

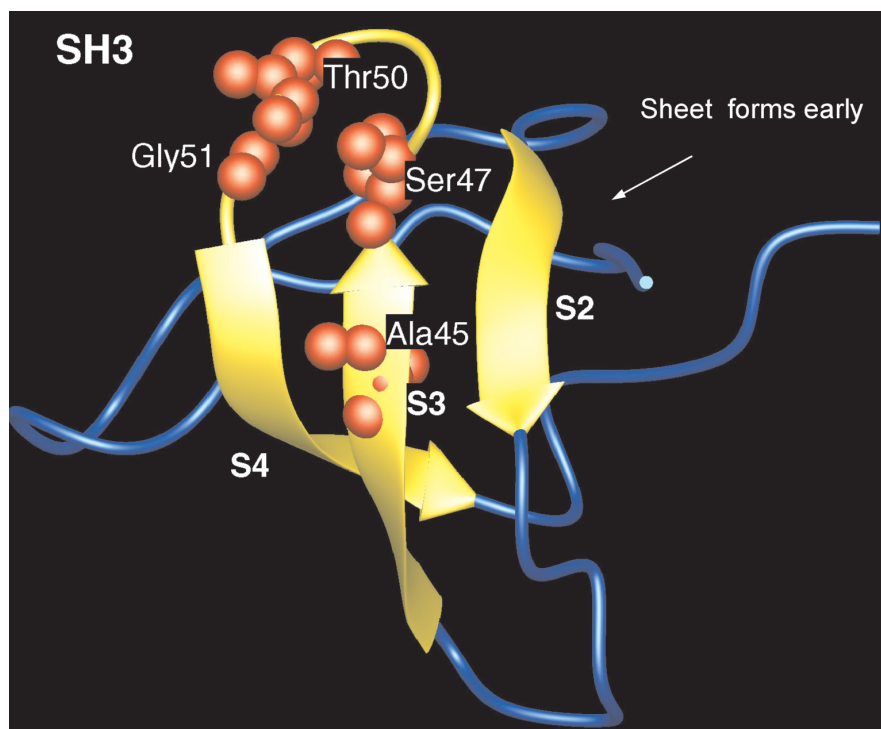
**Fig. 11.8.** Inter-residue contact map for the main transition state of the src SH3 domain (Nölting and Andert, 2000; Nölting, 2003). For explanation of the symbols see the legend to Fig. 11.2.

strand<sub>4</sub>. The src SH3 domain also displays two-state folding behavior ( $U \rightleftharpoons F$ ) (Nölting and Andert, 2000; Nölting, 2003).

Summarizing, all 4 small monomeric proteins display one or two clusters of structural consolidation in some residues which are located in the polypeptide chain about 10–30% apart from the N- and C-termini (Figs. 11.2, 11.4, 11.6, 11.8). This position in sequence of the folding nucleus appears not to be a general rule, however, as indicated by observations on other proteins, e.g., acylphosphatase for which the data coverage is not sufficient for a more thorough  $\Phi$ -value analysis (Nölting and Andert, 2000).

The transition state of the dimeric Arc repressor (Figs. 11.10, 11.11):

1. is in average relatively weakly consolidated,



**Fig. 11.9.** Consolidation of structure in the main transition state of src SH3 domain (Nölting and Andert, 2000; Nölting, 2003). Amino acid residues with high  $\Phi$ -values ( $\Phi \geq 0.8$ ) are highlighted as red spheres. For further explanation see the legend to Fig. 11.3.

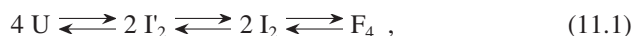
2. has  $\Phi$ -values larger than 0.4 for only two (Leu19 and Gly30) of the 27 residues probed by mutation with  $|\Delta\Delta G_{F-U}| > 0.5$  kcal mol<sup>-1</sup> (see Table 1 in Nölting and Andert, 2000),

3. has the strongest consolidation near the middle of the sequence (Fig. 11.10),

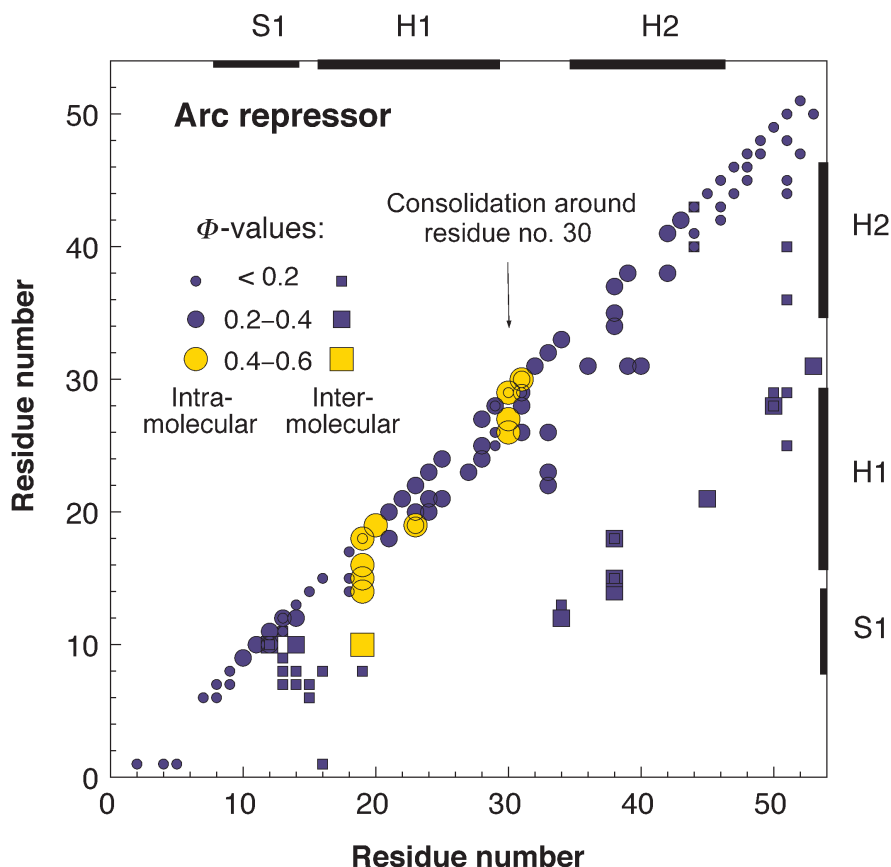
4. involves a significant number of inter-molecular interactions (Fig. 11.10).

The data show that its transition state structure is affected by both the process of folding and as well the assembly of the monomers (Nölting and Andert, 2000).

In contrast, the main transition state structure of the p53 domain (Figs. 11.12, 11.13) is highly consolidated almost everywhere. The folding model is a four-state transition (Nölting and Andert, 2000):



where U,  $I_2'$ ,  $I_2$ , and  $F_4$  are monomeric unfolded state, first dimeric intermediate state, second dimeric intermediate state, and native tetrameric state, respectively.



**Fig. 11.10.** Inter-residue contact map for the main transition state of the dimeric Arc repressor (Nölting and Andert, 2000). For explanation of the symbols see the legend to Fig. 11.2. For Arc repressor there are some quaternary structure contacts because its reaction involves folding and association of the monomers into dimers.

The main transition of this protein is the formation of the tetramer,  $F_4$ , from two dimers,  $2 I_2$ . Only  $\Phi$ -values of some mutants which probe interactions at the interface between the two dimers were found to be somewhat lower than 1 which suggests that the interactions between these two dimers are not completely formed (Fig. 11.13). On the other hand, the average of  $\Phi$  of the transition state for the formation of the early dimers,  $2 I'_2$ , from monomers,  $4 U$ , is only  $-0.01 \pm 0.03$ , so the formation of almost all secondary, tertiary, and monomer–monomer quaternary interactions of the molecule occurs in the step  $2 I'_2 \rightleftharpoons 2 I_2$  (Nölting and Andert, 2000).

Protein Folding Kinetics

Biophysical Methods

Nölting, B.

2006, XVI, 222 p. 170 illus., 12 illus. in color., Hardcover

ISBN: 978-3-540-27277-9