tetanus involved four high-frequency trains of stimulation (100 Hz for 1 s at 30-s intervals) delivered at the test intensity. Data were collected and analyzed with software written by us for this purpose under the Axobasic programming environment (Axon Instruments Incorporated, Foster City, CA). This software measured the amplitude or slope of the EPSP or EPSC. Statistical comparisons were made with the Student's *t* test, done on non-normalized data.
18. Ensemble average plots represent group means of each EPSP (or EPSC), across experiments, aligned with respect to the time of acquisition relative to the time of LTP induction by pairing. For each group of experiments, we included all the data that met the following criteria: (i) resting membrane potential of both neurons more negative than −60 mV and (ii) recordings of both cells held for at least 50 min after the induction of LTP. The group data in the ensemble averages and described in the text reflect all the data that fit these criteria. We did not exclude experiments where the paired neurons failed to exhibit LTP. For three experiments in which we had intended to impale neurons that were far apart, the biocytin data revealed that these neurons were in fact close (<300 μM). We thus switched these data to the nearby group.
19. We processed the slices for biocytin reaction with minor modifications of methods previously described [G. F. Tseng, I. Parada, D. A. Prince, *J. Neurosci. Methods* **37**, 121 (1991)]. To obtain a rough estimate of the distance between the synapses onto the paired and neighboring neurons, we measured the center to center intersomatic distance.
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25. We thank E. Schaible and I. Parada for technical assistance. We also thank J. Haley, T. Schwarz, and C. Shatz for comments on this manuscript.

19 July 1993; accepted 29 November 1993

TECHNICAL COMMENTS

Experimental Support for the "Hydrophobic Zipper" Hypothesis

In a recent report (*1*), we described the kinetics of folding of the all–β sheet protein interleukin-1β (IL-1β) with the use of nuclear magnetic resonance (NMR), far-ultraviolet dichroism, and fluorescence spectroscopy. The deuterium/hydrogen exchange quench flow experiments demonstrated that intermediates with a stable, hydrogen-bonded, secondary structure were only formed on the second time scale. Subsequent closer inspection of those parts of the IL-1β structure that are involved in these folding intermediates revealed clustering of hydrophobic residues, in particular, leucines. The five strands (Fig. 1) of the 12-stranded structure, which were detected in the NMR experiment (*1*), constitute the major site of early-forming hydrogen bonds. Within the symmetrical "trefoil" structure (*2*), they comprise hairpin 2 (strands 6 and 7) and parts of the adjacent barrel strands 5, 8, and 9. The locations of the major hydrophobic residues are also revealed (Fig. 1).

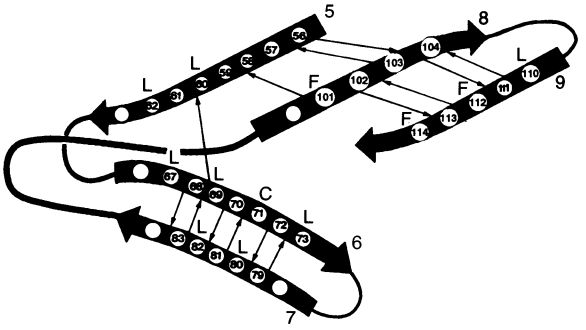

Fig. 1. Schematic picture of the early folding unit in IL-1β. Strands 5, 6, 7, and 8 represent the second of the three pseudosymmetric units of the "trefoil" fold, with strands 6 and 7 constituting the hairpin unit and strands 5 and 7 forming part of the β barrel. Early stable hydrogen bonds are indicated by arrows, and the identity of the important hydrophobic side chains is given by the one letter code.

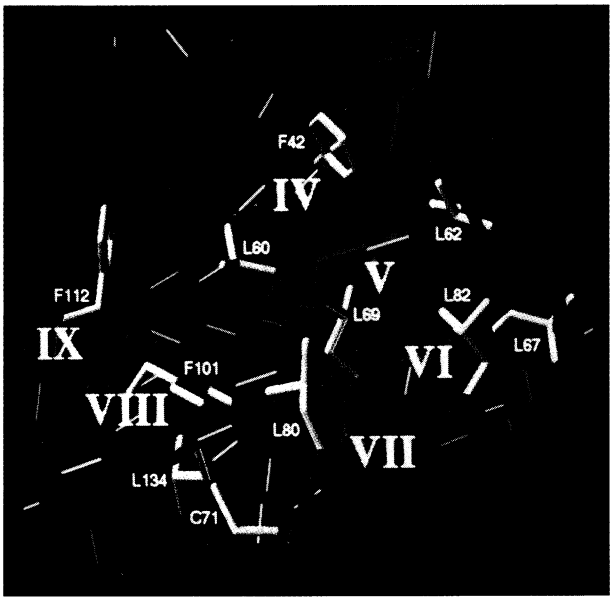

Fig. 2. Depiction of the "hydrophobic zipper" part of the IL-1β structure. The backbone (of N, C^{α}, and C atoms) is traced in red, and the side chains are shown in green. Also indicated is the residue number for the selected side chains and the numbering of the β strands (roman numerals). The structure of IL-1β is taken from (*4*) (PDB accession code 6I1B).

Our experimental data are similar to a recent theoretical model proposed by Dill *et al.* (*3*) that has been termed the "hydrophobic zipper" model of protein folding. In the initiation of folding, hydrophobic side chain pairs that are closely positioned in the sequence are brought together by a limited conformational search, with subsequent pairing of other pairs, one after another, like the zipping of a zipper. In IL-1β, the initial zipper would be made up from strands 6 and 7, with the other strands arranging around these. The location and distribution of hydrophobic side chains in this region of the protein structure add support to this notion (Fig. 2). The zipper-like arrangement of Leu^{67}, Leu^{82}, Leu^{69}, Leu^{80}, and Cys^{71}, running from right to left (Fig. 2), is most striking.

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17 August 1993; accepted 20 October 1993