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Spatial structures of tripeptides glycylglycyl-L-histidine and glycylglycyl-L-tyrosine based on residual dipolar couplings and quantum-chemical computations

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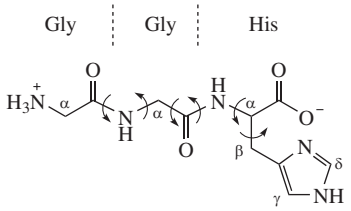
A novel approach to the determination of the spatial structure of oligopeptides on the basis of an analysis of the residual dipolar couplings ^{1}H–^{13}C assisted by quantum-chemical computations with considering solvent effects is proposed to characterize the conformations of the tripeptides GlyGlyHis and GlyGlyTyr with significant folding of the latter to left-handed helix.

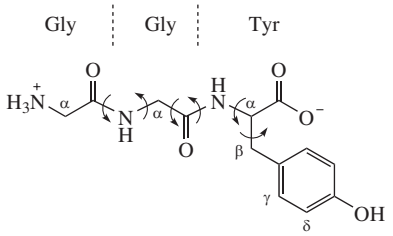
The investigation of oligopeptide conformations is important because oligopeptides can be considered as building blocks for protein structures, and the knowledge of their three-dimensional structures can be used to predict polypeptide chains and the design of proteins *de novo*.[1] Tripeptides with a terminal histidine residue in complexes with copper(II) are good models for blood copper transport form in the composition of human serum albumin.[2,3] Tyrosine in a terminal position is a constituent of many neuropeptides[4,5] and the subject of phosphorylation by kinases operating important regulatory functions in living cells.[6,7]

In continuation of our research,[8–10] we determined the spatial structure of the tripeptides glycylglycyl-L-histidine (GlyGlyHis) and glycylglycyl-L-tyrosine (GlyGlyTyr) partially aligned in a lyotropic liquid crystalline medium on the basis of an analysis of the residual dipolar couplings[11,12] combined with quantum-chemical density functional theory (DFT) calculations performed at the high level of theory with considering solvent effects.

To elucidate the spatial structures of GlyGlyHis and GlyGlyTyr tripeptides, the residual dipolar couplings between the magnetic nuclei ^{13}C and ^{1}H separated by one chemical bond ($^1D_{CH}$) were used. The ^{13}C NMR spectra of GlyGlyHis and GlyGlyTyr (in D_2O and lyotropic medium) contain six signals (we considered CH and CH_2 carbons only) with the chemical shifts collected in Tables 1 and 2.† The assignment of signals has been carried out in accordance with literature data and 2D COSY NMR experiments.[13]



GlyGlyHis



GlyGlyTyr

The direct spin–spin couplings ($^1J_{CH}$ + $^1D_{CH}$) for both tripeptides obtained from ^{13}C NMR spectra without broad-band proton decoupling are shown in Tables 1 and 2.

Table 1 ^{13}C NMR chemical shifts of carbons (δ_C/ppm relative to TMS) and direct spin–spin couplings ($^1J_{CH}$ + $^1D_{CH}$/Hz, bottom row) of the tripeptide GlyGlyHis dissolved in an isotropic solvent and lyotropic liquid crystalline medium.

Medium	αCH$_2$ Gly1	αCH$_2$ Gly2	αCH His	βCH$_2$ His	γCH His	δCH His
D_2O	40.4	41.5	54.1	27.9	116.7	134.3
	142.8	141.6	142.8	131.0	190.4	211.2
($C_{12}E_5$)/*n*-hexanol	40.4	41.6	54.2	27.9	116.8	134.4
	147.7; 146.5	147.7; 147.8	142.7	126.9; 124.5	183.1	206.3

Table 2 ^{13}C NMR chemical shifts of carbons (δ_C/ppm relative to TMS) and direct spin–spin couplings ($^1J_{CH}$ + $^1D_{CH}$/Hz, bottom row) of the tripeptide GlyGlyTyr dissolved in an isotropic solvent and lyotropic liquid crystalline medium.

Medium	αCH$_2$ Gly1	αCH$_2$ Gly2	αCH Tyr	βCH$_2$ Tyr	γCH Tyr	δCH Tyr
D_2O	40.4	42.2	56.4	36.7	115.2	130.6
	144.0	140.4	142.8	132.0	157.5	162.3
($C_{12}E_5$)/*n*-hexanol	40.4	42.2	56.3	36.7	115.3	130.7
	142.7; 142.8	152.6; 156.3	113.5	94.0; 89.1	128.2	124.0