Contents

Corrigendum

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The authors of this Communication have recognized an error in Figure 1 d and Table 1. Because of an error in the scaling of the NOE values for the MCoTI-I/trypsin complex (Figure S2 C and D in the Supporting Information), the reported S^2 values for the MCoTI-I/trypsin complex were not accurate. The correct Figure 1 and Table 1 are shown below.

The text that refers to Figure 1 d and Table 1 (page 7032, left column) is also inaccurate. It should read: "Thus, although loop 1 showed $\langle S^2\rangle = 0.75 \pm 0.29$, which is slightly lower than the value for the rest of the molecule ($\langle S^2\rangle = 0.78 \pm 0.23$), Lys^4 showed a significant lower value of S^2 upon complex formation. Several other residues in loop 2 (Cys^9), loop 5 (Cys^{27} and Arg^{22}), and loop 6 (Val^1) also showed significantly lower values of S^2 upon complex formation (Figures 1 d and 2 c). It is likely that the increase in mobility observed in these loops may help to accommodate the increased flexibility of Lys^4 in the binding loop (Figure 2 c).

Since our data clearly shows that backbone flexibility of MCoTI-I cyclotide increases in some of the MCoTI-I residues upon binding to trypsin, we decided to estimate the contribution of these motions to the overall Gibbs free energy of binding (ΔG). The energetic benefit of this increase in backbone flexibility can be estimated from the experimental relaxation data, by using the experimentally measured order parameters, S^2.[27] The estimated ΔG value was approximately 10 kJ mol^{-1} at 298 K. This value should be compared to the calculated value from the trypsin inhibitory constant of MCoTI-I (the trypsin inhibitory constant of MCoTI-I ($K_i \approx 20$ pM,[28] $\Delta G \approx -61$ kJ mol^{-1}). The calculated entropic contribution ($-T\Delta S$) at the same temperature was approximately 7 kJ mol^{-1}."

We have also included modified versions of Figure S2 C and D (showing corrected NOE enhancements and R_{ex} values for the MCoTI/trypsin complex), which are included as Supporting Information. The authors would like to point out that this error does not affect the overall interpretation of the results in the Communication.

[27] A. G. Palmer III, *Annu. Rev. Biophys. Biomol. Struct.* **2001**, *30*, 129.
[28] O. Avrutina, H. U. Schmoldt, D. Gabrijelcic-Geiger, D. Le Nguyen, C. P. Sommerhoff, U. Diederichsen, H. Kolmar, *Biol. Chem.* **2005**, *386*, 1301.

Table 1: Average order parameters of structural elements in MCoTI-I in the free state and bound to trypsin.

Structural element	Sequence	$\langle S^2\rangle$[a] Free MCoTI-I	$\langle S^2\rangle$[b] Trypsin–MCoTI-I
loop 1	3–8	0.81 ± 0.01	0.75 ± 0.29
loop 2	10–14	0.81 ± 0.01	0.93 ± 0.04
loop 3	16–18	0.84 ± 0.02	0.82[c]
loop 4	20	0.88[c]	0.98[c]
loop 5	22–26	0.92 ± 0.02	0.80 ± 0.24
loop 6	28–34	0.76 ± 0.05	0.71 ± 0.34
cystine knot	2,9,15,19,21,27	0.84 ± 0.02	0.62 ± 0.33

[a] S^2 values for residues 5 and 23 from free MCoTI-I are not included in the average because the relaxation data could not be fitted to a monoexponential function. [b] S^2 values for residues 2, 5, 8, 18, 19, 23, 29, 31, 32, and 33 from trypsin-bound MCoTI-I are not included in the average because of the lack of signal intensity or because the relaxation data could not be fitted to a monoexponential function. [c] $\langle S^2\rangle$ contains the S^2 value for a single residue.

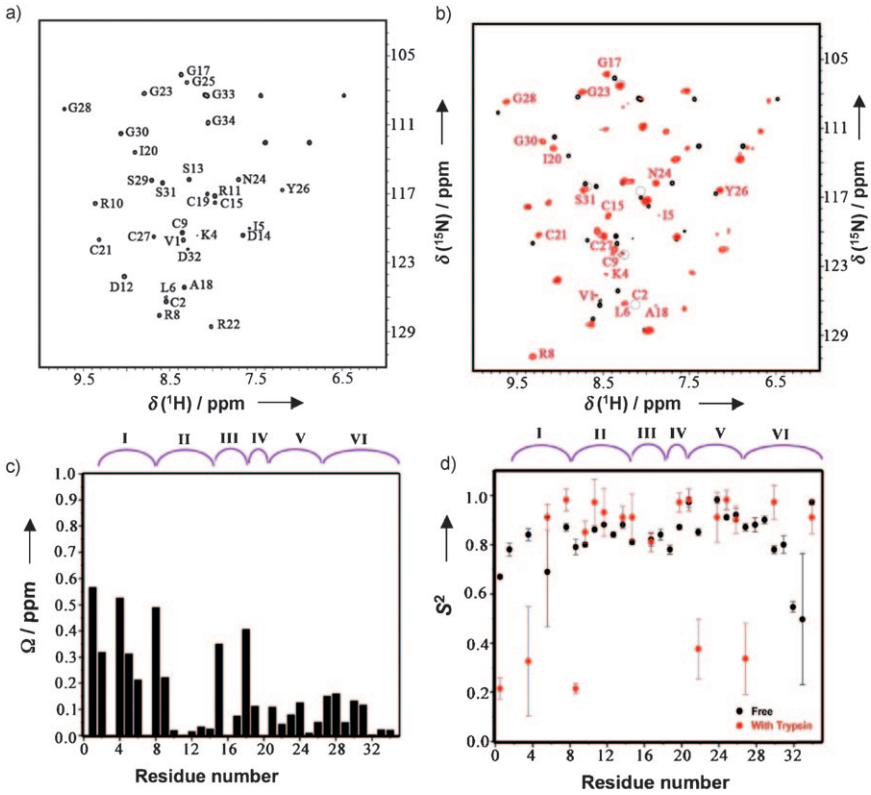

Figure 1. NMR analysis of the backbone dynamic of free and trypsin bound MCoTI-I. a) $\{^{15}N,^{1}H\}$NMR heteronuclear single quantum correlation (HSQC) spectrum of free MCoTI-I. Chemical shift assignments of the backbone amides are indicated. b) Overlay of the $\{^{15}N,^{1}H\}$ HSQC spectra of free (black) and trypsin bound MCoTI-I (red). Residues with large average amide chemical shift differences between two different states (>0.3 ppm) are indicated. Peaks that are broadened in trypsin bound MCoTI-I are indicated by grey circles. c) Average amide chemical shift difference for all the assigned residues in free and trypsin bound MCoTI-I. Chemical shift difference was calculated as: $\Delta\Omega = [(\Delta\Omega^2_{NH} + 0.04\,\Delta\Omega^2_{N})/2]^{1/2}$, where $\Delta\Omega_{NH}$ and $\Delta\Omega_{N}$ are the changes in the amide proton and nitrogen chemical shifts (ppm), respectively. d) Order parameter, S^2, for the free (black) and the trypsin bound MCoTI-I (red). The S^2 value is a measure of backbone flexibility and represents the degree of angular restriction of the N–H vector in the molecular frame. The MCoTI-I loops are shown on top of panels (c) and (d). Small unassigned peaks in the spectra of both free and trypsin-bound of MCoTI-I are from a minor conformation of the protein, and result from a known isomerization of the backbone at an Asp-Gly sequence in loop 6 of MCoTI-I.