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Seven-Membered Lactams as Constraints for Amide Self-Recognition

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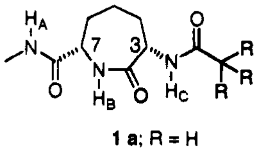
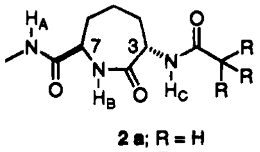
Simple lactams dimerize weakly in organic solvents.[1] As part of a program to design disubstituted seven-membered lactam β-turn mimetics,[2] *cis*-**1** and *trans*-**2**, we have encountered a remarkable example of cooperativity in dimerization. We present evidence that the *cis*-disubstituted lactams **1** self-associate in nonpolar solvents such as dichloromethane and chloroform in a unique head-to-tail manner involving donor and acceptor sites remote from one another along the carbon backbone. The *trans* isomer **2a** adopts a type VI β-turn[3] conformation in the crystal, whereas in solution the pivaloyl analog **2b** exhibits a very weak self-association.



1 a; R = H
b; R = Me



2 a; R = H
b; R = Me

The synthesis of the seven-membered lactam intermediates **4** and **5** is summarized in Scheme 1. The amino acid precursor **3** is readily prepared from serine[4] and can be cyclized[5] and protected[6] to give **4**. Azidation using the Evans protocol[7] afforded the *trans*-azide **5**. Removal of the BOC groups with acid, reduction of both the azide and olefinic groups by catalytic hydrogenation, *N*-acylation, oxidation of the hydroxymethyl group to the carboxylic acid,[8] and esterification with diazomethane gave the 7*R* methyl ester. Treatment with methylamine gave a 2:1 mixture of the *cis*- (**1a**) and *trans*-*N*-methylamides (**2a**).[9] Aminolysis of the (7*R*)-pentafluorophenate ester afforded (7*R*)-**2a**. The pivaloyl derivatives **1b** and **2b** were prepared analogously.

The crystal structure of **1a** revealed an extended conformation, while that of the diastereoisomer **2a** resembled a type VIa β-turn[3] as predicted by molecular modeling. Monte Carlo conformational searches and molecular dynamics calculations were performed on **1a** and **2a**, using MM2, MM3, and AMBER force fields, as implemented on MacroModel version 4.0.[10] For **1a** MM2 predicted a global minimum having a type VIa β-turn, stabilized by an intramolecular hydrogen bond between H_A and the acetamide carbonyl oxygen of length 2.11 Å, whereas MM3 and AMBER predicted an extended form, with no intramolecular hydrogen bonds.

^1H NMR and IR experiments were employed to determine the preferred conformation of **1a** in solution. A significant NOE was observed between the methine protons at H-7 [δ_H (CD_2Cl_2) 4.47, dd, $J = 10.6, 5.9$ Hz] and H-3 [δ_H (CD_2Cl_2) 4.16, dd $J = 10.4, 5.5$ Hz], which supported the existence of an extended conformation for **1a**. In addition, variable temperature (VT) ^1H NMR spectra of **1a** were recorded in various polar and nonpolar solvents. In CD_2Cl_2 and $CDCl_2CDCl_2$, the chemical shift of NH_A (assigned by its coupling to the N*Me* δ 2.85, d, $J = 4.7$ Hz) exhibited a uniquely large temperature dependence ($\Delta\delta/\Delta T = -14$ ppb/K at a concentration of 0.009 mol dm^{-3}). This implied a rapid equilibrium between two states of comparable enthalpy, one of which involved a strong hydrogen bond to H_A.[11] The chemical shift of amide proton NH_A of **1a** was strongly concentration dependent at concentrations greater than about 10^{-5} mol dm^{-3}, suggesting that **1a** was experiencing *intermolecular* interactions. This concentration dependence was supported by IR measurements. At high concentrations of **1a** in CH_2Cl_2, the IR spectrum exhibited four bands between 3280 and 3500 cm^{-1} attributable to NH stretching frequencies. Whereas the intensity of the band at 3300 cm^{-1} (NH_A in the dimer) diminishes with decreasing concentration and cannot be observed at concentrations below *ca.* 0.002 mol dm^{-3}, the intensity of the band at 3446 cm^{-1} (NH_A in the monomer) increases significantly. The two remaining IR bands at 3351 and 3399 cm^{-1} were assigned to NH_B and NH_C, respectively, by comparison with reference materials.[12]

All the data suggest that lactam **1a** exists in equilibrium with the "head-to-tail" dimer **6** in nonpolar solvents, rather than forming an oligo- or polymeric association as observed in the crystal.[13] This is supported by the observation of a concentration-dependent (intermolecular) NOE between the NH_AMe and NHCO*Me*.[14] Although the occurrence of intermolecular NOEs is much less frequent, we note that they have previously been

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[1] Krikorian, S. E. *J. Phys. Chem.* **1982**, *86*, 1875–1881. Chen, J.-S. *J. Chem. Soc., Faraday Trans.* **1994**, 717–720.

[2] Kahn, M., Ed. Tetrahedron Symposia-in-Print Number 50. *Tetrahedron* **1993**, *49*, 3433–3689.

[3] For classifications of β-turns, see: Richardson, J. S. *Adv. Protein Chem.* **1981**, *34*, 167–339. Wilmot, C. M.; Thornton, J. M. *Protein Eng.* **1990**, *3*, 479–493.

[4] (*S*)-Serine was protected as the *N*-BOC oxazolidine derivative, and the carboxylic acid was reduced to aldehyde and subjected to a Wittig reaction with ethyl 4-triphenylphosphonium butyrate followed by deprotection to give **3**. Garner, M.; Park, J.-M. *Org. Synth.* **1991**, *70*, 18–28. Beaulieu, P. J.; Duceppe, J.-S.; Johnson, C. *J. Org. Chem.* **1991**, *56*, 4196–4204.

[5] Of all the reagents investigated, only Bu_2SnO would effect this cyclization in acceptable yield. Steliou, K.; Poupart, M.-A. *J. Am. Chem. Soc.* **1983**, *105*, 7130–7138. The Mosher ester of the lactam derived from **4** indicated an enantiomeric purity in excess of 95%.

[6] This appears to be the first use of a BOC carbonate as a hydroxyl protecting group, which has the advantages of stability toward base and acid lability.

[7] Evans, D. A.; Britton, T. C.; Ellman, J. A.; Dorow, R. L. *J. Am. Chem. Soc.* **1990**, *112*, 4011–4030. The major diastereoisomer was the 3*S*,7*R trans* compound; see: Evans, P. A.; Collins, I.; Hamley, P.; Holmes, A. B.; Raithby, P. R.; Russell, K. *Tetrahedron Lett.* **1992**, *33*, 6859–6862.

[8] Carlsen, P. H. J.; Katsuki, T.; Martin, V. S.; Sharpless, K. B. *J. Org. Chem.* **1981**, *46*, 3937–3938.

[9] Under these reaction conditions the *trans*-methyl ester was apparently partially epimerized to the *cis* isomer. The *trans*-amide **2a** could be completely converted into the *cis* isomer **1a** in refluxing methanol containing potassium carbonate.

[10] Mohamadi, F.; Richards, N. G. J.; Guida, W. C.; Liskamp, E.; Lipton, M.; Caulfield, C.; Chang, G.; Hendrickson, T.; Still, W. C. *J. Comput. Chem.* **1990**, *11*, 440–467. Still's continuum model for chloroform was used for all calculations reported, although calculations *in vacuo* gave qualitatively similar results. See: Still, W. C.; Tempczyk, A.; Hawley, R. C.; Hendrickson, T. *J. Am. Chem. Soc.* **1990**, *112*, 6127–6128.

[11] Gellman, S. H.; Dado, G. P.; Liang, G. B.; Adams, B. R. *J. Am. Chem. Soc.* **1991**, *113*, 1164–1173. In polar solvents (DMSO-d_6 and CH_3CN-d_3), all three amide protons showed similar and small ($|\Delta\delta(NH)/\Delta T| < 4.6$ ppb/K) temperature dependencies.

[12] Dado, G. P.; Gellman, S. H. *J. Am. Chem. Soc.* **1992**, *114*, 3138–3139. Liang, G. B.; Desper, J. M.; Gellman, S. H. *J. Am. Chem. Soc.* **1993**, *115*, 925–938. As observed for **1a**, the pivaloyl derivative **1b** showed a similar behavior, and its NH-stretch bands can be attributed as follows: $NH_{A,dimer}$ (3305 cm^{-1}), NH_B (3349 cm^{-1}), NH_C (3416 cm^{-1}), and $NH_{A,monomer}$ (3446 cm^{-1}).

[13] The crystal-packing diagram of crystalline **1a** indicates an association involving hydrogen bonding between $MeNH_A$ of one molecule with the *N*-acetyl C═O of an adjacent molecule in the next layer.

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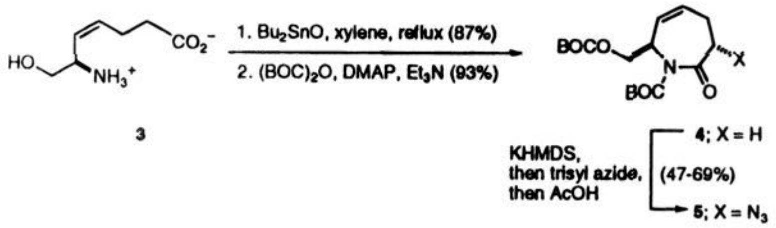
Scheme 1



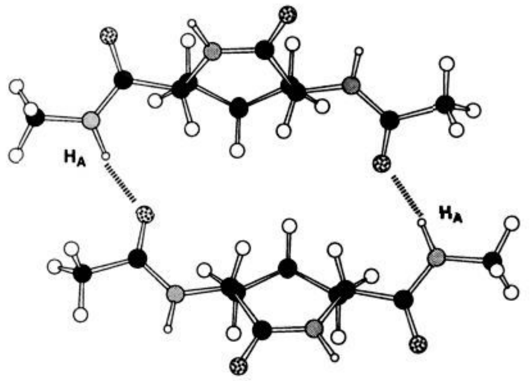


Figure 1. Amber-minimized structure of dimer **6** showing the hydrogen bond between H$_A$ and the MeCO oxygen atom.

used to examine molecular recognition processes.[15] Vapor pressure osmometry measurements provided firm support for the existence of a dimer such as **6**.[16]

Curve fitting to a plot of ^{1}H NMR chemical shift *vs* concentration for the NH$_A$ proton of **1a** at 298 K in CDCl$_2$-CDCl$_2$ yielded the dimerization constant K_{dim} = *ca.* 170 dm^3 mol^{-1} and limiting values for δ at low and high concentration as 5.6 and 8.1, respectively. The K_{dim} is much higher than values for simple lactams and other amides.[1] Furthermore, measurement of K_{dim} at several temperatures over the range 298–265 K (in CD$_2$Cl$_2$) enabled values for ΔH_{dim} and ΔS_{dim} to be estimated from a van't Hoff analysis, as -19 ± 3 kJ mol^{-1} and -23 ± 10 J mol^{-1} K^{-1}, respectively. The structure proposed for the dimer (Figure 1) not only satisfies all experimental data for **1a** but also is supported by molecular mechanics and molecular dynamics calculations.[10,17]

The *trans* compounds **2** were evaluated similarly. Because **2a** barely dissolved in chloroform and dichloromethane, it was necessary to use the pivaloyl analog **2b**. Vapor pressure osmometry, VT NMR, and VC-IR measurements[18] together with curve fitting of variable concentration NMR data indicated that **2b** dimerized only weakly (K_{dim} = *ca.* 5 dm^3 mol^{-1}) in a manner comparable to that of simple lactams and amides.[1,19]

In summary, this study, which was aimed at synthesizing a constrained β-turn analog, has produced a remarkable example of self-recognition between relatively unconstrained secondary amides in preference to a preoriented secondary lactam.[20] It illustrates how molecular recognition phenomena are crucially dependent on molecular structure, as the inversion of a single stereocenter (**1** → **2**) almost completely removes the tendency for association and reverses the relative orientation of the halves of the dimer.

Acknowledgment. We thank the Science and Engineering Research Council (EPSRC/BBSRC), U.K., for supporting this work and provision of the Swansea Mass Spectrometry Service, SmithKline Beecham Pharmaceuticals, for a CASE award (A.N.), the Schweizerische Studienstiftung, the Cambridge Overseas Trust, the CVCP (ORS award), Ciba-Geigy PLC (S.D.), The Royal Society for the award of a Royal Society Leverhulme Senior Research Fellowship (A.B.H.), Pfizer Central Research (Sandwich) for generous financial support, and Senn Chemicals AG (Switzerland) for the generous donation of chemicals. We thank Drs. A. E. Edwards and H. R. Powell for the X-ray analyses, Professor D. A. Evans for helpful advice on azidations, Dr. P. Grice for some NOE difference experiments, and Professors P. A Evans and G. Helmchen (ARC Program) and Drs. R. Bonar-Law and M. Cristofaro for their interest and advice on many aspects of this work.

Supporting Information Available: Experimental details for lactamization of **3**; spectroscopic data for lactams **1** and **2**; IR data for reference lactams; variable concentration IR spectra of lactams **1a**, **1b** and **2b**; vapor pressure osmometry of lactam **1a** in chloroform; ^{1}H NMR data at various concentrations and temperatures in either CD$_2$Cl$_2$ or CDCl$_2$CDCl$_2$, curve fitting and van't Hoff analysis of lactam **1a**; details of the conformational searches for **1a** and **2a** and molecular dynamics simulations; details of the X-ray structure determinations, tables of atomic coordinates, isotropic displacement parameters, anisotropic displacement parameters, bond lengths, and bond angles for **1a** and **2a** (this data has been deposited with the Cambridge Crystallographic Database) (37 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, can be ordered from the ACS, and can be downloaded from the Internet; see any current masthead page for ordering information, and Internet access instructions. Molecular Mechanics data is available over the World-Wide-Web: http://www.ch.cam.ac.uk/MMRG/lactamdimer.html.

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(14) ^{1}H NMR NOE difference spectra of **1a** were recorded in CDCl$_3$ on a Bruker DRX 500 MHz spectrometer. At 0.05 mol dm^{-3}, irradiation at the N*Me* frequency led to a 2.8% enhancement in the signal due to NHCO*Me*. The reciprocal enhancement was 0.9%. At 0.02 mol dm^{-3}, the corresponding figures were 0.5% and 0.5%, respectively. At 0.006 mol dm^{-3} NOEs could not be detected. All NOE difference experiments were performed with identical spectrometer parameters, and other *intramolecular* NOEs were of comparable intensity at all three concentrations. After prolonged standing of **1a** in chloroform and dichloromethane solutions, extra amide NH resonances in the ^{1}H NMR could be observed as shoulders on the original signals. The origin of these new peaks is presently uncertain, but all the reported IR and NMR data were collected on samples in which these peaks were absent.

(15) Chan, S. I.; Kreishman, G. P. *J. Am. Chem. Soc.* **1970**, *92*, 1102–1103. Bergeron, R. J.; Channing, M. A.; McGovern, K. A. *J. Am. Chem. Soc.* **1978**, *100*, 2878–2883. Pirkle, W. H.; Pochapsky, T. C. *J. Am. Chem. Soc.* **1986**, *108*, 5627–5628. Jaime, C.; Redondo, J.; Sánchez-Ferrando, F.; Virgili, A. *J. Org. Chem.* **1990**, *55*, 4772–4776.

(16) Vapor pressure osmometry measurements were performed over the concentration range 0.005–0.043 mol dm^{-3} in CHCl$_3$ at 310 K on a Wescor 5500 instrument using benzil as a reference standard. See: Schrier, E. E. *J. Chem. Educ.* **1968**, *45*, 176–180.

(17) Dimer **6** was analyzed using the AMBER force field, using energy-minimized monomer structures as a starting point. The lowest energy dimeric structures from conformational searches were subjected to molecular dynamics simulations at 300 K for 100 ps. Dimer **6** remained intact with intermolecular hydrogen bonds of length 1.808 Å.

(18) VT ^{1}H NMR spectra of **2b** revealed temperature dependencies of both the N*H*$_A$ and N*H*$_C$ protons which are consistent with a very weak self-association. At high concentrations of **2b** in CH$_2$Cl$_2$ (>0.05 mol dm^{-3}) an IR band at 3345 cm^{-1} was observed.

(19) The pivaloyl group does not appear to be inhibiting dimerization of **2b** on steric grounds since the *cis* isomer **1b** shows spectroscopic behavior identical to that of **1a**.

(20) A referee has drawn our attention to the elegant work of Wuest and Ducharme (Wuest, J. D., Ducharme, Y. *J. Org. Chem.* **1988**, *53*, 5787–5789) involving the very strong self-association of rigidly linked 2-pyridones. The work described in the present communication reports the surprising association between non-lactam amides at remote ends of a semiflexible spacer unit.