggestion, formation of the six-helix bundle structure brings the two membranes into close proximity for membrane fusion because the N-terminal fusion peptide region and the transmembrane helix of gp41 are embedded in the target cell and viral membranes, respectively. Little is known about how this membrane apposition overcomes the energy barrier for membrane fusion.

Asteres 1a model for gp41-mediated membrane fusion suggests that the six-helix bundle formation is intimately associated with the viral and cellular membranes during the virus binding and fusion (15, 20, 23, 27). Biochemical evidence also suggests that more than just the N-terminal fusion peptide region of gp41 can interact with the lipid membrane (29). These considerations led us to surmise that the fusion-active gp41 ectodomain core interacts with lipid bilayers. The results described above indicate that the six-helix bundle structure is stabilized by interaction with SDS or βOH micelles and that the atomic structures of the gp41 core crystallized from detergent micellar media are essentially the same as that in water. Our results also indicate that the N34(L6)C28 model of the gp41 core can fold into a fully helical conformation in DMPC and POPE bilayer vesicles. Taken together, these data do not support the kind of “spray and insertion” model proposed on the basis of electron paramagnetic resonance spectroscopic studies for apposing virus and cell membranes (28). According to this model, the six-helix bundle splits apart and “melts” into lipid bilayers. Instead, our results support a fusion model in which the gp41 core causes close membrane apposition as the six-helix complex is assembled for membrane fusion (20, 23, 27), because this model predicts that the gp41 core binds to lipid membranes. We propose that this membrane binding plays a critical role in driving the gp41 conformational change during fusion activation and may therefore be of fundamental importance in membrane apposition and fusion. Understanding the determinants for the gp41 core-membrane interaction is likely to provide insights into the basic property of the conformational change that renders the gp41 molecule able to bind to and alter the shape of the lipid bilayer.

Acknowledgments—We are grateful for Yu Luo for help with calculating search models and crystallographic computation. We also thank Malcolm Cupel of beamline X12B at the National Synchrotron Light Source laboratories for support and Jennifer Poitras for secretarial help, Temple Burling for assistance with data collection, and Chris Lima and Jun Dong for suggestions on structural refinement.

REFERENCES

1. Carr, C. M., and Kim, P. S. (1993) Cell 73, 823–832
2. Bullough, P. A., Hughson, F. M., Skehel, J. J., and Wiley, D. C. (1994) Nature 371, 37–43
3. Chen, J., Wharton, S. A., Weissenhorn, W., Calder, L. J., Hughson, F. M., Skehel, J. J., and Wiley, D. C. (1996) Proc. Natl. Acad. Sci. U. S. A. 93, 12205–12229
4. Carr, C. M., Chaudhry, C., and Kim, P. S. (1997) Proc. Natl. Acad. Sci. U. S. A. 94, 14306–14313
5. Wiley, D. C., and Skehel, J. J. (1987) Annu. Rev. Biochem. 56, 365–394
6. Stegmann, T., and Helenius, A. (1995) in Viral Fusion Mechanisms (Bentz, J., ed) pp 89–111, CRC Press, Boca Raton, FL
7. Hernandez, L. D., Hoffman, L. R., Wolfsberg, T. G., and White, J. M. (1996) Annu. Rev. Cell Dev. Biol. 12, 427–461
8. Stegmann, T., Delfino, J. M., Richards, F. M., and Helenius, A. (1991) J. Biol. Chem. 266, 18404–18410
9. Tsurudome, M., Gluck, R., Graf, R., Falchetto, R., Schaller, U., and Brunner, J. (1992) J. Biol. Chem. 267, 20225–20232
10. Lucir, P. A. (1996) in Fields Virology (Fields, B. N., Knipe, D. M., Howley, P. M., Chanock, R. M., Melnick, J. L., Monath, T. P., Roizman, B., and Straus, S. E., eds) pp. 1881–1952, Lippincott-Raven Publishers, Philadelphia
11. Turner, B. G., and Summers, M. F. (1998) J. Mol. Biol. 285, 1–32
12. Kwong, P. D., Wyatt, R., Robinson, J., Sweet, R. W., Sodroski, J., and Hendrickson, W. A. (1998) Nature 393, 648–655
13. Rizzuto, C. D., Wyatt, R., Hernandez-Ramos, N., Sun, Y., Kwong, P. D., Hendrickson, W. A., and Sodroski, J. (1998) Science 280, 1949–1953
14. Moore, J. P., Jameson, B. A., Weiss, R. A., and Sattentau, Q. J. (1993) in Viral Fusion Mechanisms (Bentz, J., ed) pp. 253–269, CRC Press, Boca Raton, FL
15. Chan, D. C., and Kim, P. S. (1998) Cell 93, 681–684
16. Lu, M., Blacklow, S. C., and Kim, P. S. (1996) Nat. Struct. Biol. 2, 1075–1082
17. Lu, M., and Kim, P. S. (1997) J. Biochem. Structure Dyn. 15, 465–471

FIG. 7. Stereo view of the superposition of residues 564–571 of N34 and 628–633 of C28 in the N34(L6)C28 structures in water (red), SDS (green), and βOH (white), showing a cross-section of helix packing near the conserved hydrophobic cavity in the gp41 core. Figure was generated with the program SETOR (56).
Interactions between gp41 Core and Detergents

18. Lu, M., Ji, H., and Shen, S. (1999) J. Virol. 73, 4433–4438
19. Chan, D. C., Fass, D., Berger, J. M., and Kim, P. S. (1997) Cell 89, 263–273
20. Weissenhorn, W., Dessen, A., Harrison, S. C., Skehel, J. J., and Wiley, D. C. (1997) Nature 387, 426–430
21. Tan, K., Liu, J., Wang, J., Shen, S., and Lu, M. (1997) Proc. Natl. Acad. Sci. U. S. A. 94, 13426–13430
22. Judice, J. K., Tom, J. Y. K., Huang, W., Wrin, T., Vennari, J., Petropoulos, C. J., and McDowell, R. S. (1997) Proc. Natl. Acad. Sci. U. S. A. 94, 13426–13430
23. Furuta, R. A., Wild, C. T., Weng, Y., and Weiss, C. D. (1998) Nat. Struct. Biol. 5, 276–279
24. Munoz-Barroso, I., Durell, S., Sakaguchi, K., Appella, E., and Blumenthal, R. (1988) J. Cell Biol. 140, 315–323
25. Jiang, S., Lin, K., and Lu, M. (1998) J. Virol. 72, 10213–10217
26. Fass, D., Harrison, S. C., and Kim, P. S. (1997) Nature 387, 426–430
27. Hughson, F. M. (1997) Curr. Biol. 7, R565–R569
28. Yu, Y. G., King, D. S., and Shin, Y.-K. (1994) Science 266, 2465–2469
29. Rabenstein, M., and Shin, Y. K. (1995) Biochemistry 34, 13390–13397
30. Studier, F. W., Rosenberg, A. H., Dunn, J. J., and Dubendorff, J. W. (1990) Methods Enzymol. 185, 65–89
31. Edelhoch, H. (1987) Biochemistry 6, 1948–1954
32. Shu, W., Ji, H., and Lu, M. (1999) Biochemistry 38, 5378–5385
33. Chen, Y. H., Wang, T. C., and Chau, K. H. (1974) Biochemistry 13, 3350–3359
34. Cantor, C., and Schimmel, P. (1980) Biophysical Chemistry, Part III, pp. 1131–1132, W. H. Freeman Co., New York
35. Lauer, T. M., Shah, B. D., Ridgway, T. M., and Pelletier, S. L. (1992) in Analytical Ultracentrifugation in Biochemistry and Polymer Science (Harding, S. E., Rowe, A. J., and Horton, J. C., eds) pp. 90–125, Royal Society of Chemistry, Cambridge, United Kingdom
36. Otwinowski, Z., and Minor, W. (1996) Methods Enzymol. 276, 307–326
37. Navaza, J. (1994) Acta Crystallogr. Sect. A 50, 157–163
38. Jones, T. A., Zou, J.-Y., and Cowan, S. W. (1991) Acta Crystallogr. Sect. A 47, 110–119
39. Brünger, A. T. (1992) X-PLOR Version 3.1: A System for X-ray Crystallography and NMR, New Haven, CT, Yale University Press
40. Lamzin, V. S., and Wilson, K. S. (1993) Acta Crystallogr. Sect. D 49, 129–147
41. CCP4 (1994) Acta Crystallogr. Sect. D 50, 760–763
42. van de Ven, F. J. M., van Os, J. W., Wymenga, S. S., Remerowski, M. L., Konings, R. N., and Hiberus, C. W. (1993) Biochemistry 32, 8322–8328
43. Roth, M., Lewit-Bentley, A., Michel, H., Deisenhofer, J., Huber, R., and Oesterhelt, D. (1989) Nature 340, 659–662
44. Barber, J. (1989) Nature 340, 601
45. Hoyt, D. W., and Giersas, L. M. (1991) Biochemistry 30, 10155–10163
46. Gordon, L. M., Curtain, C. C., Zhang, Y. C., Kirkpatrick, A., Mobley, P. W., and Waring, A. J. (1992) Biochim. Biophys. Acta 1139, 257–274
47. Li, S. C., and Deber, C. M. (1994) Nature Struct. Biol. 1, 368–373
48. Roterin, B. V., Ohms, J. P., and Hagenmaier, H. (1976) Eur. J. Biochem. 70, 601–610
49. Li, S.-C., and Deber, C. M. (1993) J. Biol. Chem. 268, 22975–22978
50. Blumenthal, R., Henkart, M., and Steer, C. J. (1983) J. Biol. Chem. 258, 3409–3415
51. Glaser, R. M., and Jap, B. K. (1985) Biochemistry 24, 6398–6401
52. Mao, D., and Wallace, B. A. (1984) Anal. Biochem. 142, 317–328
53. Ji, H., Shu, W., Burling, F. T., Jiang, S., and Lu, M. (1999) J. Virol. 73, 8578–8586
54. Skehel, J. J., and Wiley, D. C. (1998) Cell 85, 871–874
55. Qiao, H., Pelletier, S. L., Hoffman, L., Hacker, J., Armstrong, R. T., and White, J. M. (1998) J. Cell Biol. 141, 1335–1347
56. Evans, S. V. (1993) J. Mol. Graphics. 11, 134–138