Proline isomerases are folding enzymes and thus have the potential to catalyze their own folding. We show here that the folding of cytosolic FKBP12 (FK 506 binding protein) is an autocatalytic process both for the mature protein and for a fusion protein with an amino-terminal extension of 16 residues. Native FKBP contains seven trans-prolyl peptide bonds, and the cis-to-trans isomerizations of some or all of them constitute the slow, rate-limiting events in folding. The rate of an autocatalytic reaction increases with reactant concentration, because the product catalyzes its own formation. Accordingly, the folding of the fusion protein was more than 10-fold accelerated when the protein concentration was increased from 0.05 μM to 10 μM. At high concentrations of both forms of FKBP12 autocatalysis was very efficient, and the observed folding rate seemed to approach the rate of the fast direct folding reaction of the protein molecules with the correct (all trans) peptidyl-prolyl bond conformation.

Protein folding in vitro and in vivo is often decelerated because it is coupled with prolyl isomerization (1-5). Cis/trans equilibria are usually established at the prolyl peptide bonds in an unfolded polypeptide chain, and, as a consequence, denatured proteins are heterogeneous mixtures of species which refold with different rates. Only the molecules with the native-like prolines1 can refold directly in a rapid reaction. The molecules with incorrect prolines refold in slow reactions that are limited in rate by the cis/trans isomerizations of these prolines. Proline-limited folding reactions are catalyzed in vitro and in vivo by peptidyl-prolyl cis/trans isomerase activity. Four families of these ubiquitous proteins are now known (13-16), and their functions are not confined to catalyzing slow steps in protein folding (13, 17).

We asked here whether prolyl isomerases could catalyze their own folding. To search for autocatalytic folding, we used human FKBP122 (18, 19), a prolyl isomerase of the large family of FK 506 binding proteins. These enzymes catalyze proline-limited protein folding reactions (20), and they are inhibited by the immunosuppressant FK 506 (18, 19). FKBP12 is a small single-domain protein. It contains seven proline residues, which, in the native state, are all preceded by trans-peptide bonds (21-23). Denaturant-induced unfolding of FKBP12 is reversible (24) and refolding can be followed by a change in protein fluorescence and by the regain of the prolyl isomerase activity.

In an autocatalytic reaction the product accelerates its own formation and thus its rate is expected to increase with reactant concentration. For a proline-limited folding reaction, autocatalysis should thus lead to an increase in rate with protein concentration until the rate of direct fast refolding is approached. Therefore, in our refolding experiments, we varied the concentration of FKBP12 in a wide range, and in some folding experiments FK 506 was added to inhibit the prolyl isomerase activity of the refolded molecules. We found that autocatalysis contributes indeed to the refolding of most unfolded FKBP12 molecules. A strong autocatalytic rate enhancement was found in the folding of a variant of FKBP12 for which the direct and the proline-limited folding reactions differ vastly in rate.

EXPONENTIAL PROCEDURES

Materials—Urea (ultrapure) and guanidinium chloride (ultrapure) were from ICN Biomedicals, o-chymotrypsin and recombinant human cyttoplasmic Cyp18 were from Boehringer-Mannheim, LICI and CF₂CH₂OH were from Fluka, the assay peptide Suc-Ala-Phe-Pro-Phe-nitroanilide was from Bachem. All other chemicals were from Merck-Darmstadt. Recombinant human FKBP12 and the fusion protein EK-FKBP12 were expressed and purified as described by Zarnt et al. (25). The concentrations of the two proteins were determined spectrophotometrically by using an absorption coefficient of 9530 m⁻¹ cm⁻¹ at 280 nm (25). EK-FKBP12 contained an amino-terminal extension of the following 16 residues: TMITNSMHHHDDDDDK. Residues 1-6 represent a fragment from the NH₂ terminus of β-galactosidase, they are followed by a tetrahistidine tag and by the recognition site for cleavage by enterokinase (25). FK506 was a gift of Fujisawa Corporation.

Prolyl Isomerase Assays—The procedure described by Zarnt et al. (25) was used to assay the prolyl isomerase activities of FKBP12 and EK-FKBP12. Suc-Ala-Phe-Pro-Phe-nitroanilide served as the assay peptide. Mature FKBP12 and EK-FKBP12 showed identical specific activities in this assay. Both retained more than 80% of their activities in the presence of 0-10 mM urea.

Equilibrium Unfolding Transitions—Native protein was incubated in 0.1 M Tris/HCl, pH 8.0, in the presence of varying concentrations of urea for 14 h at 10°C. The extent of unfolding was determined for each solution by measuring the fluorescence emission at 354 nm (10-nm

1 To facilitate reading we use the terms cis-proline and trans-proline for proline residues that are preceded by a cis or a trans peptide bond, respectively, in the folded protein and "native-like" and "incorrect, non-native" to denote whether in an unfolded state a particular prolyl peptide bond shows the same conformation as in the native state or not. Further, we use the expression "isomerization of ProX" for the isomerization of the prolyl peptide bond preceding ProX. The folding reactions that involve Xaa-Pro isomerizations as rate-limiting steps are denoted "proline-limited" reactions; the (usually) rapid folding of the unfolded molecules which have the Xaa-Pro peptide bond in the same conformation as the native protein is denoted as the "direct" folding reaction.

2 The abbreviations used are: FKBP12, recombinant cytosolic human FK 506 binding protein; EK-FKBP12, a version of FKBP12 with an amino-terminal extension of 16 residues; Cyp18, recombinant human cyttoplasmic cyclophilin.
Autocatalytic Protein Folding

RESULTS AND DISCUSSION

Autocatalytic folding of a prolyl isomerase can be observed only when several requirements are met. 1) The proline-limited folding reactions should be much slower than the direct fast refolding of the molecules with the correct prolines to provide a wide time window for measuring potential autocatalytic rate enhancements. 2) The crucial prolines should remain accessible for catalysis when folding intermediates are formed. 3) The catalytic activity of the prolyl isomerase under investigation should be high in the presence of moderate concentrations of denaturant as present in the refolding experiments.

Refolding of Mature FKBP12—The fluorescence of the single tryptophan (Trp-59) of FKBP12 is strongly quenched in the folded protein and increases more than 10-fold upon unfolding. This provides a very sensitive and convenient probe for following the folding kinetics as a function of the protein concentration. The refolding kinetics were measured between 0.2 and 2.0 \( \mu \text{M} \) FKBP12 at 10 °C, pH 8.0 and 0.4 M urea, conditions under which folded FKBP12 is catalytically active, and prolyl isomerizations are slow. Fig. 1 shows that refolding becomes indeed faster with increasing protein concentration. The observed changes in fluorescence follow a complex time dependence and account for 70–80% of the total decrease in fluorescence upon folding. A similarly modest increase in the folding rate with FKBP concentration was found by Veeraraghavan et al. (28).

To confirm that proline-limited steps occur in the folding of FKBP12 we investigated whether its refolding could be accelerated by human cytosolic Cyp18, a prolyl isomerase with a high activity as a folding catalyst and with a very broad substrate specificity concerning the residue Xaa in Xaa-Pro peptide bonds (29). Folding is indeed more rapid when Cyp18 (Fig. 1) is present at a very high concentration (3 \( \mu \text{M} \)) during the refolding of 1 \( \mu \text{M} \) FKBP12, suggesting that prolyl isomerizations are rate-limiting events in its folding. Folding could not be further accelerated by increasing the concentration of Cyp18 to 6 \( \mu \text{M} \). Probably, the catalysis by Cyp18 reaches a limiting value because the proline-limited and the direct folding reactions of FKBP differ only marginally in rate. So, the direct folding reaction is approached at high concentrations of Cyp18, and consequently the upper limit for catalysis is reached. In contrast to Cyp18, FKBP12 itself shows a very narrow substrate specificity (30). Therefore only a fraction of its own seven prolyl bonds are good substrates in autocatalysis. In addition, some of these prolyl peptide bonds might not be fully accessible for catalysis in partially folded intermediates of FKBP12, and this would further decrease the efficiency of autocatalysis.

To enlarge the autocatalytic rate enhancement we tried to destabilize potential folding intermediates and to increase the rate of the direct folding reaction by varying the final denaturant concentration, the temperature of refolding and the nature of the denaturant. Unfortunately, the observable autocatalysis in the folding of FKBP12 could not be improved by all these variations.

FKBP12 with an Amino-terminal Extension—A strong autocatalytic effect was found, however, in the refolding of a slightly destabilized variant of FKBP12, which, at low protein concentrations, folded more slowly than the wild-type protein. This variant (EK-FKBP12) possesses an amino-terminal extension of 16 amino acids, composed of the first 6 residues of \( \beta \)-galactosidase, a tetrahistidine tag and the recognition site for enterokinase. It was used in the recombinant production of FKBP12, and the mature protein was obtained from this fusion protein (EK-FKBP12) by cleaving it with the protease enterokinase (25). EK-FKBP12 is a stably folded protein. It shows the same catalytic activity as the mature protein, and the enzymatic activity depends linearly on protein concentration. The tryptophan fluorescence in native EK-FKBP12 is quenched to the same extent as in the native mature protein. The confor-
protein concentration. Between 4 and 10 m
found at 0.3 m of protein concentration, and identical transition curves were
folded EK-FKBP12 was diluted to 0.9 M urea (pH 8.0) at 10 ºC, urea-induced unfolding (data not shown).
EK-FKBP12 and thus strongly stabilizes the protein toward
folding of EK-FKBP12. The inhibitor FK 506 binds tightly to
demonstrates that protein associations are not involved in the
shifted from 3.9 M (as measured under slightly different condi-
tions by Egan et al. (24)) to 2.9 M. The stability is independent
of protein concentration, and identical transition curves were
found at 0.3 µM and at 3.0 µM fusion protein (Fig. 2). This
demonstrates that protein associations are not involved in the
folding of EK-FKBP12. The inhibitor FK 506 binds tightly to
FKBP12 and thus strongly stabilizes the protein toward
urea-induced unfolding (data not shown).
Refolding Kinetics of EK-FKBP12—To initiate refolding, un-
folded EK-FKBP12 was diluted to 0.9 M urea (pH 8.0) at 10 ºC,
and refolding was followed by the decrease in protein fluores-
cence at varying protein concentrations (Fig. 3). The refolding
of EK-FKBP12 is a complex reaction. At a protein concentration
of 0.2 µM it is more than 20-fold slower than the refolding of the mature protein (cf. Fig. 1) and requires nearly an hour for
completion. Unlike in the refolding of mature FKBP12 (Fig. 1)
we find a very strong increase in the refolding rate with in-
creasing protein concentration, and the half time of refolding
decreases from 270 s to 24 s when the EK-FKBP12 concentra-
tion is increased from 0.05 to 10.0 µM. The acceleration is most
pronounced after extended times of refolding, when the ob-
served kinetics are determined by the prolyl isomerizations.
The measurements were confined to protein concentrations
> 0.05 µM, because the changes in fluorescence upon folding were too small at lower concentrations.

At very low protein concentrations (between 0.05 and 0.2 µM) the autocatalytic rate enhancement was small, but between 0.2
and 2 µM EK-FKBP12 the folding rate increased strongly with
protein concentration. Between 4 and 10 µM EK-FKBP12 the
autocatalytic refolding reached a maximal rate and approached the Cyp18-catalyzed folding reaction (cf. the dashed line in Fig.
3A). This suggests that, as in the folding of mature FKBP12 (cf.
Fig. 1), efficient autocatalysis is no longer observed at high
protein concentration, because the direct folding reaction be-
comes rate-limiting for overall folding. Direct folding is not
limited by prolyl isomerizations and thus not affected by prolyl isomerases. Apparently, the autocatalytic rate enhancement is
much stronger in the folding of the fusion protein, because the
proline-limited and the direct folding reactions differ more
strongly in rate for EK-FKBP12 than for the mature protein.

Folding of EK-FKBP12 was also strongly accelerated when
instead of Cyp18 0.4 µM native EK-FKBP12 was present during

![Fig. 2. Urea-induced unfolding transition of EK-FKBP. The increase in fluorescence at 354 nm is shown as a function of urea concentration for 3.0 µM (C, right ordinate numbering) and for 0.3 µM (left ordinate numbering) EK-FKBP12 in 0.1 M Tris/HCl, pH 8.0 at 10 ºC.](http://www.jbc.org/)

![Fig. 3. Refolding kinetics of EK-FKBP12 at eleven different protein concentrations. A, refolding measured by the decrease in fluorescence at 354 nm. The curves were obtained at protein concentrations of (from top to bottom) 0.05, 0.08, 0.1, 0.2, 0.4, 1.0, 2.0, 3.0, 4.0, 6.0, and 10.0 µM. The identical refolding traces of 1 µM EK-FKBP12 in the presence of 3 and 6 µM Cyp18 are shown by the dashed line. B, kinetics of reactivation of EK-FKBP12 at protein concentrations of (c) 0.2 µM and (■) 3.0 µM. Refolding at 10 ºC was initiated by diluting the unfolded protein (in 4.5 M urea, 0.1 M Tris/HCl, pH 8.0, 10 ºC) to 0.9 M urea in the same buffer, 10 ºC. For the comparison the relative changes in fluorescence are shown. The abso-
lu-te amplitudes and the final values increased linearly with protein concentration. B, kinetics of reactivation of EK-FKBP12 at protein concentrations of (c) 0.2 µM and (■) 3.0 µM.](http://www.jbc.org/)
refolding of EK-FKBP12 also by the regain of its prolyl isomerase activity. The results obtained at 0.2 μM and at 3.0 μM Cyp18 (Fig. 3B) demonstrate that the rate of reactivation of EK-FKBP12 also strongly depends on protein concentration. In the reactivation kinetics performed at 0.2 μM EK-FKBP12 only 10% of the activity is regained after 10 s of refolding, and reactivation follows the refolding kinetics as monitored by fluorescence. This coincidence confirms that the rapid fluorescence changes in the dead time of the refolding experiments (3 s) are not caused by a rapid formation of 20–30% native protein. Rather, this fluorescence change reflects the formation of partially folded intermediates, and the direct folding reaction of the unfolded EK-FKBP12 molecules with correct prolyl isomers occurs in the early time regions of the measured kinetics. Unfortunately, the amount of directly folding molecules with correct prolyl isomers cannot be determined easily by the conventional double-mixing procedure (32) because prolyl isomerases can catalyze the equilibration between the various species in the second (refolding) step of this assay.

If the folding of EK-FKBP12 is indeed an autocatalytic reaction, it should be decelerated when the prolyl isomerase activity of the already folded molecules is inhibited. We therefore measured the folding kinetics of EK-FKBP12 at 0.4 M and at 0.9 M urea in the absence and in the presence of the inhibitor FK 506. FK 506 indeed decelerated folding, but this deceleration remained small at all concentrations of EK-FKBP12 and of FK 506 that were used. In all cases the kinetics in the presence of FK 506 were still significantly faster than those measured at a very low protein concentration (0.1 μM), where autocatalysis was found to be weak (cf. Fig. 3A). It is possible that FK 506 has multiple effects on the folding of EK-FKBP12. In addition to inhibiting the autocatalysis it could also accelerate folding if it binds already to refolding intermediates prior to the rate-limiting step of folding. An acceleration of folding by coenzymes or inhibitors was found for several proteins (33–35).

To test for such a possibility we investigated the refolding of EK-FKBP12 at a high final urea concentration of 2.15 M, near the onset of the equilibrium transition (cf. Fig. 2). It was found for many proteins that partially folded intermediates are destabilized in the transition region and thus are not populated during refolding (36). At 2.15 M urea folded EK-FKBP12 is only marginally stable, but retains its activity as a prolyl isomerase (data not shown). Its refolding kinetics still depend on protein concentration, albeit to a much smaller extent than at 0.9 M urea, and the half time of folding decreases about 2.5-fold when the protein concentration is varied between 0.02 μM and 3.7 μM (Fig. 4). Interestingly, identical refolding kinetics were observed when either a high concentration of EK-FKBP12 was employed (3.7 μM), or when 0.25 or 0.5 μM of Cyp18 were added during the refolding of 0.7 μM EK-FKBP12. This suggests that under these conditions of either good autocatalysis or good catalysis by another prolyl isomerase the rate of direct folding is approached, which at 2.15 M urea seems to be slow with a half time of 190 s. At 0.9 M urea a half time of about 20 s was found for this reaction (cf. Fig. 3A). It is commonly observed that protein folding reactions decrease in rate when the transition region is approached (36, 37). In the presence of 20 μM FK 506 the refolding of 0.7 μM EK-FKBP12 is significantly retarded (Fig. 4). As expected, this retardation is weak immediately after the initiation of refolding and becomes much stronger with increasing time. After about 1000 s the time course of folding in the presence of FK 506 approaches the refolding kinetics which were measured at a very low protein concentration (0.02 μM) and beyond 1000 s it becomes even slower than this folding reaction (Fig. 4). The refolding of 0.02 μM EK-FKBP12 was only slightly retarded by 20 μM FK 506 (data not shown), probably because autocatalysis is weak at this very low protein concentration. When the refolding of 0.7 μM EK-FKBP12 was carried out in the presence of both 20 μM FK 506 and 0.25 μM Cyp18, folding was accelerated as in the presence of 0.25 or 0.5 μM Cyp18 alone. This is expected, because FK 506 does not inhibit the prolyl isomerase activity of Cyp18, which substitutes for the inhibited autocatalysis in this experiment. Together, the experiments of Fig. 4 show that the autocatalysis in the folding of EK-FKBP12 is indeed suppressed by the inhibitor FK 506. This effect could be measured only at a high, but still non-denaturing concentration of urea. It is most clearly seen in the late region of folding, because this part of the kinetics is determined by the prolyl isomerization(s).

The measured refolding kinetics show complex time dependencies, and a quantitative analysis of the folding kinetics such as in Fig. 4 is not possible because they contain contributions from the direct refolding reaction as well as from the isomerizations at several or all of the seven proline residues of FKBP12. The direct and the proline-limited folding reactions are not well separated in time, and therefore they are coupled kinetically in a complex manner, which is different in the presence and in the absence of autocatalysis or of catalysis by Cyp18.

Native FKBP12 contains seven trans-prolines. They are flanked by different residues (18), and probably they remain not equally accessible during folding. Owing to the high substrate specificity of FKBP (29) only two of them (F15-P16 and I91-P92) should be good substrates for the native FKBP molecules. Therefore, in the autocatalysis of its own folding, FKBP12 will accelerate the prolyl isomerizations with strongly different efficiencies. These additional complexities also preclude a detailed kinetic analysis, and it is not possible to present a kinetic mechanism for the autocatalytic folding of FKBP. Complex folding kinetics were also observed for other proteins which contain trans-prolines only (38–42).

Cellular folding is aided not only by folding enzymes, but also by molecular chaperones. They act as folding helpers not by catalyzing rate-limiting events, but by inhibiting aggregation (43) and by unfolding nonproductive intermediates (44). They can also facilitate their own assembly (45, 46), but by a process...
which is “self-chaperoning” (45), rather than autocatalytic.

Many large proteins (including heat-shock proteins) contain FKBP-, cyclophilin-, or parvulin-like domains (13, 15, 17, 47), but the functions of these prolyl isomerase modules are not known. It is possible that they serve a role as intermolecular or even intramolecular catalysts of the folding or of major conformational rearrangements that are necessary for the biological functions of these proteins. At present there is, however, no evidence yet in support of such a role.

Conclusions—As shown here for FKBP12, prolyl isomerases as folding enzymes can accelerate their own refolding in an autocatalytic manner. The extent of autocatalysis that can be observed experimentally in the folding of a prolyl isomerase is limited by the difference in rate between the slow, proline-limited reactions and the fast, direct refolding of the molecules with correct prolyl isomers. This difference is not very large for mature FKBP12 and therefore autocatalysis was not very pronounced.

A strong autocatalytic rate enhancement could be observed for FKBP12, because for this form the proline-limited folding was much slower than the direct folding reaction. Because it is more stable, mature FKBP probably can form a partial structure during folding even with incorrect prolines. This increases the rate of isomerization and at the same time interferes with autocatalysis or catalysis by other prolyl isomerases.

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