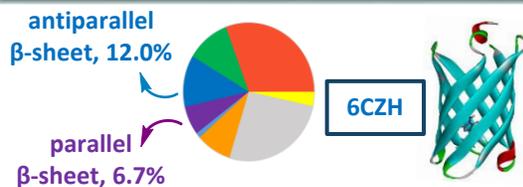


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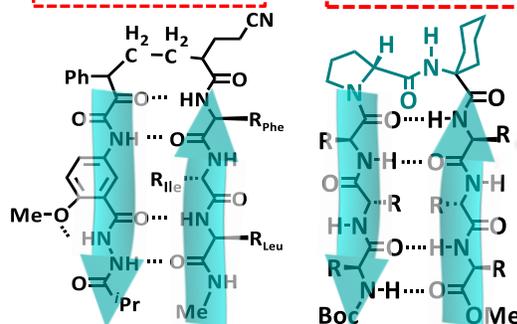
1. Importance of β -sheet



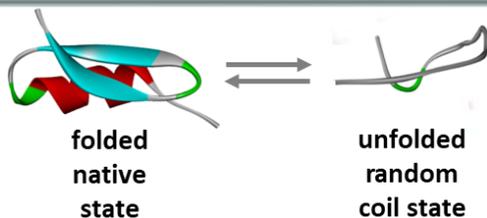
2. Models to mimic static β -sheet

constrained β -strand mimic

peptidic β -turn mimic

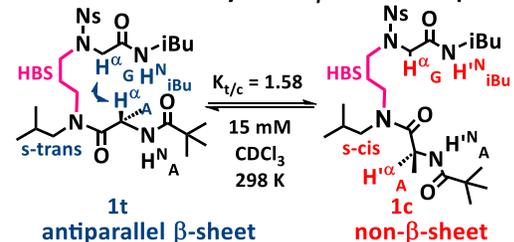


3. Dynamism in β -sheets

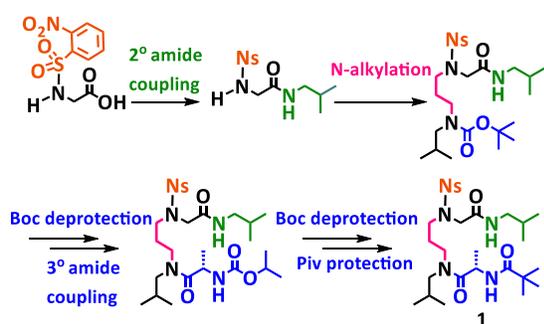


4. Dynamic β -sheet template

HBS-constrained dynamic β -sheet template



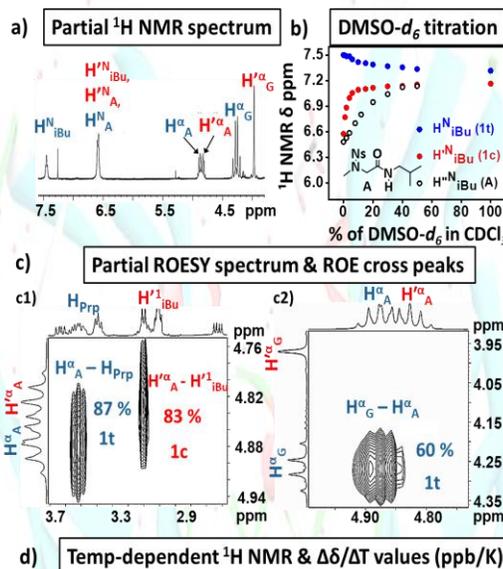
5. Synthesis of HBS β -sheet template



6. List of all templates

No.	X	Y	R ₁	R ₂	R ₃	R ₄	R ₅	R ₆
1	Ns	iBu	H	iBu	H	^t Bu	H	Me
2	Ns	iBu	H	iBu	H	O ^t Bu	H	Me
3	Ns	iBu	H	iBu	Me	^t Bu	H	Me
4	Ns	iBu	Et	Et	H	^t Bu	H	Me
5	H	iBu	H	iBu	H	^t Bu	H	Me
6	Ns	Bn	H	iBu	H	^t Bu	H	Me
7	Ns	Bn	H	iBu	H	O ^t Bu	H	Me
8	Ns	Bn	H	iBu	H	O ^t Bu	H	H
9	Ns	Bn	H	iBu	H	O ^t Bu	Me	Me
10	Ns	Bn	H	iBu	H	O ^t Bu	H	H
11	Ns	iBu	H	iBu	H	O ^t Bu	H	H

7. Establishing β -sheet conformation



8. Inter residue compaction

No.	X	R ₁	R ₂	R ₃	R ₄	H ^{α} _G ...H ^{α} _A *
1	Ns	H	iBu	H	^t Bu	60
2	Ns	H	iBu	H	O ^t Bu	43
3	Ns	H	iBu	Me	^t Bu	33
4	Ns	Et	Et	H	^t Bu	5
5	H	H	iBu	H	^t Bu	0

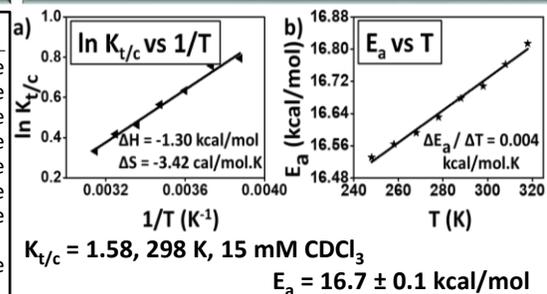
* the relative ROE% was calculated w.r.t 100% intensity of H ^{α} _A...H ^{β} _A ROE

9. Non-aggregating peptidomimic

No.	X	R ₁	R ₂	R ₃	R ₄	$\Delta\delta/\Delta C^*$
1	Ns	H	iBu	H	^t Bu	-0.4
5	H	H	iBu	H	^t Bu	-4.0

* ppb/mM

10. Thermodynamic parameters



11. Scope for template tethering

No.	Y	R ₁	R ₂	R ₃	R ₄	$K_{t/c}^*$
1	iBu	H	iBu	H	^t Bu	1.58
6	Bn	H	iBu	H	^t Bu	1.64

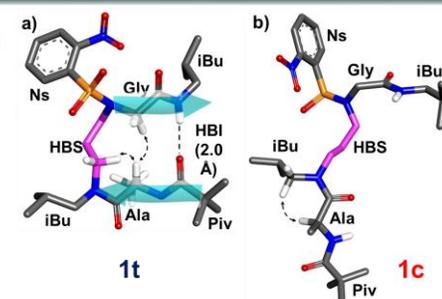
* 298 K, 15 mM CDCl_3

12. Suitable residual a.a. pair

No.	Y	R ₅	R ₆	ROE%*	$\Delta\delta/\Delta T^a$	$K_{t/c}^{\#}$
2	iBu	H	Me	44	-8.68	0.75
7	Bn	H	Me	43	-8.71	0.77
8	Bn	H	H	0	-6.97	0.34
9	Bn	Me	Me	0	-3.49	- ^b
10	Bn	Me	H	0	-2.94	0.47
11	iBu	H	H	0	-6.74	0.34

* inter-strand H ^{α} ...H ^{α} cross peak %; ^a ppb/K; [#] 298 K, 15 mM CDCl_3 ; ^b Merged signals

13. EM structure of conformers



14. Summary

- (1) First HBS-constrained dynamic β -sheet template with shortest possible β -strand.
- (2) HBS, Thorpe-Ingold effect from a 3° amide, a Ns group and inter-strand interactions compact the 14-membered H-bonded anti-parallel β -sheet.
- (3) Torque at the 3° amide forces a slow equilibrium between the β -sheet and non- β -sheet states.

15. References

- (1) Kardos et al., *PNAS*, **2015**, *112*, E3095-E3103
- (2) Nowick, *Org. Biomol. Chem.*, **2006**, *4*, 3869-3885
- (3) Balaram et al. *Chem. Eur. J.*, **2007**, *13*, 5917-5926
- (4) Prabhakaran et al., *ChemBioChem*, just accepted.