Synthesis and NMR Studies of Activated Derivatives of *cis*- and *trans*-5-Amino-6-oxopiperidine-2-carboxylic Acid and the Corresponding Bicyclic Dilactam 2,5-DBO: Potential Building Blocks for Stereoregular Polyamides and Peptides

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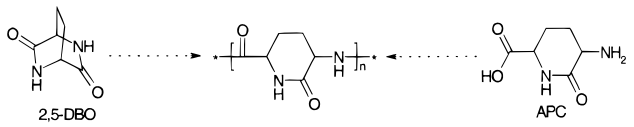
ABSTRACT: Presented here are the syntheses of bicyclodilactams as precursors of polymeric lactams. A new preparation for the 2,5-diazabicyclo[2.2.2]octa-3,6-dione was developed. The four possible dimers were prepared from the N-protected *cis*- and *trans*-5-amino-6-oxopiperidine-2-carboxylates (Apc's). Base treatment of the trans activated ester led to the polymer. Synthesis of the isomeric 2,6-diazabicyclo-[2.2.2]octan-3,5-dione was not successful even under conditions in which substituted compounds were found. From the ^{1}H NMR spectral data for the monomers and dimers, we concluded that the H−H coupling constants for the *cis*- and *trans*-Apc monomers are consistent with the low-energy pseudo-chair conformations inferred from structures optimized at the B3PW91/6-31G* level of density functional theory. The two-dimensional NMR spectra of the oligomers give no evidence for β-turn formation in DMSO-d_6.

Introduction and Background

The synthesis and characterization of bicyclic lactams and lactam-containing polymers have been the subject of continuing research in these and other laboratories.[1−6] It was of interest to extend previous studies of polymers having rings in the backbone[7] to those in which the rings were lactams. We also wanted to investigate possible synthetic routes toward stereospecific poly-(piperazinediones) with the aim of constructing self-assembled asymmetric structures with nonlinear optical properties.[8,9] These structures are also attractive because of the possibility that lactam oligomers might structurally mimic naturally occurring β-turns in peptides and proteins.[10−15] This is a very active current area of research in which the techniques of multidimensional NMR and molecular dynamics provide the most common methods of probing conformations associated with β- and γ-turn structures.[16−24]

The synthesis of polyamides containing lactam units in the main chain can be attempted in two ways: ring-opening polymerization[25−30] of bicyclic dilactams and the polycondensation of monomers containing the lactam unit. Presented here are the improved preparation and attempts at ring-opening polymerization of the bicyclic lactam 2,5-diazabicyclo[2.2.2]octane-3,6-dione (2,5-DBO). Also described are the synthesis and oligomerization of the monolactam 5-amino-6-oxopiperidine-2-carboxylic acid (Apc), its activated ester, and the activated ester of the dimer.



Conformationally constrained polypeptides, which are forced to adopt β- and γ-turn conformations, have been studied extensively.[10−24,31−35] Such turns are present in the active conformations of numerous biologically important peptides and proteins,[31−35] and lactam-based constraints are used extensively.[36−38] It was shown that Apc can be used as a peptide spacer and/or conformational modifier.[39] One of the characteristic features of the type VI turn is the presence of a *cis*-peptide bond at the $i + 2$ position. As a consequence, Apc could be used as a mimic for type VI turns. Also, type VI turns have been spectroscopically detected in the solution conformation of several highly potent peptide hormone analogues and have been implicated in the function of biologically important proteins. An interesting feature of Apc is that it is a nonaromatic heterocyclic amino acid that contains an internal *cis*-peptide linkage. Because there are two chiral carbons, there are four possible stereoisomers. In addition, Apc may be considered to be an alanine dimer in which two alanine molecules are fused through the side chains, and the resulting 2,5-diaminoadipic acid cyclizes to a lactam.

The synthesis of the bicyclic lactam 2,5-diazabicyclo-[2.2.2]octan-3,6-dione (2,5-DBO, **4**) (Scheme 1) has been previously described.[40−43] The enantiomer (*S,S*)-(+)-2,5-DBO was also prepared by Kemp and co-workers from L-homoserine.[43] Recently, HPLC purification of the *p*-methoxybenzyl derivatives of the racemic mixture of 2,5-DBO was described in connection with X-ray structure determination of the racemate (±)-2,5-DBO and enantiomerically pure (−)-2,5-DBO.[44] It has been shown that the chiral nature of the substance determines the supramolecular architecture generated by hydrogen-bonding self-assembly, giving an infinite zigzag chain for the racemate and a cyclic tetramer for the enantiomer. In our work, the monomer 2,5-DBO in racemic form was obtained from *meso*- or DL-dialkyl α,α-dibromoadipate using a new method developed in these laboratories.

Stereoisomeric new polyamides can in principle be obtained by ring-opening polymerization of 2,5-DBO. The ring-opening polymerization of atom-bridged bicyclic lactams was first investigated by Hall.[1] Most relevant to the present study was lactam 2-azabicyclo-

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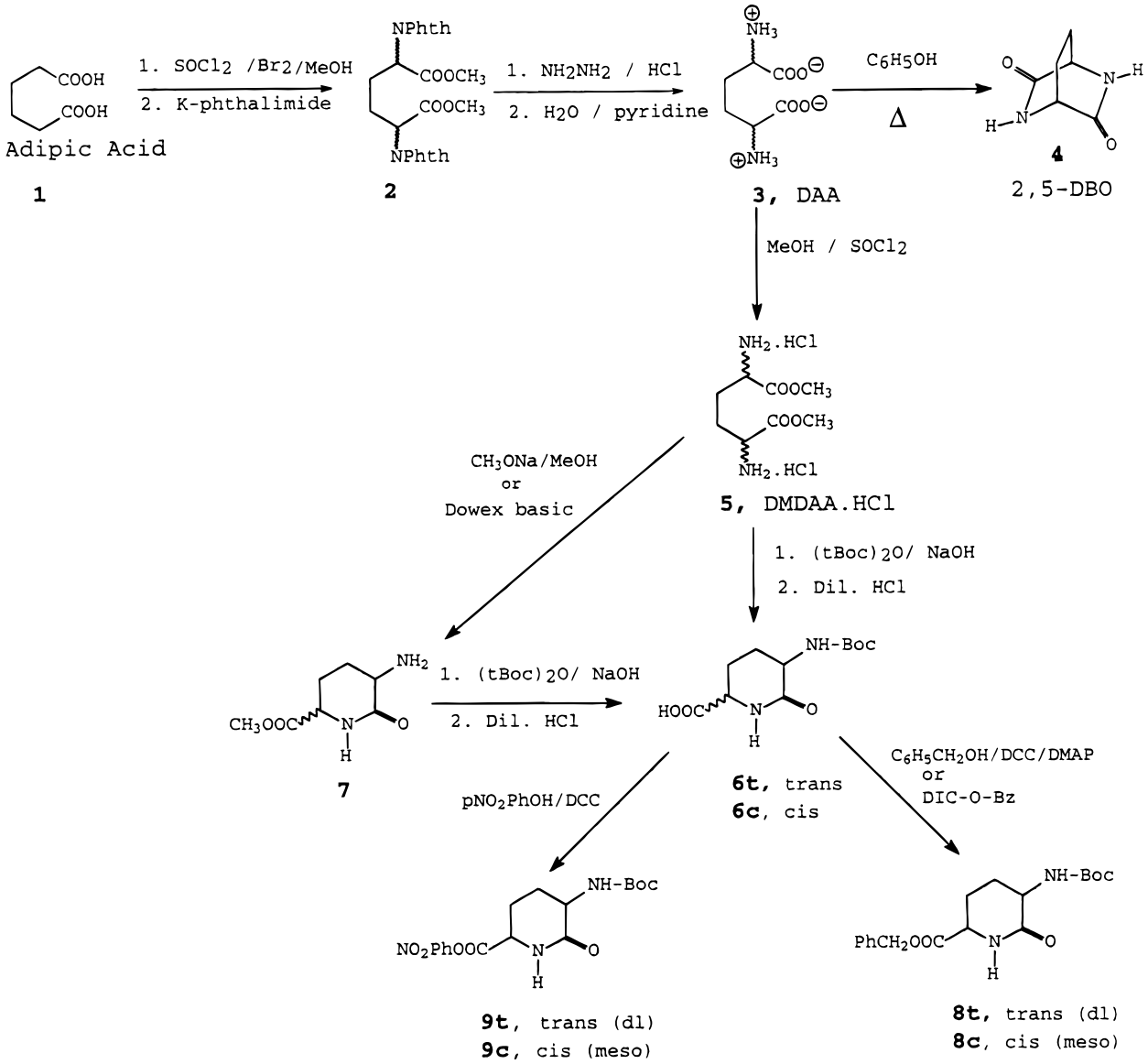
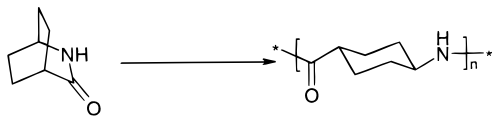
Scheme 1



[2.2.2]octan-3-one, whose anionic polymerization yielded a stable trans polymer resulting from epimerization of the initial cis structure, which may assist polymerization. The H−H repulsion in the two bridges of the boat form was deemed responsible for destabilizing the monomer relative to the polymer.



Comparison of 2,5-DBO (**4**) with 2-azabicyclo[2.2.2]-octan-3-one shows that half of these H−H eclipsing interactions are absent in the former, replaced by a *cis*-amide link. Although the latter is slightly less favorable energetically than a *trans*-amide link, we must expect that 2,5-DBO (**4**) will be less likely to polymerize. Moreover, in 2,5-DBO the dipoles neutralize each other. On the other hand, in the isomeric 2,6-diazabicyclo-[2.2.2]octane-3,5-dione (2,6-DBO), the dipoles are parallel to each other. Therefore, we would expect the 2,6-DBO isomer to have a higher tendency to polymerize than 2,5-DBO. We did not find a description of this unsubstituted monomer in the literature, although the 1-methyl derivative is known.[45,46] As will be seen, polymers similar to the one expected to be generated by 2,5-DBO polymerization will be synthesized using polycondensation of Apc activated monomer or its dimer.

Experimental Section

General Procedures. Melting points were taken on a Thomas-Hoover capillary melting point apparatus and are corrected. Thin-layer chromatography was performed on silica gel plates (GF02521 Analtech Inc.) with UV, I_2, and ninhydrin detection. Solvents used were (A) chloroform:methanol:water (20:40:4), (B) chloroform:methanol (9:1), and (C) hexane:ethyl acetate (1:1). Acrolein was obtained from Pfaltz and Bauer, Waterbury, CT. Other chemicals and solvents were reagent or HPLC grade. Final product solutions were dried over anhydrous Na_2SO_4 (unless otherwise noted) prior to evaporation on a rotary evaporator. The DMF was freshly vacuum distilled from ninhydrin to eliminate any traces of secondary amines and received over 4 Å molecular sieves. The DMSO was also vacuum distilled from calcium hydride and stored over 4 Å molecular sieves.

Characterization. The ^1H and ^{13}C NMR spectra were obtained in $CDCl_3$ or DMSO-d_6 at ambient temperature using Bruker Instruments WM-250 or AM-500 FT NMR spectrom-

eters. The ^{1}H shifts are given in ppm referenced either directly to internal TMS or indirectly from the residual DMSO-d_5 multiplet signal at 2.49 ppm. All two-dimensional NMR experiments (COSY, NOESY, and ROESY) were performed at 500.137 MHz on the AM-500 spectrometer. Infrared spectra were obtained on a Perkin-Elmer model 983 infrared spectrometer, and mass spectra were obtained on an Hewlett-Packard model 5988A.

Syntheses. 5-(*tert*-Butoxycarbonylamino)-6-oxopiperidine-2-carboxylic Acid 6 (Scheme 1). i. Dimethyl 2,5-diphthalimidoadipate (2) was prepared according to the literature procedure.[47,48] The separation of the diastereomers was conducted according to the procedure outlined in the literature.[47] The meso derivative was isolated in 20−25% yield; mp 211−213 °C. ^{1}H NMR ($CDCl_3$) showed a peak at 4.81 (CHα). The racemic mixture was isolated with 13−25% yield; mp 163−164 °C. ^{1}H NMR ($CDCl_3$) exhibited a signal at δ 4.96 ppm (CHα). The other parts of the spectra were similar to each other.

ii. **2,5-Diaminoadipic acid (DAA, 3)** was synthesized according to the literature procedure[48] in 58% yield. The racemic isomer was prepared from racemic dimethyl 2,5-diphthalimidoadipate with 80% yield and mp 284 °C. The meso isomer was obtained in 75% yield and mp 302−303 °C.

iii. **Dimethyl 2,5-Diaminoadipate Dihydrochloride (DMDAA·HCl, 5).** The material was prepared from **3** according to the literature procedure[49] in 93% yield and mp 210−212 °C for the mixture. The racemic product had mp 207 °C and the meso mp 231−233 °C. ^{1}H NMR (DMSO-d_6) for racemic: δ 8.8 (s, broad, 6, NH_3), 4.1 (m, broad, 2, CH), 3.8 (s, 6, CH_3), 2.1−1.9 (m, 4 CH_2). The meso derivative had an identical spectrum except for the splitting pattern of the CH_2 region.

iv. **5-(*tert*-Butoxycarbonylamino)-6-oxopiperidine-2-carboxylic Acid (6).** *Method A*. DMDAA·HCl **5** (10 g, 36 mmol) was dissolved in 150 mL of 1:1 water:dioxane and cooled in an ice bath. The pH was adjusted to 11 by the addition of 4 N NaOH. Di-*tert*-butyl dicarbonate (12 g, 55 mmol) was added, and the pH was maintained between 10 and 10.5 with 2 N NaOH at 0 °C for 1 h and then at room temperature overnight. When the pH no longer decreased, it was increased to 11 and the reaction was continued overnight. The basic solution was evaporated to dryness and the resulting white mass washed twice with ethyl acetate (50 mL). The solid mass was dissolved in water and ice, cooled in an ice/salt bath, mixed with ethyl acetate (80 mL), and acidified with cooled 5% HCl to pH 2. The organic phase was separated, the water layer was extracted twice with cold ethyl acetate, and the pooled organic layers were washed with water and saturated NaCl. After drying, the solvent was evaporated to dryness to give a thick oil. After prolonged drying in a vacuum, 6.7 g (72%) of **6** was isolated and characterized by NMR. The R_f for both isomers was 0.72 (solvent A, I_2). IR (KBr pellet): 3500−3200 (O−H stretching), 1712 (amide I), 1687 (urea), 1649 cm^{-1} (amide II). Mass spectrum for meso: molecular ion 258 (calcd 258.27). ^{1}H NMR ($CDCl_3$) for cis isomer: δ 8.8 (d, 1, N−H lactam), 5.5 (s, broad, 1, N−H Boc), 4.2 (m, 2, CH) 2.5−1.5 (complex multiplet, 4, CH_2) 1.45 (s, 9, Boc). For trans isomer: δ 8.8 (s, broad, 1, N−H lactam) 5.3 (s, broad, 1, N−H Boc) 4.15 (m, broad, 1, CH, 6) 3.9 (m, broad, 1, CH, 3) 2.4 (m, broad, 2, CH_2) 1.8 (m, broad, CH_2) 1.4 (s, 9, Boc). Anal. Calcd for $C_{11}H_{18}N_2O_5$: C, 51.15; H, 7.02; N, 10.85. Found: C, 51.26; H, 7.05; N, 10.81.

Method B. Apc methyl ester **7** (1.0 g) was dissolved in 20 mL of 3:1 dioxane:water and cooled in an ice bath. The pH was adjusted to 11 by the addition of 4 N NaOH. Di-*tert*-butyl dicarbonate (1.5 g) was added, and the pH was maintained between 10 and 10.5 with 2 N NaOH at 0 °C for 1 h and then at room temperature overnight. Workup by a similar procedure as in method A gave 0.82 g of **6** (54%). The isolated product was characterized by NMR.

v. **Methyl 5-Amino-6-oxopiperidine-2-carboxylate (Apc Methyl Ester, 7).** This was obtained from **5** by a modified procedure from the literature.[40,50]

Benzyl 5-(*tert*-Butyloxycarbonylamino)-6-oxopiperidine-2-carboxylate (8). *Method A*. To 2.06 g (8 mmol) of **6** in dry THF (30 mL) cooled in an ice bath was added 1.9 g (8.1 mmol) of *N*,*N*-diisopropyl-*O*-benzylisourea.[51] The reaction was carried out by stirring at room temperature overnight. After evaporation of solvent the residue was taken up in ethyl acetate and the solution washed with cold 0.1 N HCl, water, 5% $NaHCO_3$, and water and dried. Evaporation of solvent gave a foamlike solid. Yields were 2.2 g for the cis isomer **8c** (79%) and 2.32 g (83%) for trans isomer **8t** . IR (thin film) showed no acid band. R_f 0.23 (C) and R_f 0.6 (B) by ninhydrin and UV for both isomers. ^{1}H NMR ($CDCl_3$) **8c** (cis): δ 7.3 (s, 5, benzyl), 7.2 (s, broad, 1, N−H lactam), 5.7 (d, broad, 1, N−H Boc), 5.2 (m, 2, CH_2 benzyl), 4.2 (m, 2, CH), 2.3 (m, broad, 2, ring CH_2), 2.1 (m, broad, 2H, ring CH_2) 1.45 (s, 9, Boc). For the trans isomer **8t**, a similar spectrum was obtained with CHα showing two multiplets (CHα) δ (4.2 and 4, 1H each) and the ring CH_2 δ (2.4 and 1.9 multiplets, 2H each).

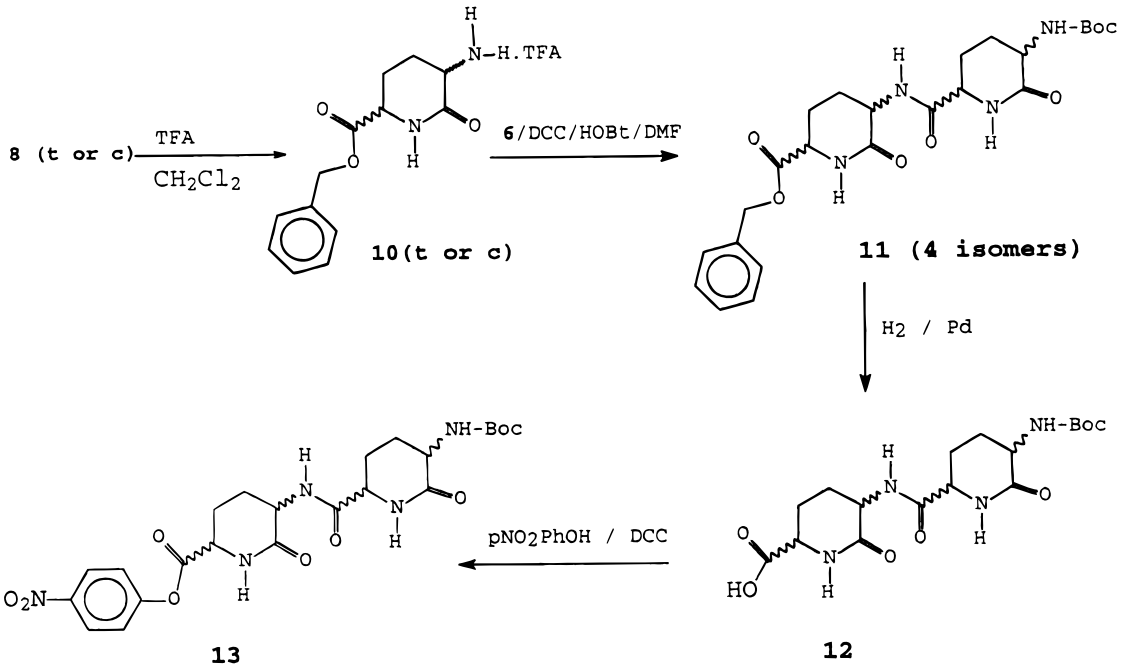
Method B. To a solution of 2.06 g (8 mmol) of **6** and 1 mL (9.6 mmol, 20% excess) of freshly distilled benzyl alcohol in 20 mL of dry THF was added 1.82 g (8.8 mmol) of dicyclohexylcarbodiimide (DCC) and 0.05 g of 4-(dimethylamino)-pyridine (DMAP), and the solution was stirred with cooling in an ice bath. After 1 h at 0 °C, the reaction was allowed to warm to room temperature and stirred for 6 h. The excess DCC was destroyed with one drop of acetic acid and precipitated DCU filtered and washed with THF. Rotary evaporation of solvent gave an oil which was dried to a foam. The yields for the cis and trans isomers were 2.05 g (73%) and 2.45 g (88%), respectively. Except for contamination by impurities the ^{1}H NMR spectra were the same as obtained by method A.

***p*-Nitrophenyl 5-(*tert*-Butyloxycarbonylamino)-6-oxopiperidine-2-carboxylate 9 t and c. 6** (2.06 g, 8 mmol) and *p*-nitrophenol (1.35 g, 9.7 mmol) were dissolved in 25 mL of dry THF and cooled in an ice bath. DCC (1.8 g, 8.75 mmol) was added in three portions,[52] and the reaction was stirred overnight at room temperature. The precipitated DCU was filtered and washed with ethyl acetate. Evaporation of ethyl acetate gave a yellow oil, **9**. The trans isomer **9t** (35%) was crystallized at room temperature from the ethyl acetate solution and recrystallized from absolute ethanol. The cis isomer **9c** was crystallized slowly from the ethyl acetate solution at −10 °C. With the exception of the aromatic region, the ^{1}H NMR spectra were similar to those of **8c** and **8t**.

2,5-Diazabicyclo[2.2.2]octane-3,6-dione (2,5-DBO, 4). A mixture of 1.1 g (4 mmol) of racemic DAA **3** and 11 g of dry phenol was sealed under vacuum in a high-pressure tube after three freeze−thaw cycles. The mixture was heated at 200 °C in an oil bath for 4 h. The tube was then cooled to room temperature and opened, and the solid was repeatedly washed with ether to remove phenol. The solid was collected and heated to reflux in chloroform and filtered while hot. The solution was rotary evaporated to dryness to give a shiny yellowish solid. Recrystallization in chloroform led to recovery of 0.29 g (52%) of 2,5-DBO; mp 272−274 °C (lit.[40] 272−273 °C). IR (KBr pellet): 3160 (lactam NH), 1680 cm^{-1} (lactam C=O). The ^{1}H NMR (250 MHz, DMSO-d_6) δ 8.6 (br. d, 1, N−H lactam), 3.7 (m, 1, bridgehead C−H), 1.85 (br. m, 2, CH_2). ^{13}C APT: δ 172 ppm quaternary lactam CO, 53.87 ppm tertiary bridgehead, 24.87 ppm, secondary bridge CH_2. Anal. Calcd ($C_6H_8N_2O_2$): C, 51.42; H, 5.75; N, 19.99. Found: C, 50.54; H, 5.79; N, 19.84.

Benzyl 5-(5′-*tert*-Butoxycarbonylamino-6′-oxopiperidine-2′-carbonylamino)-6-oxopiperidine-2-carboxylate (11) (Scheme 2). The four dimers were prepared following the same procedure. Compound **8** was dissolved in a 1:1 mixture of anhydrous dichloromethane and trifluoroacetic acid, and the reaction was monitored by TLC. The solution was evaporated to dryness, leading to a thick yellow oil which was dried over KOH in vacuo. ^{1}H NMR of a neutralized sample of **10c**: δ 9.0 (s, broad, 2, NH_2 protons), 8.0 (s, broad, 1, N−H lactam), 7.3 (s, 5, benzyl), 5.2 (m, 2, CH_2 benzyl), 4.2 (m, 2, CH 's), 2.3 (m, broad, 2, CH_2 cycle), 2.1 (m, broad, 2, CH_2 cycle). The TFA salt of **10** was dissolved in dichloromethane containing 5% DMF, and 1 equiv of triethylamine was added. To the reaction mixture, 1 equiv of **6** was added and the solution neutralized to pH 8 with more triethylamine. DCC was added in 10%

Scheme 2



excess with 2 equiv of HOBT, and the mixture was left to react for 16 h at room temperature. The precipitate was filtered off and the solvent rotary evaporated to dryness. The residue was dissolved in ethyl acetate, washed with water, 0.1 N HCl, 1% Na_2CO_3, and water, and dried over $MgSO_4$. The solvent was evaporated, and the oily product was purified by chromatography on a silica gel column and eluted with chloroform (one column volume) and chloroform containing 3% methanol. The dimers **11** appeared as colorless to light yellow oils, which did not crystallize, except for the trans−trans dimer. The IR spectrum could not be distinguishable from the starting material **8**. TLC R_f 0.32 (B), R_f 0.72 (A). ^{1}H NMR (250 MHz) **11cc** (cis−cis): very complex amide band δ (8.3 to 7.1, 3H), 7.3 (s, 5, CH aromatic), 5.9 (d, b, 1 N−H Boc), 5.2 (m, 2, CH_2 benzyl), 4.5 (m, 1, CHα), 4.1 (m, 3, CH), 2.2 (m, broad, 6, ring CH_2), 1.8 (m, 2, ring CH_2), 1.43 (s, 9, *t*But). The other **11** isomers differ in detail from this but exhibited the same general features. For the next reactions, the products were used without further purification. Except for the ester groups, the ^{1}H NMR spectra were identical to the spectra of **9**.

5-(5′-*tert*-Butoxycarbonylamino-6′-oxopiperidine-2′-carbonylamino)-6-oxopiperidine-2-carboxylic Acid, 12: In a Parr hydrogenation bottle **11** (2 g) was dissolved in methanol (50 mL), and 10% Pd/C (catalytic) was added. The bottle was purged with hydrogen five times and filled to 30 psi. After 1 h the solution was filtered through Celite and the solvent removed under vacuum to give colorless oils **12**, which were dried in a vacuum. The compounds were characterized by NMR and used in the next step without further purification.

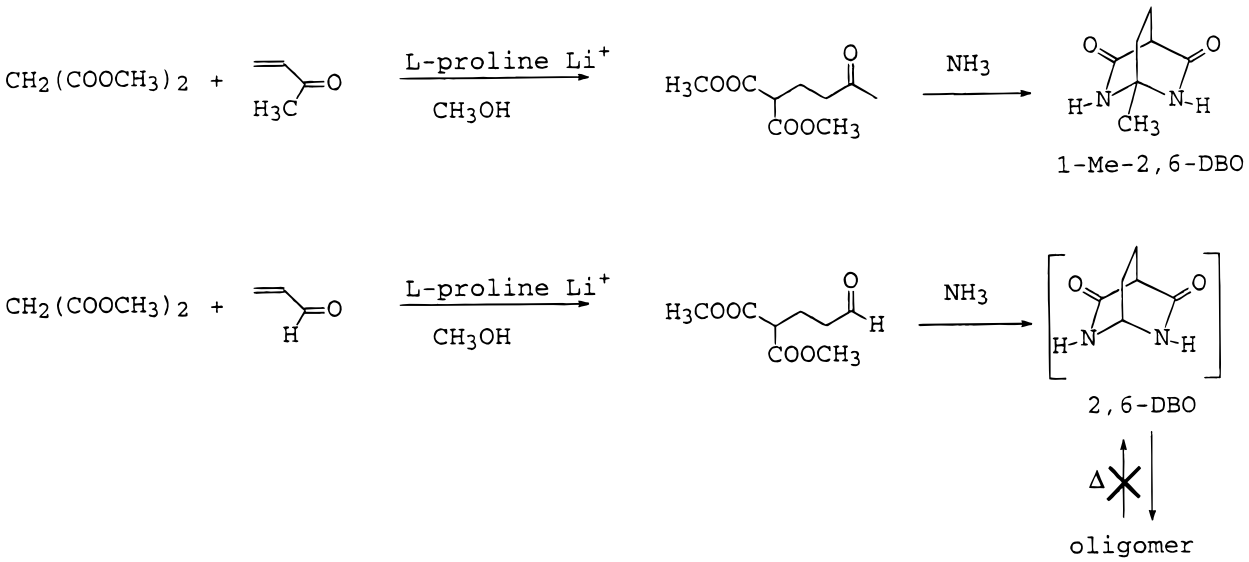
***p*-Nitrophenyl 5-(5′-*tert*-Butoxycarbonylamino-6′-oxopiperidine-2′-carbonylamino)-6-oxopiperidine-2-carboxylate, 13:** Intermediates **12** were reacted with *p*-nitrophenol in dichloromethane containing 5% DMF, using the same procedure described under **9**. These esters **13** were crystallized by the addition of ether, leading to colorless solids after ether washes. The NMR spectra were identical to the parent compounds except for the change in the ester group. These compounds were used in the polymer synthesis without further purification.

Polymerization of *p*-Nitrophenyl 5-(*tert*-Butyloxycarbonylamino)-6-oxopiperidine-2-carboxylate (Scheme 4**).** The **9t** or **9c** *N*-*tert*-Boc activated esters (1.5 g typical) were dissolved in 10 mL of dry dichloromethane, and 10 mL of trifluoroacetic acid was added and the reaction continued for 30 min. After evaporation of the solvent, the residue was dried in a vacuum over KOH to give an oily product. The trifluoroacetate salt resulting from the above treatment was dissolved in dry DMF (2 g in 2.5 mL), and triethylamine (Sequanal grade, secondary amine free) was added to the stirred solution until it was basic to wet pH paper. For both the **9c** and **9t** activated intermediates, the color of the solution increased, and there was an increase in apparent viscosity. After 24 h the solution was diluted in ethanol to give polymer **14a**. Two fractions could be separated, one being soluble in DMSO on moderate heating and the other staying insoluble. The ^{1}H NMR spectra of the two fractions were virtually identical. For the **9c** polymer precipitation in alcohol did not occur, and the spectra of the evaporated solution revealed the cyclization product 2,5-DBO (**4**) as the major component.

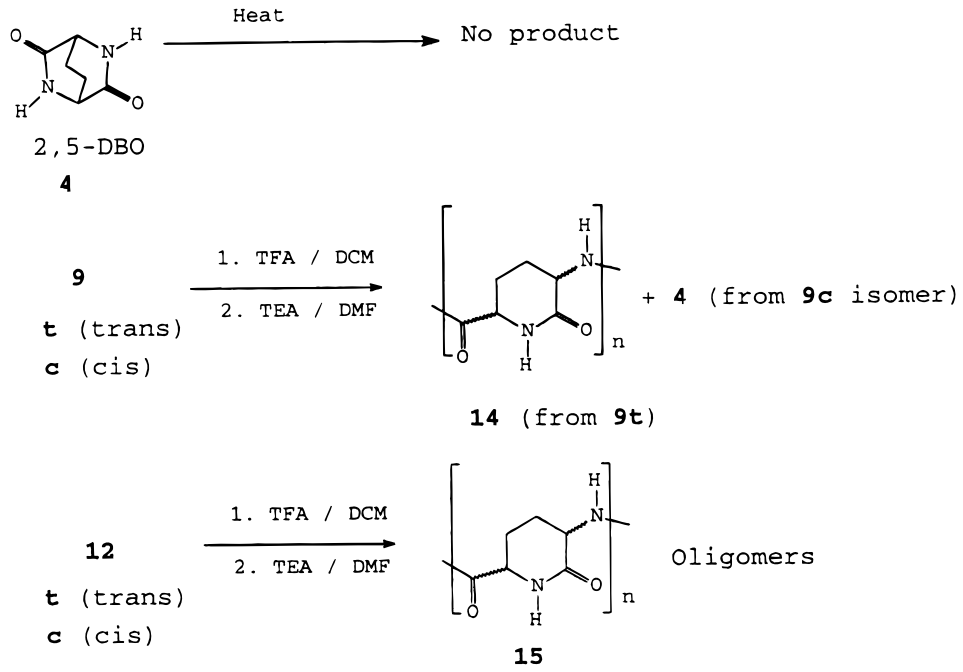
Polymerization of *p*-Nitrophenyl 5-(5′-*tert*-Butoxycarbonylamino-6′-oxopiperidine-2′-carbonylamino)-6-oxopiperidine-2-carboxylate, 13 (Scheme 4). The classical activated ester polymerization procedure[53] was used as outlined above. The trifluoroacetate salt **12** (1 g, 1.9 mmol) was dissolved in DMF (1.5 mL), and 0.4 mL (0.29 g, 2.9 mmol, 1.5 equiv) of triethylamine was added. After a few minutes, precipitation started while the color increased. DMSO was also used as solvent (same concentrations), and under these conditions precipitation did not take place. After 24 h, the mixture was precipitated in ether. The polymer **15** precipitated as a highly colored solid. It was decolorized by treatment with activated charcoal of the methanolic solution, the concentrated solution being again precipitated in ether and the polymer centrifuged out. Prolonged drying in a vacuum at 60 °C eliminated most of the remaining impurities. On the basis of solubility (soluble in DMSO on moderate heating), it was concluded that the products were only oligomeric. Alternatively, the oligomers were purified with activated charcoal in DMSO, followed by reprecipitation with ether and drying in vacuo at 60 °C for 48 h. The four polymers when examined by ^{1}H NMR were found to have spectral lines much broader than the dimers, but only two amide resonance were found and there were no signals corresponding to the blocking groups.

Attempted Polymerization of 2,5-DBO. The bicyclic lactam 2,5-DBO (**4**) was subjected to both hydrolytic and anionic polymerization conditions.[53] Hydrolytic polymerization was attempted at 200−260 °C in the presence of water or of 85% phosphoric acid. Activated anionic polymerization was attempted using DMSO, NaH, and acetic anhydride. No indication of polymerization was obtained in any experiment. The infusibility and insolubility of 2,5-DBO was a serious difficulty in these experiments.

Scheme 3



Scheme 4



Attempted Synthesis of 2,6-DBO (Scheme 3)**.** Dimethyl malonate and acrolein were condensed according to a literature procedure.[54] To a stirred solution of dimethyl malonate (19.8 g, 150 mmol) and L-proline lithium salt (1.8 g, 0.1 equivalent) in 250 mL of methanol at room temperature was quickly added 8.4 g of acrolein (150 mmol, 1 equiv) through a syringe. The reaction was stirred for 30 min before quenching with 15 mL of 1 N HCl. Most solvent was removed in vacuo, and the crude product was dissolved in ethyl acetate and washed with water (three times), dried over magnesium sulfate, concentrated and distilled using a Kugelrohr apparatus to give the product, 4,4-dicarbomethoxybutyraldehyde, as a clear liquid. Bp: 105 °C/0.3 mmHg. Yield: 9.1 g, 32%. ^{1}H NMR ($CDCl_3$): δ 2.2 (q, 2H), 2.6 (t, 2H), 3.45 (t, 1H), 3.75 (s, 6H), 9.75 (s, 1H) ppm.

The reaction with ammonia was performed according to Connors' procedure for the corresponding 1-methyl derivative.[45] Several attempts were made: 0.4 g of 4,4-dicarbomethoxybutyraldehyde in 1 mL of benzene with 0.5 mL of ammonia, stirred at room temperature in a pressure tube for 48 h or stirred for 6 h, at 80 °C, or in 1 mL of methanol in the presence of 0.5 mL of concentrated ammonium hydroxide at room temperature for 18 h. In all cases, a pale sticky yellow oil was obtained. ^{1}H NMR: δ 1.5−2.2 (m), 3.1 (s), 4.2 (m), 4.8 (s) ppm. Both ^{1}H NMR and mass spectral data indicated the formation of oligomers. Attempts to depolymerize these to the parent 2,6-DBO by heating them under vacuum did not succeed.

Results and Discussion

I. Syntheses. Bicyclic Lactams. The preparation of 2,5-DBO (**4**) was approached by two methods. The first was based on the literature procedure[40] and a new alternative method. Both procedures are outlined in Scheme 1. 2,5-Diaminoadipic acid (**3**) was synthesized according to literature methods, starting from adipic acid.[49] The two stereoisomers, racemic and meso, were separated at the dimethyl 2,5-diphthaloimidoadipate (**2**) stage. The final product 2,5-DBO in the first method was obtained by base cyclization of the hydrochloride salt of racemic α,α′-diaminoadipic acid (**3**). The best yield from this approach was about 15%. In the second

and preferred method, α,α′-diaminoadipic acid (**3**) was dissolved in phenol and placed in a sealed tube. Reaction at 200−250 °C for 6−16 h led to 2,5-DBO (**4**), which was isolated and recrystallized from hot chloroform. The average yield was 50−55% based on diaminoadipic acid (**3**). Identification of the product was based on ^{1}H NMR, IR, and mass spectra. Attempts to carry out ring-opening polymerization on 2,5-DBO under various conditions failed to give a polymer, perhaps because of insolubility.[55]

In sharp contrast, the isomeric 2,6-DBO has eluded us (Scheme 3). The synthesis of 1-methyl-2,6-DBO was carried out without difficulty following the literature procedure previously reported by Connors et al.[45] The synthesis is based on the condensation of vinyl ketone and alkyl malonate esters, monosubstituted or unsubstituted at C2, followed by cyclization under basic conditions using ammonia or primary amines. The procedure gave the expected product of 1-methyl-2,6-DBO, when starting with methyl vinyl ketone and dimethylmalonate under basic conditions. The expected product was isolated in about 60% and identified by its corresponding physical characteristics (mp and IR) as well as ^{1}H NMR.

In the attempted synthesis of unsubstituted 2,6-DBO, dimethyl malonate was reacted with acrolein. The 4,4-dicarbomethoxybutyraldehyde was condensed with anhydrous ammonia or with concentrated ammonium hydroxide under the successful conditions mentioned above. On evaporation this led to oligomeric material. It appears that the aldehyde group condensed intermolecularly with the resulting amide groups so that the monomeric 2,6-DBO was not obtained. Attempts to depolymerize this oligomeric material under vacuum gave no sublimable 2,6-DBO.

Synthesis of Activated Monomer (Scheme 1**).** Because of the unsuccessful attempts to polymerize lactam 2,5-DBO, an alternative stepwise synthetic approach for poly-Apc was explored. In this approach, the synthesis of the monolactam building block (Apc), properly protected and activated, was examined. The synthesis of Apc derivatives was based on the literature methods for the syntheses of meso and cis analogues of Apc.[40−43] A novel method for synthesis of the monoprotected Apc (*t*Boc-Apc) **6** was devised. The hydrochloride salt of dimethyl α,α′-diaminoadipate (**5**) was reacted with di-*tert*-butyl dicarbonate under aqueous, basic conditions to give the monoprotected Apc **6**. Alternatively, **6** could be obtained by initial cyclization under basic conditions to yield **7** followed by protection of the amino group with di-*tert*-butyl dicarbonate and acidic saponification of the methyl ester. The resulting two isomers of Boc-Apc **6** were converted to the cis- or the trans isomer of Boc-Apc benzyl ester **8**, using either DCC and benzyl alcohol or *N*,*N*′-diisopropyl-*O*-benzylisourea as esterifying reagents. Also, the syntheses of the *p*-nitrophenyl **9t/c** ester isomers of Boc-Apc were performed using DCC coupling following literature methods.[52]

Synthesis of Active Dimer (Scheme 2**).** The benzyl esters **8t/c** were used as the building blocks to synthesize the activated dimers. *N*-*t*Boc-Apc-O−Bz **8t/c** was deprotected with TFA to give amino-Apc-O−Bz **10t/c**. The condensation of the free carboxylic acid group of *t*Boc-Apc **6t/c** with HN2-Apc-O-Bz **10t/c** gave the expected dimers. After removal of the benzyl group from these dimers under hydrogenation conditions, the different isomers of *t*Boc-Apc-Apc-OH **12** were obtained in good yield. Active ester formation of *t*Boc-Apc-Apc-OH with *p*-nitrophenyl and DCC gave the protected activated dimers **13**.

Table 1. ^{1}H Chemical Shifts and ^{1}H−^{1}H Coupling Constants of 6t and 6c[a]

proton H	coupled to proton H′	**6t** (DMSO-d_6) δ_H	**6t** (DMSO-d_6) J(HH′)	**6c** (DMSO-d_6) δ_H	**6c** (DMSO-d_6) J(HH′)	**6c** ($CDCl_3$) δ_H	**6c** ($CDCl_3$) J(HH′)
1	2	7.50	<2	7.50	3.	8.27	<2
5		3.75		3.85		4.18	
7	5	6.90	8.2	6.90	8.4	5.50	<2
4a	5	1.70	9.3	1.70	12.0	1.58	*b*
4e	5	1.88	6.0	1.88	6.0	2.45	*b*
3a	2	2.15	9.2	2.06	5.6	2.03	9.8
3e	2	1.70	5.6	2.06	3.0	2.30	5.0
2		3.90		3.91		4.13	

[a] All chemical shifts in ppm and coupling constants in Hz. [b] This value was not obtained in the first-order analysis.

Oligomerizations (Scheme 4). Removal of the *t*Boc group from the activated Apc monomers **9** or dimers **13** and exposure of the resulting TFA salt of Apc-Apc-OX (X = *p*-nitrophenyl) to 1.5 equiv of triethylamine in DMF or DMSO gave oligomeric products in acceptable yield. The ^{1}H NMR spectra indicated the presence of oligomeric species by the occurrence of peaks due to the end groups. Only broad peaks appeared with two bands for the lactam amide protons and the inter-ring amides in the dimers. The spectrum of the trans oligomer prepared by reaction of the activated **9a** (trans) was essentially identical to that of the trans−trans oligomer prepared from **12a**. The spectra of the various oligomers differed primarily in the CH and methylene regions.

Summary of Syntheses of Monomers, Dimers, and Oligomers. Neither hydrolytic nor anionic polymerization of 2,5-DBO could be achieved. Its insolubility and nonmelting behavior contributed to the difficulty of polymerization. The fewer eclipsed H−H interactions compared to those in the previously studied bicyclic lactam 2-azabicyclo[2.2.2]octan-3-one may be responsible. Also, in 2,5-DBO the amide dipoles are paired and "neutralize" each other. This raised the question of whether the isomeric 2,6-DBO, wherein the dipoles repel each other, would polymerize.

We were unable to find unsubstituted 2,6-DBO in the literature but were successful in repeating a literature procedure of 1-methyl-2,6-DBO. However, 1-methyl-2,6-DBO showed no signs of polymerization under hydrolytic or anionic polymerization conditions. Even a single methyl group in cyclic monomers strongly favors cyclization[56,57] and disfavors polymerization by the *gem*-dimethyl effect.[58]

We tried a number of times to synthesize the unsubstituted 2,6-DBO. The replacement of methyl vinyl ketone by acrolein, as well as alternative routes, led only to linear oligomers instead of bicyclic 2,6-DBO. Polymer is formed in preference to monomer for unsubstituted 2,6-DBO. These results suggest that this unsubstituted monomer is polymerizable, owing to dipole−dipole repulsion.

Condensation Polymerization Studies (Scheme 4). On the basis of our unsuccessful attempts to use ring-opening polymerization to obtain polyamides, recourse was had to polycondensation of activated intermediates. The *cis*- and *trans*-3-amino-6-activated esters (Apc's) were synthesized. The cis isomer gave only 2,5-DBO.

Table 2. Comparisons of ^3J(H−H′) for the Energy-Optimized Structures with the Experimental Data for the *cis*- and *trans*-Apc Isomers[a]

					expt (**6c**)	
	6′c1	**6′c2**	**6′c3**	**6′c4**	DMSO	$CDCl_3$
ΔE, kcal mol^{-1}	0.15	1.11	3.37	6.09		
J(H1−H2)	3.1 (−56.3)	1.7 (−84.4)	4.8 (−39.8)	3.7 (116.5)	3.0	<2
J(H5−H4a)	12.8 (175.7)	6.5 (37.6)	4.0 (55.1)	12.0 (163.2)	12.0	
J(H5−H4e)	3.4 (−59.6)	1.8 (−79.2)	3.3 (−60.5)	4.9 (48.8)	6.0	
J(H2−H3a)	5.5 (−44.6)	12.6 (170.0)	2.2 (97.8)	12.5 (168.8)	5.6	9.8
J(H2−H3e)	2.2 (−72.2)	4.4 (52.1)	8.8 (−17.8)	4.2 (52.8)	3.0	5.0
J(H5−H7a)	1.7 (80.4)	3.8 (49.3)	2.7 (63.5)	3.0 (57.2)		
J(H5−H7b)	5.1 (−37.0)	2.3 (−66.5)	3.3 (−54.2)	9.8 (169.1)		

	6′t1	**6′t2**	**6′t3**	exp (**6t** in DMSO)
ΔE, kcal mol^{-1}	0.00	1.36	4.75	
J(H1−H2)	2.0 (−71.3)	4.1 (46.6)	1.7 (83.8)	<2
J(H5−H4a)	12.8 (174.9)	6.1 (40.0)	12.7 (−171.6)	9.3
J(H5−H4e)	3.5 (58.7)	1.9 (−76.7)	4.0 (−54.8)	6.0
J(H2−H3a)	12.4 (167.4)	5.3 (46.0)	12.4 (−167.9)	9.2
J(H2−H3e)	4.5 (51.2)	2.2 (−72.3)	4.7 (−49.8)	5.6
J(H5−H7a)	5.0 (−37.8)	3.6 (51.3)	10.1 (179.4)	8.2
J(H5−H7b)	1.7 (79.3)	2. 4 (−64.3), 2.3 (−66.6)		

[a] Coupling constants are given in Hz. Energies ΔE in kcal mol^{-1} relative to lowest energy structure (**6′t1**) −569.644 763 9 hartrees at the B3PW91/6-31G* level. Dihedral angles are given in parentheses. The H−H coupling constants were computed from the dihedral angles using eq 1a or 1b, as appropriate.

The trans isomer gave insoluble stereoregular oligomer. The four stereoisomeric activated dimers of Apc were synthesized by coupling the individual blocked Apc components in each of the four possible combinations. The trans−trans dimer gave only crystalline, insoluble oligomeric material, identical to those from the trans monomer. These dimers gave identical oligomers possessing the alternating cis−trans structure. The cis−cis dimer gave no oligomer and appeared to form the macrocyclic dimer.

II. NMR Studies of the Solution Structures of Monomers, Dimers, and Oligomers. The ^{1}H NMR spectra of the monomeric *cis*- and *trans*-Apc **6c** and **6t** were examined to gain information about the ring conformations of the dimers and oligomers. In Table 1 are entered the ^{1}H chemical shifts and $^3J_{HH}$ for **6t** and **6c**. The spectral complexity of the NMR signals in the $-CH_2-CH_2-$ moiety precluded full spectral analysis: only coupling constants associated with protons H2 and H5 were estimated in the first-order analyses. The NMR spectra for both isomers were measured in DMSO-d_6. In Table 1 the spectral data for **6c** dissolved in $CDCl_3$ are substantially different than in DMSO-d_6. The *cis*- and *trans*-Apc's (in the *N*-*t*Boc protected, free acid forms) are flexible molecules with solvent-dependent conformations. In this connection, it was of interest to use the known dependencies of coupling constants on dihedral angles to infer the solution conformations of these species. An initial survey via molecular mechanics simulations[59,60] found four conformations for each of the *cis*- and *trans*-Apc isomers **6t** and **6c**. Since the *N*-*t*Boc protecting group was not included in any of the computations described here, the structures are designated **6′t** and **6′c**. For both cis and trans isomers the two lowest and the two highest energy conformations are pseudo-chair and pseudo-boat, respectively. In the *cis*-Apc pseudo-chair conformations (**6′c1** and **6′c2**) one substituent is axial and other is equatorial, while the *trans*-Apc conformations of lowest energy (**6′t1** and **6′t2**) have both substituents equatorial or both axial. All conformations were fully optimized at the B3PW91/6-31G* level (split valence shell with polarization functions on non-hydrogen atoms) of density functional theory (DFT)[61−63] using the Gaussian94 suite of programs.[64] At this computational level one of the high-energy boat-type structures for the *trans*-Apc did not converge, and the energy ordering was reversed for the two low-energy cis conformations **6′c1** and **6′c2**. Entered in Table 2 are the computed energies ΔE (in kcal mol^{-1} relative to **6′t1**) and dihedral angles ϕ (in parentheses) for each of the optimized structures. The vicinal H−N−C−H coupling constants in Table 2 were obtained from the dihedral angles of the optimized structure using the empirical equations of Wang and Bax,[65]

$$^3J(\mathrm{H-N-C-H}) = 6.98\cos^2\phi - 1.38\cos\phi + 1.72\ \mathrm{Hz} \quad (1a)$$

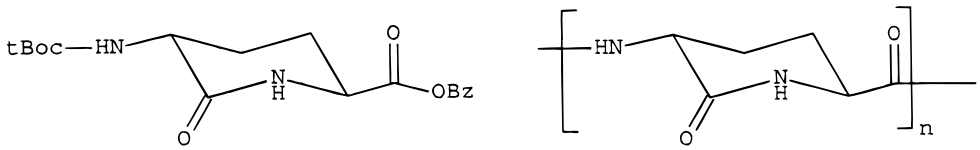
and the H−C−C−H coupling constants were obtained from the equation proposed by DeMarco et al.[66] to describe coupling constants in the side chains of amino acids and peptides,

$$^3J(\mathrm{H-C-C-H}) = 9.5\cos^2\phi - 1.6\cos\phi + 1.8\ \mathrm{Hz} \quad (1b)$$

In Table 2 the experimental coupling constant data for the cis isomer in DMSO-d_6 are in best agreement with the estimated ones for the lowest energy conformation **6c1**. The NMR data are scant for the cis isomer dissolved in chloroform-*d*, but the results in Table 2 imply that the **6c2** conformation must be an important contributor. Comparisons of the *trans*-Apc coupling constants with those for the optimized structures indicate that the lowest energy conformation **6t1** must be an important factor for the average structure in DMSO-d_6.

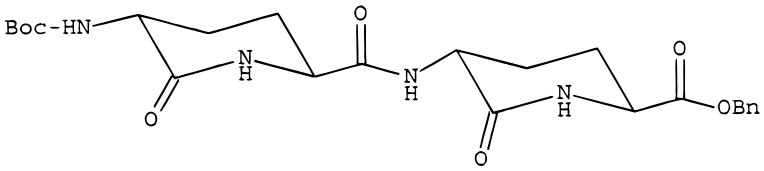
The ^{1}H chemical shifts and vicinal coupling constants for the four dimers **11tt**, **11tc 11ct**, and **11cc** (Scheme 5) from one- and two-dimensional ^{1}H NMR spectra are collected in Table 3. The spectra were recorded at 500 MHz to gather information about the dimer solution structures. Except for the cis−trans isomer which, for solubility reasons, was measured in $CDCl_3$, the solvent was DMSO-d_6. Because of the large number of isomers, no attempt was made at computational investigation of

Scheme 5

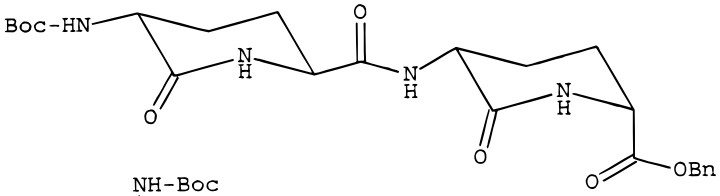


DIMERS:

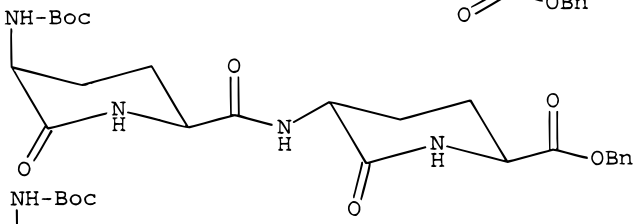
trans-trans **11tt**



trans-cis **11tc**



cis-trans **11tc**



cis-cis **11cc**

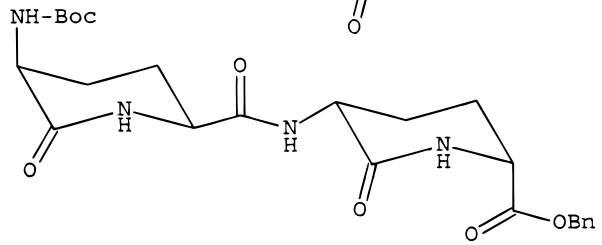


Table 3. ^{1}H Chemical Shifts and ^{1}H−^{1}H Coupling Constants of 11 tt, tc, ct, and cc Dimers (Scheme 5)[a]

proton H	coupled to proton H′	**11tt** (DMSO-d_6) δ_H	**11tt** (DMSO-d_6) J(HH′)	**11tc** (DMSO-d_6) δ_H	**11tc** (DMSO-d_6) J(HH′)	**11ct** ($CDCl_3$) δ_H	**11ct** ($CDCl_3$) J(H−H′)	**11cc** (DMSO-d_6) δ_H[b]	**11cc** (DMSO-d_6) J(HH′)[b]
1	2	7.73	2.1	7.86	2.0	7.51	2.7	7.82 (7.77)	4.1 (2.4)
7	5	8.15	8.0	8.00	8.0	7.96	8.2	8.19 (8.08)	8.1 (8.1)
5	4a	4.10	10.2	4.17	10.3	4.54	11.5	4.25	11.3
	4e		6.2		5.8		6.3		5.8
2	3a	4.10	8.7	4.14	5.9	4.17	4.6	4.13	
	3e		7.3		3.1		5.4		3.6
4a		2.15		1.70		1.69		1.58	
4e		1.75		1.90		2.10		1.90	
3a		1.95		1.77		2.19		2.16	
3e		1.75		2.14		2.18		2.05	
1′	2′	7.55	2.1	7.81	3.8	7.60	1.9	7.51	<2 (2.7)
7′	5′	6.88	8.0	6.80	8.4	5.64	6.4	6.82	8.4
5′	4a′	3.85		3.80	11.0	4.02		3.81	5
	4e′				6.3				
2′	3a′	3.80	8.8	3.80	6.1	4.09	9.9	3.85	6.0
	3e′		5.8		3.1		5.6		4.7
4a′		1.95		1.70		1.70		1.80	
4e′		1.65		1.77		1.88		1.90	
3a′		2.07		1.95		2.15		1.68	
3e′		1.65		1.95		1.70		1.90	

[a] All chemical shifts in ppm and coupling constants in Hz. Primes are used to denote the protons in the second ring. Amide protons outside the ring are designated H7 and H7′. [b] Values in parentheses apply to those cases in which diastereomer 2 differs from 1.

the conformational space. However, comparisons of the dimer coupling constant data in Table 3 with the monomer data in Tables 1 and 2 suggest that the lower energy pseudo-chair conformations of the lactam rings are also predominant in the dimers. The use of two-dimensional NMR NOE methods (e.g., ROESY) gave no

evidence of β-turn formation in DMSO-d_6, even though these might have been expected for the cis−cis and trans−cis dimers. This absence may be due to steric crowding associated with the bulky *tert*-butyl group.

The ^{1}H NMR spectra of the polymers prepared from the various dimers were different. These were also examined at 500 MHz in DMSO-d_6 solution using the ROESY technique to find evidence for the formation of intramolecular hydrogen bonds or evidence of folding. Again, in no case was there evidence of β-turn formation, probably due to the steric constraints of the rings.

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