Title:	Conformational behavior of polypeptides derived through simultaneous global conservative site-directed mutagenesis of chymotrypsin inhibitor 2
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Abstract:	The natural occurrence of conservative residue substitutions in proteins suggests that side-chain packing schemes in protein interiors can accommodate mutational replacements of residues by others of similar nature. To explore the extent to which such substitutions are tolerated, especially when introduced simultaneously and globally over the entire length of a polypeptide chain, we examined the conformational behavior of a model 65 residues-long protein, wild-type chymotrypsin inhibitor 2 (WTCI2), and two globally-mutated (GM) variants named GMCI2-1 and GMCI2-2, each incorporating 55 conservative residue substitutions. GMCI2-1, was soluble over a wide range of pH, and folded into a compact, spherical, monomer marked by (i) complete absence of surface hydrophobicity, (ii) a WTCI2-like betaII-type CD spectrum, (iii) high WTCI2-like thermal stability, and (d) 1D and 2D NMR spectra characteristic of folded protein structure. GMCI2-2 was insoluble over a wide range of pH, and could be solubilized only at pH 4.0, showing non-WTCI2-like far-UV CD spectra characterized by high helical content. These results tentatively indicate that polypeptides incorporating residues of identical nature at equivalent chain locations can show the potential to fold with similar characteristics. However, further detailed investigations would be required to determine whether indeed the structural fold of GMCI2-1 resembles that of WTCI2, and to evaluate the extent to which it does so.
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