Turning Peptides with Cyrene-Derived Amino Acid Residues

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Abstract

α,α-Disubstituted amino acids rigidify conformation and improve pharmacokinetic properties of peptides. A novel Cyrene-derived residue (Cyr) is made using the Ugi reaction and incorporated into peptides. The Cyr residue shows promise for favoring different turn conformers contingent on environment as observed in X-ray crystallographic and NMR spectroscopic analyses.

Introduction

α,α-Disubstituted residues restrain conformation in peptides through the Thorpe–Ingold effect,[1] stabilizing backbone torsion angles characteristic of 3_{10}-helices (ϕ ≈ ±60°, ψ ≈ ±30°) and α-helices (ϕ ≈ ±55°, ψ ≈ ±45°).[2–4]

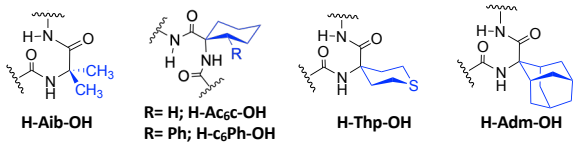


Figure 1: Representative α,α-disubstituted amino acid residues in peptides.

α,α-Disubstituted residues (**Figure 1**) alter peptide conformational preferences from extended C5 to turn and helical conformers contingent on β-substituents.[1] For example, 2-aminoadamantane- 2-carboxylic acid (H-Adm-OH)residues have been used to synthesize the first example of a single α-helical turn as well as an incipient γ-helix contingent on the C-terminal amide (**Figure 2**).[5]

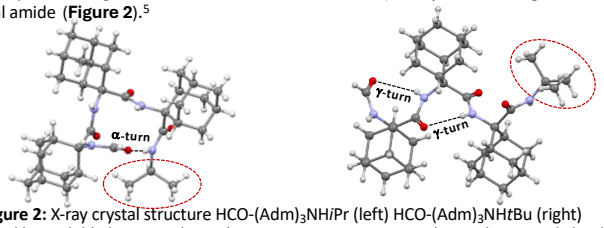
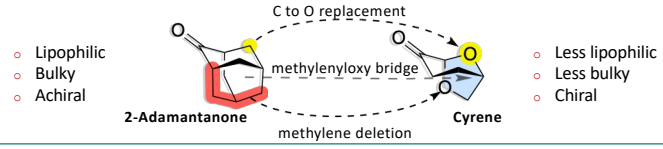


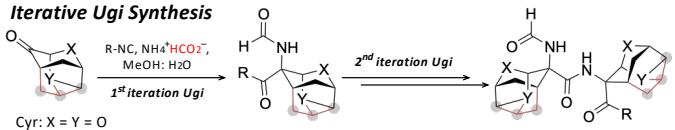
Figure 2: X-ray crystal structure HCO-(Adm)$_3$NH*i*Pr (left) HCO-(Adm)$_3$NH*t*Bu (right)

A readily available biomass-derived precursor, Cyrene was used to make a novel chiral α,α-disubstituted amino acid, Cyr, which offers complementary properties to Adm (from 2-adamantanone) for peptide conformational analysis.[6]



Result

Iterative Ugi Synthesis



Cyr: X = Y = O
Adm: X = Y = CH_2 + 'CH and 2 x CH_2'

Cyr: R = NHPhOMe
Adm: R = NH*i*Pr; NH*t*Bu

X-ray Crystallographic Analysis

In the solid state, both (4*R*)- and (4*S*)-Cyr favor α-helical conformations (**Figure 3**) in contrast to Aib and Thp, which favor 3_{10}-helices, and Adm, which favors a γ-turn (**Table 1**).[6]

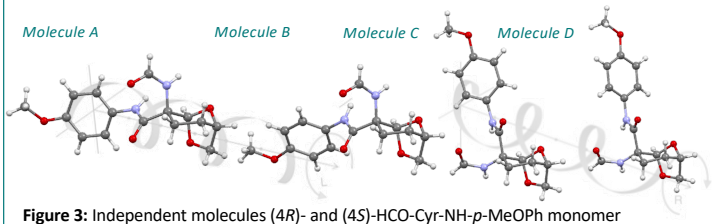


Figure 3: Independent molecules (4*R*)- and (4*S*)-HCO-Cyr-NH-*p*-MeOPh monomer

Table 1. Backbone ϕ and ψ torsion angle values in degrees

	ϕ	ψ	Type
Ideal α-helix	−55	−45	right-handed
Ideal 3_{10}-helix	−60	−30	right-handed
Ideal β-turn	60	−120	type II′
Ideal β-sheet	−154.3	154.4	parallel sheet
γ-turn	−76	83	regular
(4*R*)-HCO-**Cyr**-*p*-MeOPh (Molecule A)	52.0 (3)	48.8 (3)	left-handed
(4*R*)-HCO-**Cyr**-*p*-MeOPh (Molecule B)	58.9 (3)	45.8 (3)	left-handed
(4*S*)-HCO-**Cyr**-*p*-MeOPh (Molecule C)	−51.6 (3)	−51.6 (3)	right-handed
(4*S*)-HCO-**Cyr**-*p*-MeOPh (Molecule D)	−53.6 (3)	−48.7 (3)	right-handed
Ac-**Ac6c**-NHMe	−52	−46	α-helical
Ac-**Aib**-NHMe	−55.5 −53.8	−40.3 −46.4	3_{10}-helices
HCO-**Thp**-Ac$_6$c-Phe-OMe	−61.3	−33.9	3_{10}-helices
Cbz-**Adm**-NH*i*Pr	−72.22(15)	91.66 (14)	γ-turn

In the solid state, (4*S*, 4′*S*)-HCO-(Cyr)$_2$-NHPhOMe adopts a distorted type III β-turn,[6] distinct from the type II β-turn of HCO-(Adm)$_2$-Aib-OMe (**Table 2**),[5] with an intramolecular hydrogen bond between the formamide carbonyl oxygen and C-terminal amide NH (N···O = 3.03(16) Å; H···O = 2.30(2) Å) (**Figure 4**, left).[6]

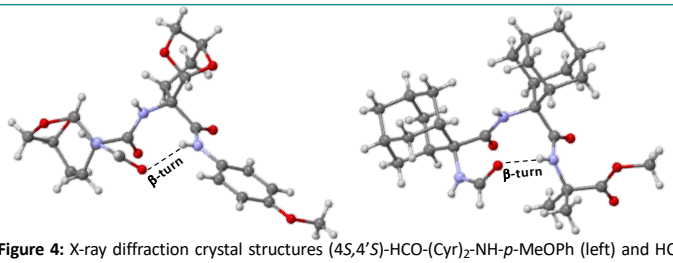


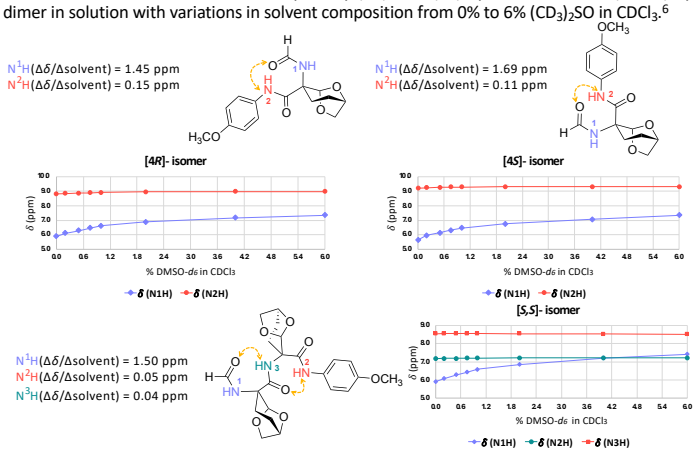
Figure 4: X-ray diffraction crystal structures (4*S*,4′*S*)-HCO-(Cyr)$_2$-NH-*p*-MeOPh (left) and HCO-(Adm)$_2$-Aib-OMe (right)

Table 2. Backbone ϕ and ψ torsion angle values in degrees

	ϕ	ψ	Type
(4*S*, 4*S*)-HCO-**Cyr**-Cyr-NH-*p*-MeOPh (4*S*, 4*S*)-HCO-Cyr-**Cyr**-NH-*p*-MeOPh	−44.41 (16) −54.98 (15)	−47.91 (15) −42.48 (15)	right-handed α-turn
HCO-**Adm**-Adm-Aib-OMe HCO-Adm-**Adm**-Aib-OMe HCO-Adm-Adm-**Aib**-OMe	63.1 (5) −51.4 (5) 56.2 (5)	−96.9(4) −49.6 (5) 43.9 (5)	type II′ β-turn

NMR Spectroscopic Analysis

The C7$^{\gamma}$-turn conformation was adapted by (4*R*)- and (4*S*)-Cyr monomer, and (4*S*,4′*S*)-Cyr dimer in solution with variations in solvent composition from 0% to 6% $(CD_3)_2SO$ in $CDCl_3$.[6]



Conclusion

The Cyr residue is a novel bio-sourced chiral α,α-disubstituted scaffold which can be readily introduced into peptides by the Ugi reaction on cyrene. In the solid state, (*R*)- and (*S*)-Cyr induced left- and right-handed helices, respectively, and Cyr dimers adopted type III β-turn. In solution, Cyr exhibited hydrogen bonding patterns characteristic of single and consecutive γ-turn conformers. In peptide design, Cyr offers interesting promise and merits further investigation in longer assemblies.

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