(Wüthrich & Wagner, 1975) was a genuine surprise for the following reasons. In the refined X-ray crystal structure of BPTI, the aromatic rings of phenylalanine and tyrosine are among the side chains with the smallest temperature factors. For each ring, the relative values of the *B* factors increase toward the periphery, so that the largest positional uncertainty is indicated for carbon atom 4 on the symmetry axis through the C^{β}—C^{1} bond, rather than for the carbon atoms 2, 3, 5 and 6 (Fig. 19.7.5.1), which undergo extensive movements during the ring flips. Theoretical studies then showed that the crystallographic *B* factors sample multiple rotation states about the C^{α}—C^{β} bond, whereas the ring flips about the C^{β}—C^{1} bond seen by NMR are very rapid 180° rotations connecting two indistinguishable equilibrium orientations of the ring. The *B* factors do not manifest these rotational motions because the populations of all non-equilibrium rotational states about the C^{β}—C^{1} bond are vanishingly small. The ring-flip phenomenon is now a well established feature of globular proteins, manifesting ubiquitous low-frequency internal motions with activation energies of 60–100 kJ mol^{-1}, amplitudes of $\gtrsim$1.0 Å and activation volumes of about 50 $Å^3$ (Wagner, 1980), and involving concerted displacement of numerous groups of atoms (Fig. 19.7.5.1).

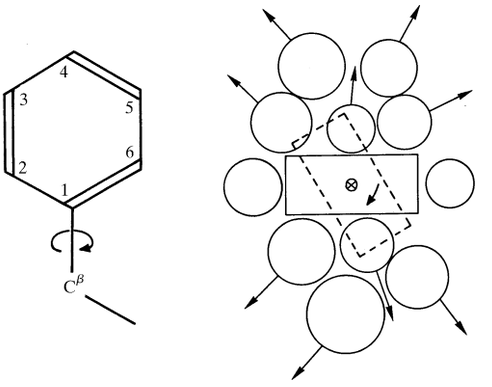

Fig. 19.7.5.1. 180° ring flips of tyrosine and phenylalanine about the C^{β}—C^{1} bond. On the left, the atom numbering is given and the χ^2 rotation axis is identified with an arrow. The drawing on the right presents a view along the C^{β}—C^{1} bond of a flipping ring in the interior of a protein, where the broken lines indicate a transient orientation of the ring plane during the flip. The circles represent atom groups near the ring, and arrows indicate movements of atom groups during the ring flip (Wüthrich, 1986).

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