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Reverse Turn Conformation of N-Thioacetyl Thioprolyl Glycine N'-Methylamide in the Crystal and in Solution[1]

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Abstract – The molecular structure of Act-Prot-Gly-$NHCH_3$/AcΨ(CSNH)-ProΨ(CSNH)-Gly-$NHCH_3$/ (1) is reported. In the crystal 1 adopts a conformation with a Z(*trans*) tertiary (thioacetyl pyrrolidine) thioamide bond and torsion angles (Φ_2 = -73.2°, Ψ_2 = 151.9°, Φ_3 = 83.5°, Ψ_3 = 5.5°) which are rather close to the values of a type II β-turn. The sulfur atom of the thioacetyl group is the acceptor of a 1←4 intramolecular H-bond. Based on 400 MHz ^1H and ^{13}C NMR studies, including ^1H NOE experiments, the conformational equilibrium in $CDCl_3$ solution is dominated by the conformer which is present in the crystal. The chiroptical properties of 1 are also discussed, in comparison to those of mono- and dithionated models of β-turns.

INTRODUCTION

X-ray crystallographic studies have revealed that the thioamide function is an isosteric surrogate of the peptide bond.[1-6] The increased dimension and modified H-bond forming ability of the thioamide group are, however, expected to result in subtle conformational changes of thionated peptides.[6,7] This may play a role in biological recognition processes and have importance in the design of peptide-based drugs.[8]

It has been shown that the thioamide group can not only donate but also accept strong intramolecular H-bonds.[2-4,9-18] Thus, it may be embedded into both β- and γ-folded structures if the formation of the stabilizing intramolecular H-bond is not hindered by unfavourable steric interactions between the thioamide C=S and the neighbouring side chain groups.[6]

Recently we have described the synthesis and spectroscopic characterization of several single- and double-thionated simple models of γ- and β-turns.[13-16] IR and NMR experiments in nonpolar solution showed that in Boc(Ac)-Alat-$NHCH_3$ (Alat = -NH-$CHCH_3$-CS-) the 1←3 C=O···H-N-CS "mixed" intramolecular H-bond (MIH) is not strong enough to fix a γ-turn structure.[14,15] Instead, the molecule adopts a semiextended conformation as supported by the torsion angles (Φ = -85.7°, Ψ = 130.8°) of Boc-Alat-$NHCH_3$ in the solid state.[16] The C=S···H-N-CO H-bond in Act-Ala-$NHCH_3$ (Act = CH_3CS-)

[1]This work is dedicated to the memory of Prof. Márton Kajtár, a pioneer of stereochemistry and chiroptical spectroscopy in Hungary.

and related models appears to be more favoured.[15] On the other hand, IR and ^{1}H NOE data suggest the adoption of 1←4 bonded β-turn conformations by Boc(Ac)-Aaa-Glyt-$NHCH_3$ and Act-Aaa-Glyt-$NHCH_3$ (Aaa = Ala, Pro).[14-16] In the latter models containing alternating thioamide-amide-thioamide groups, a type II β-turn structure is fixed by a strong C=S···H-N-CS thioamide-thioamide intramolecular H-bond (TTIH).

Act-Prot-Gly-$NHCH_3$ (**1**) (Fig. 1) features consecutive thioamide functions. This paper reports a comparison of its conformation in the crystal and in solution.

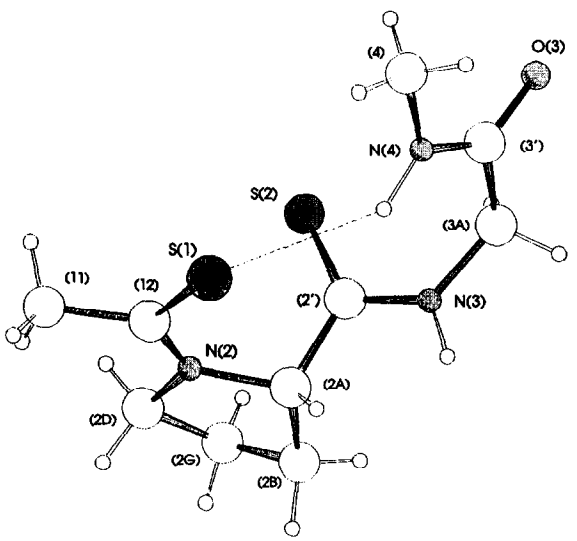

Fig.1. Perspective drawing of the solid state conformation of Act-Prot-Gly-$NHCH_3$ (**1**). The numbering of atoms is also shown.

RESULTS AND DISCUSSION

**Conformation in the crystal*

The solid-state conformation of compound **1** with the atomic numbering is shown in Fig.1. Pertinent experimental data are given in Table 1. Chemical bonds and angles (Tables 2 and 3) are normal and fall in the range expected for thionated peptides (Refs. 1-5). There is a small difference between the two C=S bonds. The S atom having the longer C=S distance (C(12)-S(1) = 1.678(3) Å maintains a marginal 1←4 intramolecular hydrogen bond. The S atom with the shorter C=S distance (C(2')-S(2) = 1.649(3) Å does not take part in any appreciable attractive interaction. Torsion angles are given in Table 4. The pyrrolidine ring of Pro is in a C_2 twisted form with the approximate 2-fold axis passing through atom N2 and the middle of the opposing C-C bond. Selected bonding and conformational parameters for thionated peptides are listed in Table 5 for similar moieties obtained from the Cambridge Crystallographic Database.[19] The gross molecular shape is presumably influenced by the development of a weak 1←4 H-bond (Table 6) between H-

Table 1. Summary of X-ray experimental data

Formula:	$C_{10}H_{17}S_2ON_3$	Total no. of coll. data	1459
F. w.	259.39 a.m.u.	No. of data with $I>3*\sigma(I)$	1419
a	7.675(1)Å	θ range	1.5 - 75.0
b	10.763(1)Å	Scan angle width =	$0.45+0.14*\tan(\theta)$
c	8.519(1)Å	No. of abs. corrected refl.'s	1435
β	109.68(1)°	Min./Max./Ave. abs. corr.:	0.595/1.305/0.959
V	662.7(3)Å^3	No. of atoms/variables in LS	33 / 145
Space group:	$P2_1$ (No.4)	No. of obs ($F^2 > 3.0*\sigma(F^2)$)	1417
$D_{(calc)}$	1.300 Mg/m^3	R, / R_w, / $R_{(tot)}$	0.039/0.066 /0.041
μ(CuKα,λ=1.5418 Å)	34.70 cm^{-1}	Largest Δ/s	0.15
$S=[\Sigma(w(\Delta F)^2/(No-Nv)]^{1/2}$	2.60	High peak in ΔF map	0.18 e/A^3

Table 2. Bond lengths (Angstrom) with e.s.d.'s

S(1)-C(12)	1.678(3)	N(2)-C(12)	1.306(3)	C(2')-C(2a)	1.521(4)	N(2)-C(2d)	1.459(4)
S(2)-C(2')	1.649(3)	N(3)-C(2')	1.327(3)	C(2a)-C(2b)	1.532(4)	N(4)-C(4)	1.455(5)
O(3)-C(3')	1.219(5)	N(3)-C(3a)	1.454(4)	C(2b)-C(2g)	1.500(5)	C(3a)-C(3')	1.515(4)
N(2)-C(2a)	1.468(3)	N(4)-C(3')	1.335(3)	C(2g)-C(2d)	1.541(4)	C(11)-C(12)	1.518(4)

Table 3. Bond angles (deg.) with e.s.d.'s

C(2a)-N(2)-C(2d)	111.9(4)	C(2')-C(2a)-C(2b)	112.8(4)	N(3)-C(2')-C(2a)	112.2(4)
C(2a)-N(2)-C(12)	122.5(4)	C(2a)-C(2b)-C(2g)	105.5(5)	N(2)-C(2a)-C(2')	111.0(3)
C(2d)-N(2)-C(12)	125.6(4)	C(2b)-C(2g)-C(2d)	102.7(5)	N(2)-C(2a)-C(2b)	102.6(4)
C(2')-N(3)-C(3a)	122.8(4)	N(2)-C(2d)-C(2g)	104.8(5)	N(2)-C(12)-C(11)	116.1(4)
C(3')-N(4)-C(4)	121.6(5)	N(3)-C(3a)-C(3')	114.8(4)	N(4)-C(3')-C(3a)	118.0(4)
S(2)-C(2')-N(3)	124.4(3)	O(3)-C(3')-N(4)	123.7(5)	S(1)-C(12)-N(2)	123.0(4)
S(2)-C(2')-C(2a)	123.4(3)	O(3)-C(3')-C(3a)	118.2(5)	S(1)-C(12)-C(11)	120.9(4))

Table 4. Torsion angles (deg.) with e.s.d.'s

N(2)-C(2a)-C(2')-S(2)	-29.8(3)	C(2d)-N(2)-C(2a)-C(2b)	-13.2(4)
N(3)-C(2')-C(2a)-N(2)	151.9(4)	C(2d)-N(2)-C(12)-S(1)	-179.4(5)
N(3)-C(3a)-C(3')-O(3)	-177.1(5)	C(2d)-C(2g)-C(2b)-C(2a)	-35.7(4)
N(4)-C(3')-C(3a)-N(3)	5.5(4)	C(3a)-N(3)-C(2')-S(2)	0.1(3)
C(2a)-N(2)-C(12)-S(1)	1.5(3)	C(3a)-N(3)-C(2')-C(2a)	178.4(5)
C(2b)-C(2a)-C(2')-S(2)	84.8(4)	C(3')-C(3a)-N(3)-C(2')	83.5(5)
C(2b)-C(2a)-C(2')-N(3)	-93.5(4)	C(4)-N(4)-C(3')-O(3)	2.5(6)
C(2b)-C(2g)-C(2d)-N(2)	27.2(4)	C(4)-N(4)-C(3')-C(3a)	179.8(6)
C(2g)-C(2b)-C(2a)-N(2)	30.5(4)	C(11)-C(12)-N(2)-C(2a)	179.9(6)
C(2g)-C(2b)-C(2a)-C(2')	-89.0(5)	C(11)-C(12)-N(2)-C(2d)	-0.9(5)
C(2g)-C(2d)-N(2)-C(2a)	-8.6(4)	C(12)-N(2)-C(2a)-C(2')	-73.2(4)
C(2d)-N(2)-C(2a)-C(2')	107.6(4)	C(12)-N(2)-C(2a)-C(2b)	166.0(5)
C(12)-N(2)-C(2d)-C(2g)	172.2(6)		

N(4) and S(1) and the Φ and Ψ torsion angles (Φ_2 = -73.2°, Ψ_2 = 151.9°, Φ_3 = 83.5°, Ψ_3 = 5.5°) are close to those of an "ideal" type II β-turn (Φ_2 = -60°, Ψ_2 = 120°, Φ_3 = 80°, Ψ_3 = 0°).[20] The corresponding torsion angles in the crystal structure of Boc-L-Prot-L-Leu-Gly-NH_2[3] are -77°, 131.8° and 71.8°, 15.6°. In both structures the Ψ_2 torsion angles are higher than 120°. In the case of Boc-L-Prot-L-Leu-Gly-NH_2 the deviation is likely due to the repulsion of the sulfur atom and the bulky side chain of Leu. The high Ψ_2 (151.9°) value in **1** may be ascribable to a probable combination of a strong lattice and weak intramolecular effects. The interaction between H-N(3) and screw related O(3) atom which keeps atom N3 fixed in its steric position along the chain direction of hydrogen bonding (Fig. 2) is an eminent effect of the former type. The weak intramolecular interactions are primarily the 1←4 hydrogen bond and the steric effects of the relatively short C(2')-S(2) bond. Steric congestion caused by the atom S repels atoms in the immediate vicinity thus widening the SCN and SCC bond angles (Table 3). As large as ~30° offset from the typical value (120°) of Ψ_2 in type II (oxo)amide turns may be indicative of a relative shallow potential well in this region of the molecule. Crystal packing (Fig. 2) is in other aspects determined by weaker repulsive and dispersion forces.

Table 5. Selected bonding and conformational parameters of thionated peptides from the CCDB[19]

	DIDYIY*	FEVBEN	FUSMIP	FUSMOV	SAFYUT/A	SAFYUT/B
C–S	1.663	1.655	1.664	1.676	1.665	1.651
N–C	1.447	1.445	1.448	1.458	1.460	1.445
Φ	156.05	177.50	-77.01	113.91	-75.40	-77.61
Ψ	142.15	-168.49	131.77	143.03	139.6	142.07

*Reference codes, abbreviated names and references from the Cambridge Crystallographic Database: DIDYIY (Boc-Glyt-Ala-Aib-OMe)[2], FEVBEN (Cbz-Glyt-Glyt-Gly-OBzl)[21], FUSMIP (Boc-Prot-Leu-Gly-NH_2)[3], FUSMOV (Top-Leu-Gly-NHEt, Top = L-5-thioxoprolyl)[3], SAFYUT (Act-Ala-Aib-Ala-OMe, conformer A and B)[4].

Table 6. Summary of hydrogen bond parameters in **1**

Acceptor	A···H	H	H–D	D	A···H–D	A···D
$O(3)_{[2-x,y-0.5,2-z]}$	1.821	H(N3)	1.00	N(3)	175	2.821(3)
S(1)	2.718	H(N4)	1.01	N(4)	143	3.582(3)

MM calculations resulted in a low-energy conformation (ΔE < 0.1 kcal/mol) with torsion angles Φ_2 = 70°, Ψ_2 = 158.4°, Φ_3 = 65.8°, Ψ_3 = 22.6°. This conformation is very close to that adopted in the crystal, except that the type II β-turn is more "opened". In the minimum energy state the Gly residue is involved in a γ-turn conformation (Φ_{Gly} = 74.30°, Ψ_{Gly} =-107.1°) instead of a β-turn.

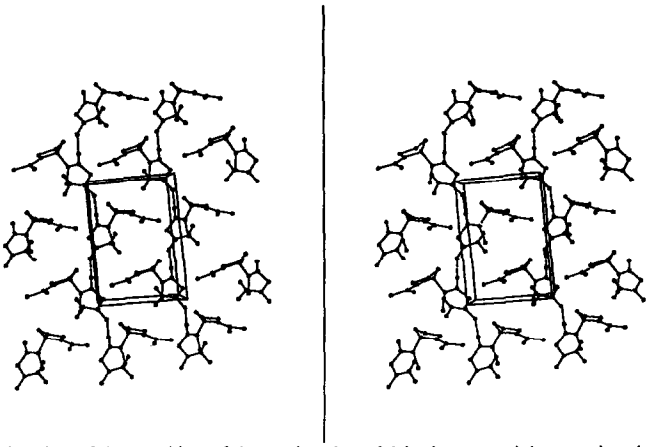

Figure 2. Stereoscopic drawing of the packing of the molecules of 1 in the crystal. Intermolecular hydrogen bonds are indicated in borken lines. No hydrogen atoms are shown for the sake of clarity

Conformation in $CDCl_3$ solution

In the ^{13}C and ^1H NMR spectra in $CDCl_3$ solution of **1** there are two sets of resonance signals which reflects the presence of two conformations. The ^{13}C chemical shifts of proline are comparable with those of thiopeptides Act-Prot-$NHCH_3$, Act-Pro-Gly-$NHCH_3$ and Act-Pro-Glyt-$NHCH_3$.[15] Based on the chemical shifts of the Pro C^β and C^γ atoms (32.62 and 24.80 ppm, respectively), the dominant conformer features a *trans* (Z) CH_3-CS-N(Pro) tertiary amide bond. The chemical shifts of the C^β (35.40 ppm) and C^γ atoms (22.61 ppm) in the minor conformer are characteristic of a Pro residue with a *cis* tertiary thioamide bond.[15] In the 400 MHz ^1H NMR spectrum the resonance signals are also doubled. From the integrated intensities of the non-overlapping NH and Pro $C^\alpha H$ signals, the amount of the *trans* (Z) conformer is 91-92%. Difference ^1H NOE experiments strongly support the β-folded structure of the *trans* form. Irradiation of the $NH(CH_3)$ signal at 6.79 ppm gives rise to definite positive NOE's of the Gly NH(CS) and Pro $C^\alpha H$ resonances (8.76 and 5.36 ppm, respectively), in addition to those of the Gly $C^\beta H_2$ (4.45 and 4.24 ppm) and $CH_3(NH)$ proton (2.78 ppm). Saturation of the Gly NH(CS) proton signal results in significant enhancements of the Pro $C^\alpha H$ and $NH(CH_3)$ resonances and *vica versa*. These findings are compatible with the steric vicinity of the $C^\alpha H$ - NH(CS) - $NH(CH_3)$ protons and suggest the adoption of a predominant type II β-folded backbone geometry which is close to that of the crystal conformation.

In the IR spectrum in dilute CH_2Cl_2 solution there are bands at 3430, 3366.5 and 3323 cm^{-1}. The band at 3323 cm^{-1} may be correlated with the NH of the amide group involved in a strong 1←4 C=S···H-N intramolecular H-bond.[14,15] However, the strong band at 3366.5 cm^{-1} and the presence of three NH bands, relative to the two NH groups, sug-

gests an equilibrium of more than one major conformers featuring free and differently H-bonded NH groups.

Table 7. CD spectra in Acetonitrile of Act-Prot-Gly-$NHCH_3$ (1) and Selected Thionated Models of β-Turns

Compound	Conc. (mmol/L)	λ nm (Δε) nπ* (thioamide)		ππ* (thioamide)	Other bands
Act-Prot-Gly-$NHCH_3$	1.21	349 (1.05)	298.5 (0.68)	264 (-14.80)	217 (2.47)sh
1					199.5 (11.24)
Act-Pro-Glyt-$NHCH_3$[16]	2.8	340.5 (0.90)	280 (4.41)	260 (-17.67)	213 (6.11)
					193 (-2.42)
Act-Prot-$NHCH_3$[16]	4.4	355 (1.47)	289.5 (-0.65)	260 (-7.01)	223 (0.84)
					201.5 (4.29)
Act-Pro-Gly-$NHCH_3$[16]	2.7	348.5 (1.21)		275 (-7.47)	212.5(5.44)
Boc-Pro-Glyt-$NHCH_3$[16]	2.3	351 (-0.005)		261.5 (1.79)	211 (1.47)
		318 (0.02)			197.5 (-1.09)

The CD spectra of Act-Prot-Gly-$NHCH_3$ (1) were measured in CH_3CN and DMSO and compared with the spectra[16] of mono and dithio derivatives of the turn-forming dipeptide Ac-Pro-Gly-$NHCH_3$. The CD spectrum of 1 in CH_3CN shows resemblance with the corresponding spectra of Act-Pro-Glyt-$NHCH_3$ and Act-Prot-$NHCH_3$ but not with the spectra of Act-Pro-Gly-$NHCH_3$, and Boc-Pro-Glyt-$NHCH_3$ (Table 7, see also Ref. 16). It appears that the chiroptical properties of proline-containing thioamide models are dominated by the CD of the thioacetyl pyrrolidine chromophore. The chiral contribution of the second thioamide group, located in central or terminal position of a possible β-turn, is less significant. However, the backbone conformation also plays an important role in determining the optical activity. In the prevailing conformers of Act-Prot-Gly-$NHCH_3$ (1) and Act-Pro-Glyt-$NHCH_3$, the tertiary Act-Pro thioamide groups are Z(*trans*) and accept 1←4 intramolecular H-bonds. Contrary to this, the tertiary thioamide group of Act-Pro-Gly-$NHCH_3$ is involved in a 1←3 H-bonded inverse γ-turn.[15] Its CD spectrum in CH_3CN (and other solvents) is marked by a red-shifted negative ππ* band of lower intensity (Δε = -7.47 at 275 nm)[16].

CONCLUSION

The tertiary amide and thioamide bonds of proline peptides have been shown to occur in both *trans* (Z) and *cis* (E) forms.[3,15,17] Due to the higher energy barrier, the presence of *thioamide* rotational isomers can be detected by thin-layer chromatography, ^1H and ^{13}C NMR experiments at room temperature, contrary to *amide* rotamers, the observation of which in linear peptides generally requires low-temperature experiments.

In nonpolar solution, the ratio of the *cis* conformer in Boc-Prot-$NHCH_3$, Act-Pro-$NHCH_3$ and Act-Prot-$NHCH_3$ is between 20 and 40%.[15] In the ^{13}C and ^1H NMR spectra of

Boc-Pro-Glyt-$NHCH_3$, Act-Pro-Gly-$NHCH_3$ and Act-Pro-Glyt-$NHCH_3$ the resonance signals, which can be assigned to the *cis* rotamer, are not present or appear with negligible intensity. Apparently, the *cis* to *trans* shift of thioamide rotational equilibria is due to the formation of the favoured ten-membered (C_{10}) 1←4 H-bond, with an acceptor C=O or C=S and a donor N-H group belonging to either an amide or a thioamide function. In Act-Prot-Gly-$NHCH_3$ (**1**) the consecutive thioamide groups allow the formation of both 1←3 and 1←4 C=S···H-N-CO intramolecular H-bonds. The prevailance of the 1←4 bonded β-turn conformer in the crystal and in solution reflects the higher stability of the C_{10} C=S···H-N-CO H-bond, relative to the C_7 structure. However, in solution studies on Act-Pro-Gly-$NHCH_3$ and Act-Ala-Gly-$NHCH_3$ have suggested[15] that these models adopt a repeating γ-turn conformation fixed by two successive (C=S···H-N-CO and C=O···H-N-CO) 1←3 intramolecular H-bonds instead of a single 1←4 H-bond of the former type. In Act-Prot-Gly-$NHCH_3$ (**1**) the adoption of a 1←3 C=S···H-N-CO H-bond is likely hindered by the replacement of Pro C=O by the bulky C=S. But the presence of ≤10% of the *cis* conformer shows that the C=O to C=S replacement also weakens the 1←4 bond.

It is well-known that turn regions of polypeptides contain proline, glycin as well as residues with H-bond accepting and/or donating side chain capability. Our studies on thioamide-labeled turn models give support to the idea that in proline peptides the prevailance of one single conformation (e.g. a type I β-turn) is the result of delicate equilibria between rotational isomers, as well as 1←4 and 1←3 backbone and likely various side-chain-backbone H-bonded (or stabilized) forms. In tertiary amides the energy barrier of rotational isomerism is somewhat lower than in tertiary thioamides. Thus, solvational or other effects may easily trigger a *trans* to *cis* amide isomerization and, through the breakage of intramolecular H-bonds in critical position, refolding of the polypeptide chain.

EXPERIMENTAL

Materials

The synthesis of Boc-Prot-Gly-OMe and Boc-Prot-Gly-$NHCH_3$ have been described.[13,14] The Boc-group of the latter compound was removed with 4 M HCl/dioxane and the hydrochloride salt was converted into Act-Prot-Gly-$NHCH_3$ (**1**) by using thioacetyl thioglycolic acid (TATG).[21] The crude product was purified by flash chromatography on a Kieselgel 60 (E. Merck) column using eluent a (ethyl acetate - methanol 8:2). The crystals used for X-ray analysis were grown from a methanol - ether mixture. Compound **1** was characterized by elemental analysis, ^1H and ^{13}C NMR spectra. Thin layer chromatography on precoated silica gel foils (DC-Alufolien, Kieselgel 60, E. Merck) resulted, in a variety of eluent systems, two spots of differing intensity. (R_f values in a are 0.40 and 0.43, intensity ratio ~7:3). Chromatographic methods, including RP-HPLC failed to separate the components which, on the basis of NMR studies, proved to be *cis-trans* isomers.

X-Ray diffraction analysis

A colorless prism shaped crystal of 0.25 x 0.25 x 0.60 mm size was mounted on an automated four circle diffractometer. Using θ - 2θ scans 1459 independent reflexions were measured.[22] Initial structure model was devised from an E-map phased by direct methods which yielded all non-hydrogen positions. Hydrogen atoms were in part generated and those of the N-H moieties taken from difference electron den-

sity maps near to refinement termination. Full-matrix refinement of parameters with anisotropic atomic displacement of non-hydrogen atoms led to the final R of 0.039. Hydrogen atoms contributions to the structure factor were considered but their parameters were not refined in any way. Pertinent details of the measurement and numeric procedures[23] are summed up in Table 1.

Spectroscopic studies

400 MHz ^{1}H and 101 MHz ^{13}C *NMR spectra* were measured on a Varian XL-400 spectrometer at ambient temperature. ^{1}H-{^{1}H} NOE spectra were recorded in the difference mode. Concentration of the $CDCl_3$ solution used for NOE experiments was ~10 mg/ml. *CD spectra* were measured on a Jobin-Yvon dichrograph Mark VI in 0.02 and 1.00 cm cells. Spectrograde solvents (Uvasol, E. Merck) were used. The $\Delta\varepsilon$is expressed in $cm^2 mmol^{-1}$. IR spectra were recorded in 4-0.5 cm Infrasil cells on a Specord IR75 instrument (Carl Zeiss, Jena).

Molecular mechanics calculations

Molecular mechanics (MM) calculations were performed with the program QCPE 395 using MMX87 parametrization. Fully relaxed potential energy maps were calculated from starting geometries having a fixed Φ_1 angle (-70°), and Ψ_1 angles in the *cis*' (Ψ_1 -30°) and *trans*' (Ψ_1 ~120°) region. The Φ_2 and Ψ_2 angles of Gly were changed by 15°.

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