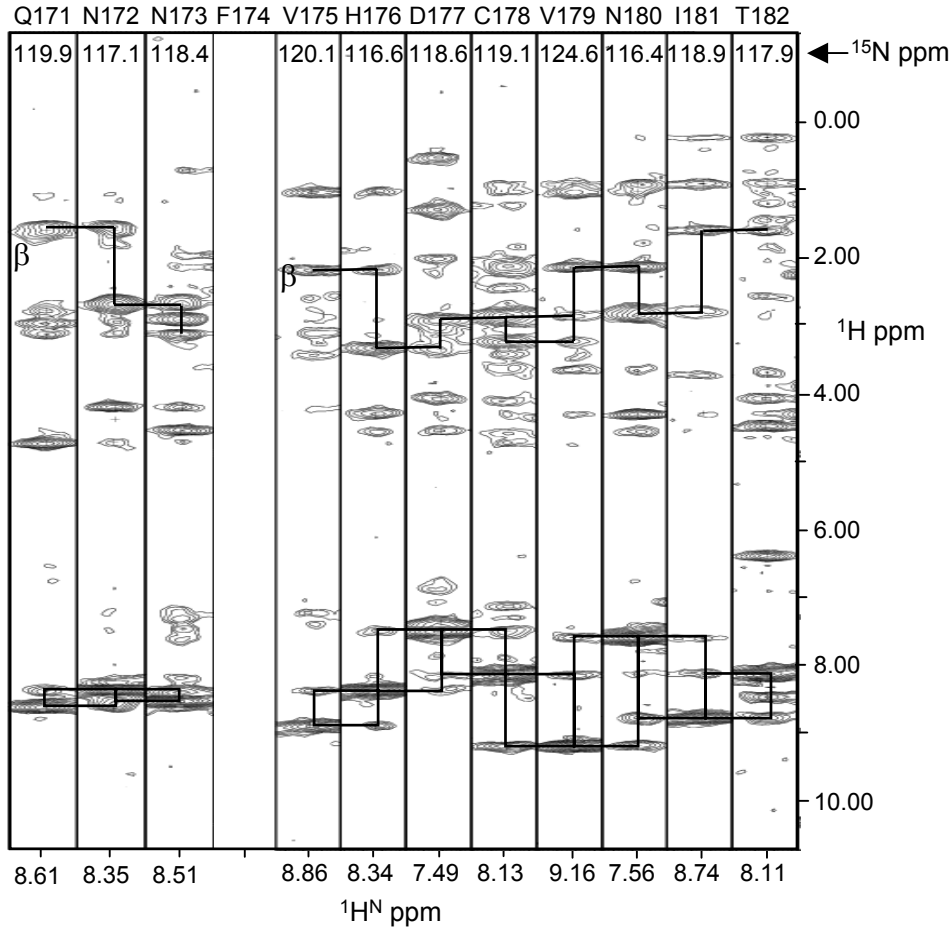
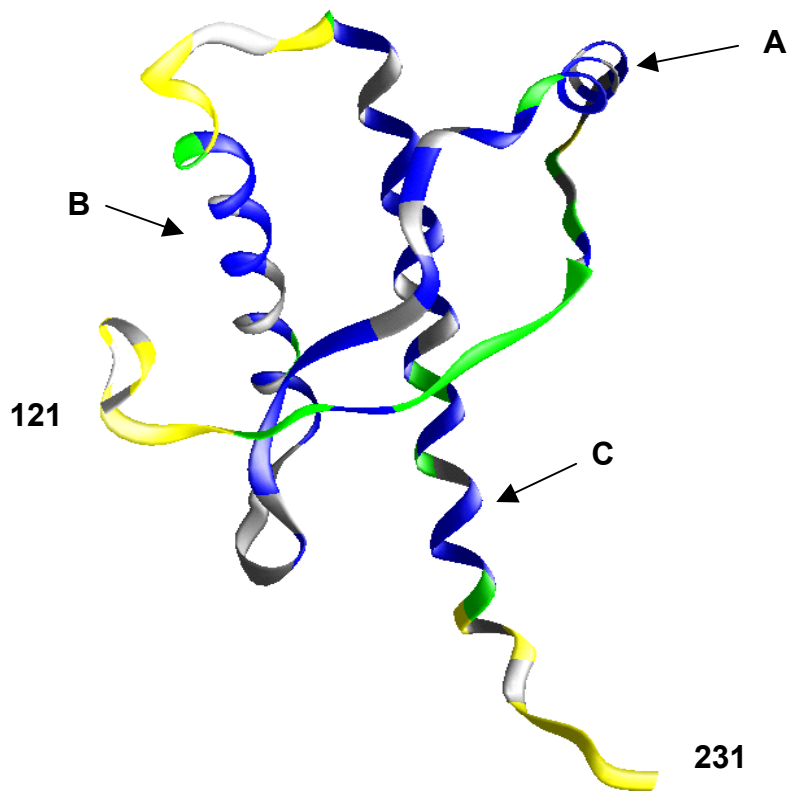
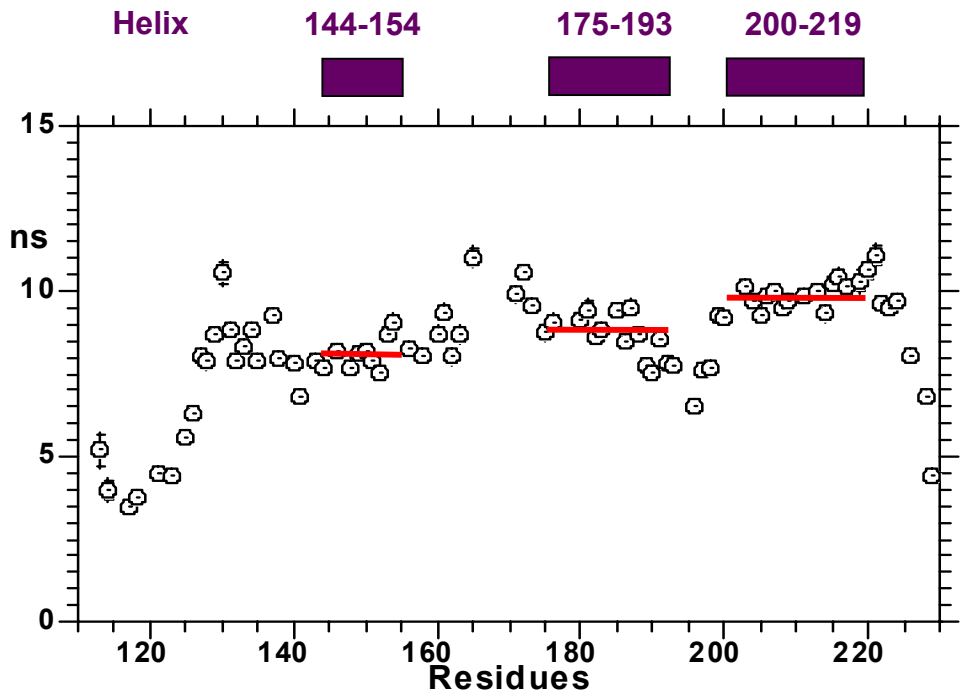


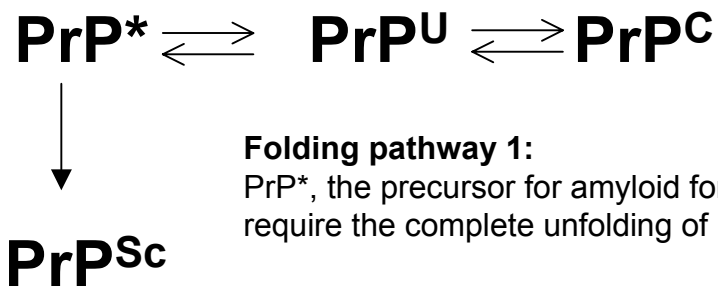
Supplemental Figure S1: Series of strips from ^{1}H-$1H_{N}$ slices of the 3D ^{15}N NOESY-HSQC. Each strip corresponds to a single residue within helix-B; Q171-T182. Solid lines highlight sequential β-β connectivities and NH-NH connectivities. Characteristic i-i+3 NOEs are clearly apparent in many strips. A strip corresponding to F174 could not be assigned, we note a proline for mouse PrP has been reported at this position [12].



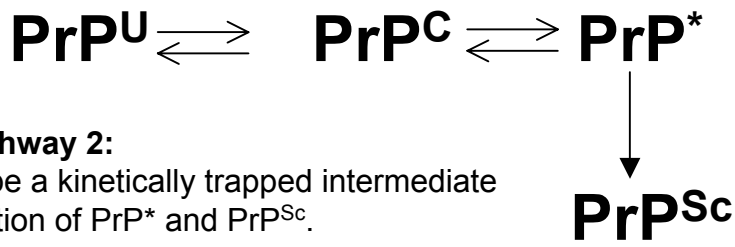
Supplemental Figure S2: Values for $J(0.87\omega_H)$ for mPrP(113-231) mapped onto the structure of $mPrP^C$, (1xyx) $J(\omega_H)<0.006$ ns in blue indicate little fast internal motions. Green $0.006<J(\omega_H)<0.008$ ns while yellow > 0.008 ns indicates the regions with significant fast-motion flexibility. Residues in gray have no $J(0.87\omega_H)$ value calculated.



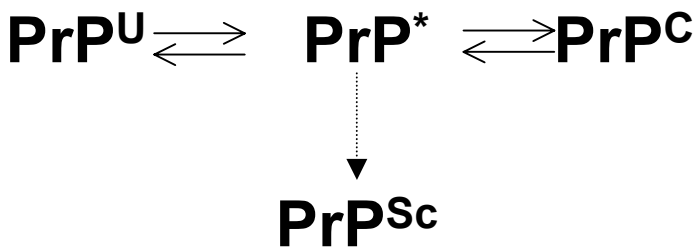
Supplemental Fig S3: **Rotational correlation times per residue (τci).**
Calculated from spectral densities, equation (2). Mean values for the three helices are highlighted in red. Mean values for helix A, B and C are; 8.1, 8.6, 9.9 ns respectively



Folding pathway 1:
PrP*, the precursor for amyloid formation, could require the complete unfolding of PrP^C



Folding pathway 2:
PrP^C could be a kinetically trapped intermediate to the formation of PrP* and PrP^{Sc}.



Folding pathway 3:
PrP* might represent a sampled conformation formed on the way to a more stable native PrP^C.

Supplemental Figure S4: PrP folding intermediates

U, unfolded; *intermediate; Sc scrapie; C cellular

$$\sigma_{NH} = R_1(NOE - 1)\gamma_N/\gamma_H$$
$$J(0) = (6R_2 - 3R_1 - 2.72\sigma_{NH})/(3d^2 + 4c^2)$$
$$J(\omega_N) = (4R_1 - 5\sigma_{NH})/(3d^2 + 4c^2)$$
$$J(0.87\omega_H) = 4\sigma_{NH}/(5d^2)$$

where $d = \mu h \gamma_N \gamma_H r^{-3}$ and
$c = \omega_N \Delta\sigma 3^{-1/2}$

Supplemental Figure S5: Equations to calculate reduced spectral densities at these three frequencies were obtained from the relaxation rates R_1 ($1/T_1$), R_2 ($1/T_2$) and the hetero-nuclear NOE Taken from Farrow et al. (43)