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Formation of Oligomeric and Macrocyclic Ureas Based on 2,6-Diaminopyridine

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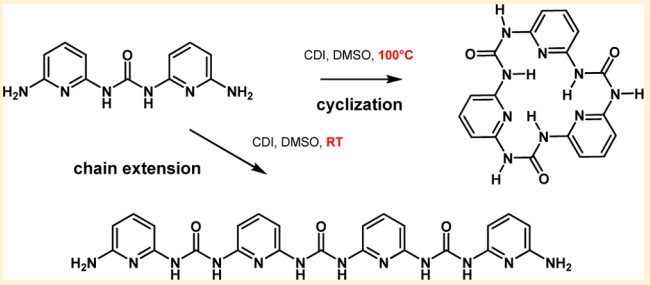
Supporting Information

ABSTRACT: The conversion of 1,3-bis-(6-amino-pyridin-2-yl)-urea (**1**) with *N*,*N*′-carbonyldiimidazole at high temperatures in DMSO yielded a mixture of defined cyclic trimers and tetramers. On the basis of model reactions, exchange reactions were evidenced, which convert the cyclic tetramer into a stable cyclic trimer. Linear even numbered oligomers were obtained in acetone under reflux where side reactions were suppressed. The pronounced tendency of cyclization is attributed to a preferred folded conformation of the urea bond between two pyridyl units.



INTRODUCTION

In the past decade, great interest has been shown in the design and development of foldamers, synthetic oligomers with a defined conformational backbone structure.[1] Induced noncovalent forces, for example, hydrogen bonds, can cause foldamers to form specific secondary structure elements such as helices, sheets, and turns.

Among hydrogen-bonded aromatic oligomers, oligoamides have been the most studied class of unnatural foldamers.[2−5] Huc et al.[6−13] examined oligopyridine-dicarboxamide strands folding into helices in appropriate solvents. This conformation is caused by a hydrogen-bond-induced folding. Furthermore, the influence of the oligomer length[7] and the role of side chains[6,13] on the dimerization constant of the hybridization into double helical dimers were studied. A new class of aromatic oligoamides based on phenanthroline dicarboxamides and the linkers diaminoanthraquinones was published by Hu and coworkers.[14−16] These oligoamides adopt well-defined helical structures in solution and in the solid state. Conformational investigations lead to the conclusion that the aromatic linkers can control the relative orientation of the helical oligomers.

As another class of aromatic foldamers, heterocyclic ureas were described, for example, by Zimmermann et al.[17−21] They synthesized a series of folded, intramolecularly hydrogen-bonded ureas such as *N*,*N*′-di-2-pyridylurea and their corresponding unfolded, multiple hydrogen-bonded complexes. The latter can be achieved in the presence of a suitable hydrogen-bonding complement, such as naphthyridyl templates. Xing et al.[22] examined the preparation and characterization of naphthyridine and pyridazine containing macrocycles connected via urea linkages. They found that these materials formed closed cyclic structures rather than oligomers by intramolecular hydrogen bonding.

The approach described here is based on our earlier study[23] dealing with the synthesis of polymeric and macrocyclic ureas based on aromatic diamines. It could be shown that the conversion of 2,6-diaminopyridine with *N*,*N*′-carbonyldiimidazole did not result in the formation of polyurea as initially expected but quantitatively in the formation of cyclic structures (see Scheme 1).

The reason for the pronounced tendency of cyclization is the folded conformation of the urea linkage between two 2,6-substituted pyridine rings. From NMR and MALDI-TOF-MS studies, it could be concluded that the main reaction product is a mixture of two cyclic trimers (**M2**, **M3**). Additionally, small amounts of a cyclic tetramer (**M1**) were found. The assumed structures of the trimers are shown in Scheme 2.

In this Article, we describe our efforts to overcome these ring formations to get open-chain aromatic polyureas, which are assumed to form helical structures. Provided the urea groups in the open-chain oligomers adopt the same conformation as in the trimers, the first winding of a helix should already be observed in an open tetramer with overlapping terminal groups as shown in Scheme 3. The structure shown in the scheme is based on ab initio energy optimizations as described in the Experimental Section.

Our concept in preventing cyclization is based on the assumption that the use of dimer **1** instead of 2,6-diaminopyridine as starting monomer will result in the formation of open-chain oligomers because the main reaction product at the beginning of the expected step growth reaction was assumed to be an open tetramer. Provided that no exchange reactions or other side reactions occur, the formation of cyclic trimers should be prevented in this way.

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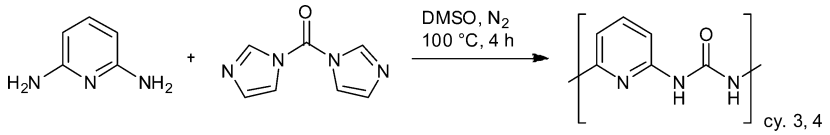
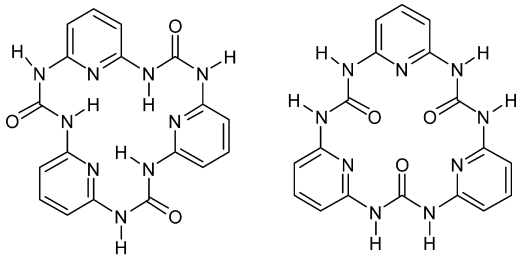
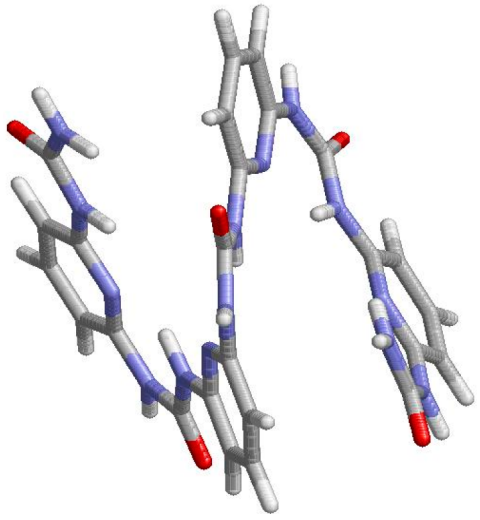
Scheme 1. Conversion of 2,6-Diaminopyridine with *N,N′*-Carbonyldiimidazole



Scheme 2. Possible Structures of the Cyclic Trimer



Scheme 3. Helical Structure of an Open Tetramer Based on Ab Initio Energy Optimization As Described in the Experimental Section



In this Article, we show that ring formation is very pronounced even if dimer **1** is used as starting monomer. This allows some conclusions concerning the mechanism of the reaction used here. It will be shown that open-chain oligomers are only available at low temperature where side and exchange reactions become less dominant.

RESULTS AND DISCUSSION

With the aim to prevent the formation of trimers, dimer **1** and *N,N′*-carbonyldiimidazole were converted at 100 °C in DMSO. These are exactly the same reaction conditions as were used earlier for the conversion of 2,6-diaminopyridine.[23] Surprisingly, the ^{1}H NMR spectra of the reaction products based on dimer **1** (see Figure 1) and 2,6-diaminopyridine,[23] respectively, do not differ strongly from each other. Three doublet signals at 7.22, 7.26, and 7.46 ppm and a signal group of three overlapping triplets centered at 8.29 ppm can be assigned to the protons of pyridine rings. From NMR and MALDI-TOF-MS studies, the existence of a mixture of three different cyclic compounds was concluded. The signal b1 at 7.21 ppm was assigned to a cyclic tetramer (**M1**), whereas the signals b2 at

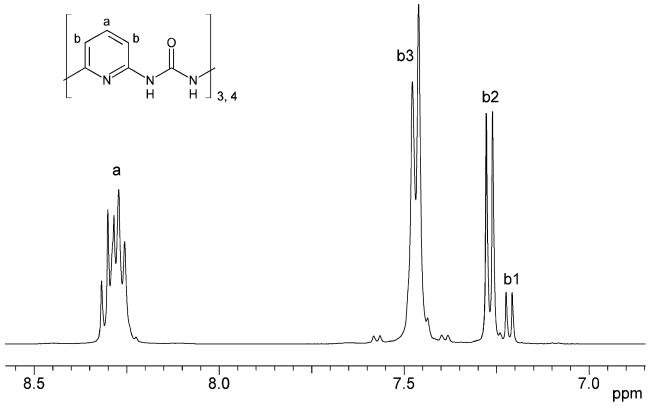


Figure 1. ^{1}H NMR spectrum of the products formed in the reaction of dimer **1** and *N,N′*-carbonyldiimidazole (solvent: TFA-*d*). NH protons cannot be observed due to fast exchange with *d* of TFA-*d*.

7.26 ppm and b3 at 7.46 ppm were assigned to the cyclic trimers **M2** and **M3**, respectively. The latter has proved to be insoluble in DMSO, whereas **M2** was slightly soluble.[23] Further small signals indicate the presence of open-chain oligomers, which, however, appear only in traces.

Isolation of **M1** from the mixture made it possible to conclude its structure from NMR spectroscopic measurements. Absence of end group signals in the ^{1}H NMR spectrum (Figure 2) points to a cyclic structure, which was identified as a

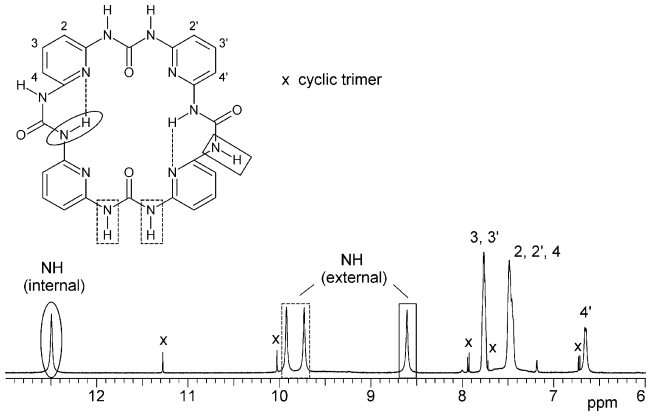


Figure 2. ^{1}H NMR spectrum of the cyclic tetramer **M1** containing 3 mol % of the cyclic trimer **M2** (solvent: DMSO-d_6). The bond angles around carbon 5 are 120° but are distorted in the drawing.

tetramer by MS spectrometry (molecular ion peak for MH^+: m/z = 541.3). Four NH signals of same intensity indicate a 2-fold rotational axis. Furthermore, the significantly low-field shifted signal at 12.50 ppm showing no concentration dependency is characteristic for intramolecular hydrogen bonds formed by two of the eight urea protons. Thus, the structure given in Figure 2 is in accordance with the experimental findings. Interestingly, the spectrum taken at 120 °C (not depicted) shows extreme exchange broadening for all NH signals, whereas for the planar

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cyclic trimer **M2**, narrow signals for internal and external NH protons were observed at this temperature.[23] Moreover, the residual water in the solvent is not involved in the exchange process, that is, no fast proton exchange, but conformational exchange causes NH signal broadening. This is the reason for the assumption that the cyclic tetramer **M1** has lower conformational rigidity, most probably because of a nonplanar crown-like structure.

The identified reaction products of the reaction of dimer **1** and *N,N′*-carbonyldiimidazole at 100 °C in DMSO show that the use of dimer **1** as starting monomer did not result in the formation of the desired open-chain oligomers under these conditions. Instead, cyclic trimers were obtained as the major product as already observed in the direct reaction of 2,6-diaminopyridine.

To gain deeper insight into this pronounced cyclization reaction, the influence of temperature on the formation of **M1**, **M2**, and **M3** was investigated. For this, conversions of 2,6-diaminopyridine and dimer **1** with *N,N′*-carbonyldiimidazole in DMSO were carried out at different temperatures between 80 and 180 °C. The outcomes are shown in Figure 3 for dimer **1** and in Figure 4 for 2,6-diaminopyridine (see also Tables 1 and 2).

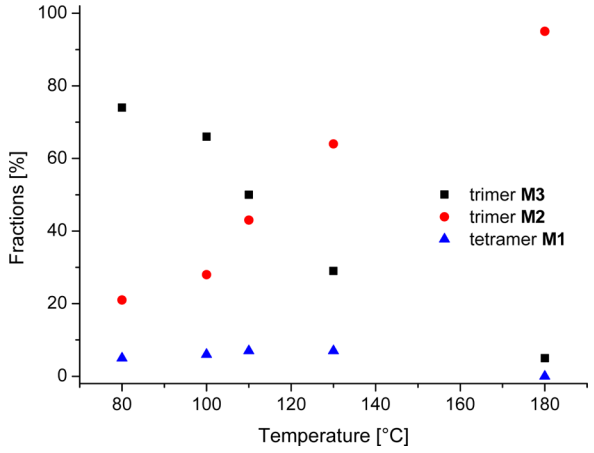

Figure 3. Conversion of dimer **1** with *N,N′*-carbonyldiimidazole at different temperatures—composition of the reaction product.

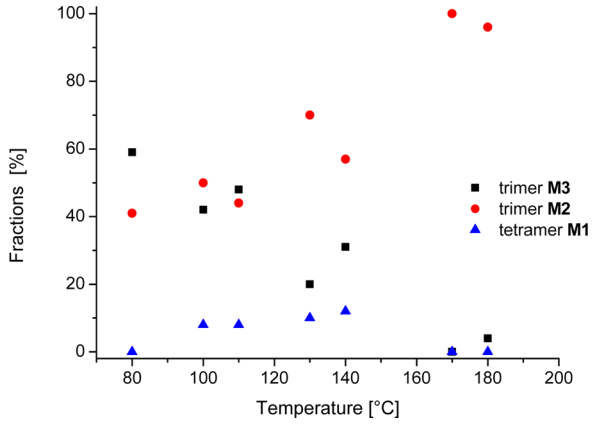

Figure 4. Conversion of 2,6-diaminopyridine with *N,N′*-carbonyldiimidazole at different temperatures—composition of the reaction product.

Table 1. Fractions of Cycles in the Reaction Product of the Conversion of Dimer 1 with CDI in DMSO

sample	temperature [°C]	insoluble trimer (**M3**) [%]	soluble trimer (**M2**) [%]	tetramer (**M1**) [%]	yield [%]
R1	80	74	21	5	96
R2	100	66	28	6	68
R3	110	50	43	7	97
R4	130	29	64	7	61
R5	180	5	95		76

Table 2. Fractions of Cycles in the Reaction Product of the Conversion of 2,6-Diaminopyridine with CDI in DMSO

sample	temperature [°C]	insoluble trimer (**M3**) [%]	soluble trimer (**M2**) [%]	tetramer (**M1**) [%]	yield [%]
R6	80	59	41	0	69
R7	100	42	50	8	98
R8	110	48	44	8	79
R9	130	20	70	10	
R10	140	31	57	12	83
R11	170		100		40
R12	180	4	96		64
R13[a]	180	0	100		
R14[b]	56		traces		

[a]Sample **R8** heated in DMSO for 8 h at 180 °C. [b]Synthesized in acetone under reflux. Beside traces of **M2**, the sample contains open-chain oligomers.

Regarding the reaction of 2,6-diaminopyridine, one can see that at 80 °C the insoluble trimer **M3** is preferably formed. Its fraction tends to decrease with increasing temperatures. At about 170 °C, the formation of the soluble trimer **M2** becomes predominant, whereas **M3** only appears in traces. In the intermediate temperature range, small amounts (8−12 mol %) of the cyclic tetramer **M1** are formed. The same tendency was found in the reaction of dimer **1** (see Figure 3). Also here, the soluble trimer **M2** is primarily formed at higher reaction temperatures. In contrast to the reaction of 2,6-diaminopyridine, the reaction of dimer **1** resulted already at 80 °C in the formation of cyclic tetramers (5 mol %).

To investigate whether the isomers **M2** and **M3** are convertible in each other, a mixture of **M1**, **M2**, and **M3** (**R8**) was heated in DMSO for 8 h at 180 °C. After this treatment, only **M2** was found (**R13**). From this, one can conclude that apart from conformational changes (**M3** → **M2**), also exchange reactions must occur, which convert the cyclic tetramer into the cyclic trimer (**M1** → **M2**). Obviously, **M2** is thermodynamically the most stable conformation.

The fact that cyclic trimers are formed even if dimer **1** was used as starting monomer gives rise to the assumption that side or exchange reactions similar to transesterification and transamidation between at least two dimers must occur. Otherwise, the formation of cyclic trimers cannot be explained. It is conceivable that exchange reactions may take place between the urea and the NH_2-groups of the dimer. Further experiments were done to clarify this possibility.

To figure out whether exchange reactions take place between two urea groups, the two linear urea compounds **2** and **3** without amino groups were heated in DMSO at 180 °C for 8 h (see Scheme 4). ^{1}H NMR spectroscopic investigations revealed that under these experimental conditions no mixed ureas were

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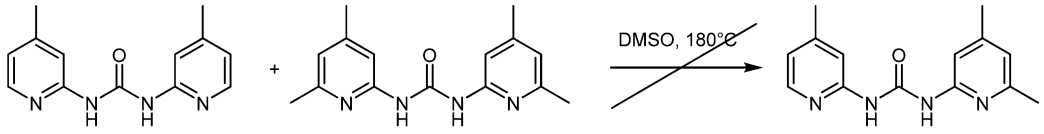
Scheme 4. Test of Probable Exchange Reactions between Model Compounds 2 and 3



2 3

formed. This is in contrast to the above observation that a cyclic tetramer turns into a cyclic trimer provided the temperature is high enough (180 °C). In our opinion, conformational stress in the tetramer or traces of unreacted amino groups may facilitate this process.

To explore the role of amino groups in these exchange reactions, compound **2** was heated together with 2,6-diaminopyridine. Experiments carried out at 100, 120, and 180 °C revealed that insertion reactions took place. Apart from 2-amino-4-picoline, different mixed ureas were found. Hence, the free amino groups of 2,6-diaminopyridine exert an important influence on exchange reactions, leading finally to the formation of cyclic trimers. To confirm this, dimer **1** was heated at different temperatures. After 4 h heating at 120 °C in DMSO, precipitation was observed, which has proved to be trimer **M2**. Figure 5 shows the ^{1}H NMR spectrum of the soluble part of the sample. Apart from the signals of unconverted dimer **1**, distinct signals of 2,6-diaminopyridine are visible. Additionally, small signals of linear trimers and tetramers can be identified. The signal assignment of the linear trimers and tetramers is given in the Experimental Section.

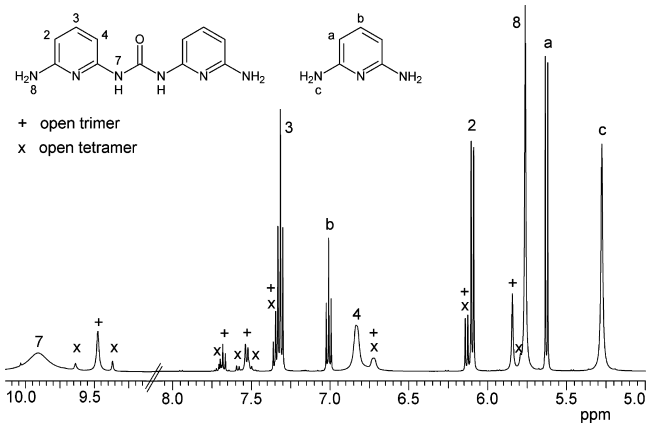


Figure 5. ^{1}H NMR spectrum of dimer **1** after 4 h heating at 120 °C in DMSO (DMSO soluble part). Solvent: DMSO-d_6.

Obviously, the dimer does not require *N*,*N*′-carbonyldiimidazole to form cyclic structures. It is very likely that an exchange reaction between an amino group of one dimer molecule and the urea group of another dimer molecule takes place, resulting in the formation of one monomer and one open trimer. In the same manner, an open tetramer can be formed, which after intramolecular cyclization forms a cyclic trimer. The assumed helical conformation of an open tetramer (see Scheme 3) would support intramolecular cyclization because the amino group of an open tetramer is located in close proximity to one urea group of the same molecule.

At lower temperatures (100 °C), these exchange reactions become less significant. After heating at 100 °C, only small amounts of linear trimers and tetramers were found. Cyclic trimer did not precipitate. In contrast, heating at 180 °C resulted in the formation of the cyclic trimer to a great extent.

These investigations show that exchange reactions between amino and urea groups generally may contribute to the formation of cyclic trimers when the reaction is started from dimer **1**. However, the extent of these reactions is too low to explain the strong tendency of trimer formation during the conversion of **1** with CDI. As shown in Table 1, the cyclization yields are generally high even at 80 °C where exchange reactions become less significant. It is reasonable to assume that additional side reactions during the conversion of dimer **1** with *N*,*N*′-carbonyldiimidazole are responsible for the formation of cyclic trimers. An explanation delivers the observation of Staab and Benz.[24] The authors describe dissociation of imidazole-1-carboxyamides into isocyanate and imidazole in solution at room temperature. In our system, imidazole-1-carboxyamide **4** should be formed as intermediate by the reaction of *N*,*N*′-carbonyldiimidazole with one amino group of dimer **1** (see Scheme 5). Hence, isocyanates (e.g., **5**) should also appear temporarily. Isocyanates are known to react with ureas to form buirets (e.g., **6**).[25] At elevated temperatures, biurets are metastable and decompose to urea and isocyanate.[25] During these reactions, an exchange of the NH-substituents on the urea is possible. In our system, this exchange reactions should yield the open trimer **7** and 6-isocyanatopyridin-2-amine (**8**), which after reaction with dimer **1** may also form a linear trimer. The latter is the immediate precursor of the cyclic trimers found in our system.

Our results clearly show that side reactions occurring in DMSO at elevated temperatures prevent the formation of open-chain structures. To suppress side reactions, different solvents were used and the reaction temperature was decreased. In one example, the reaction of dimer **1** and *N*,*N*′-carbonyldiimidazole was performed in acetone under reflux (4 h, 56 °C). The ^{1}H NMR (DMSO-d_6) spectrum of the reaction product (**R14**, spectrum not depicted) shows small signals of the cyclic trimer (11.28, 10.03, 7.93, 6.72 ppm). The major product, however, was the linear tetramer. Additional signals in this range indicate that higher oligomers might be present in the mixture. The final confirmation for the existence of linear oligomers is provided by MALDI-TOF MS measurements.

Figure 6 shows the MALDI-TOF spectrum of the above sample **R14**. In the range between 500 and 600 Da (see Figure 6a), distinct signals of the protonated linear tetramer at 515 Da as well as of its sodium and potassium ions at 537 and 553 Da, respectively, can be seen. Respective signals of the cyclic tetramer are visible at 541, 563, and 579 Da, however, in much lower intensity. The spectrum above 600 Da (see Figure 6b) is dominated by signals of even-numbered linear oligomers up to the dodecamer. Further small signals indicate small amounts of the linear pentamer as well as of cyclic penta- and hexamers. These results confirm that at lower reaction temperatures, step growth polymerization of dimer **1** becomes predominant. Cyclization and exchange reactions cannot completely be

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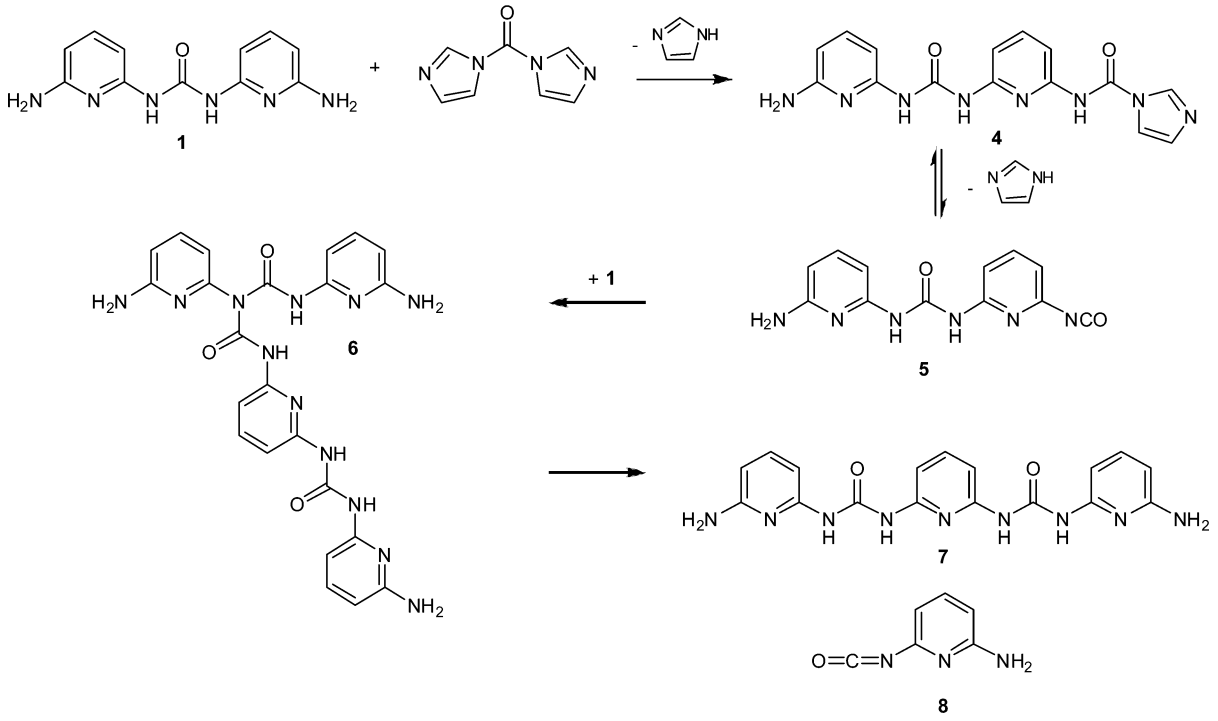
Scheme 5. Interchange Reactions at Higher Temperatures



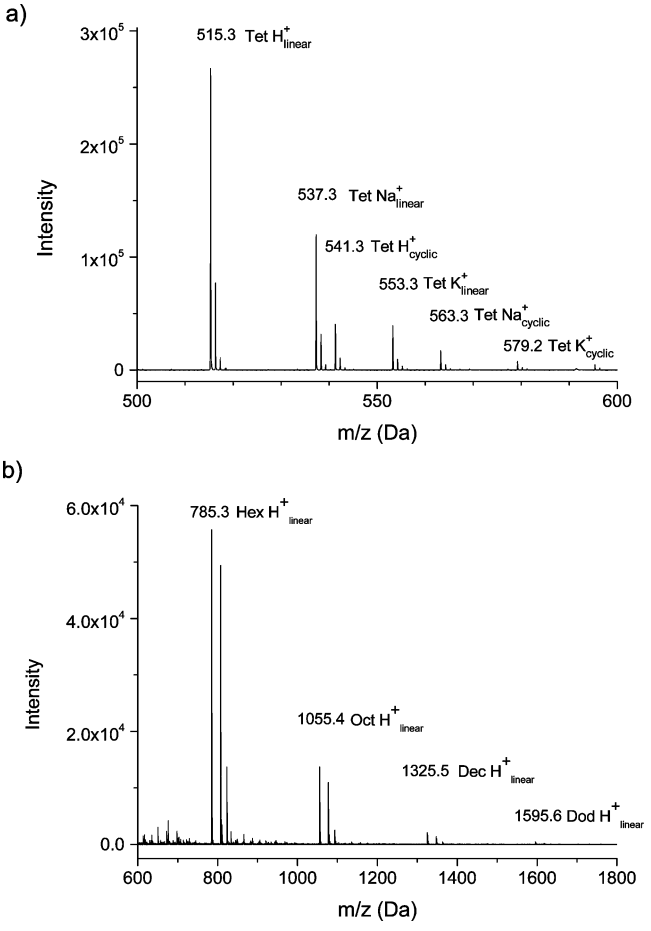


Figure 6. MALDI-TOF spectrum of **R14** (sample synthesized in acetone under reflux) (a) from 500 to 600 D and (b) from 600 to 1800 D (with stretched axis of abscissae).

prevented but are only of minor importance. As a consequence, the resulting product is a mixture consisting primarily of even-numbered linear oligomers.

Further decrease in the reaction temperature prevents side reactions almost completely, but decreases the reaction rate in an unacceptable manner. At ambient temperature, noticeable conversions are only obtained after weeks. Such samples usually contain relatively high amounts of linear tetramer as compared to the amount of higher oligomers. From a sample synthesized in THF at ambient temperatures (28 d), we tried to isolate the linear tetramer utilizing differences in solubility. A mixture (**R15**) with a high content of tetramer and small amounts of dimer **1** was obtained, the ^{1}H NMR spectrum of which is shown in Figure 7. Further enrichment of the sample failed, most probably because of strong interactions between the dimer and the tetramer.

■ CONCLUSION

The reaction of 1,3-bis-(6-amino-pyridin-2-yl)-urea (**1**) with CDI in DMSO at temperatures higher than 80 °C resulted primarily in the formation of cyclic trimers and tetramers. This contradicts the expectation that in the case of a step-grow mechanism even-numbered linear oligomers should be formed. Model reactions showed that at higher temperatures exchange reactions occur that destroy the initial double sequence of the starting monomer **1**. These exchange reactions include reactions of the amino groups and most probably also of intermediately formed isocyanates with the urea bond. At 180 °C, exchange reactions convert the cyclic tetramer completely into the structurally preferred planar cyclic trimer. The urea groups of the letter adopt a folded conformation, which is assumed to be the main reason for the pronounced tendency of cyclization. The extent of exchange reactions in this system was unexpected. Further exploration thereto may lead to the establishment of an interesting dynamic covalent system.

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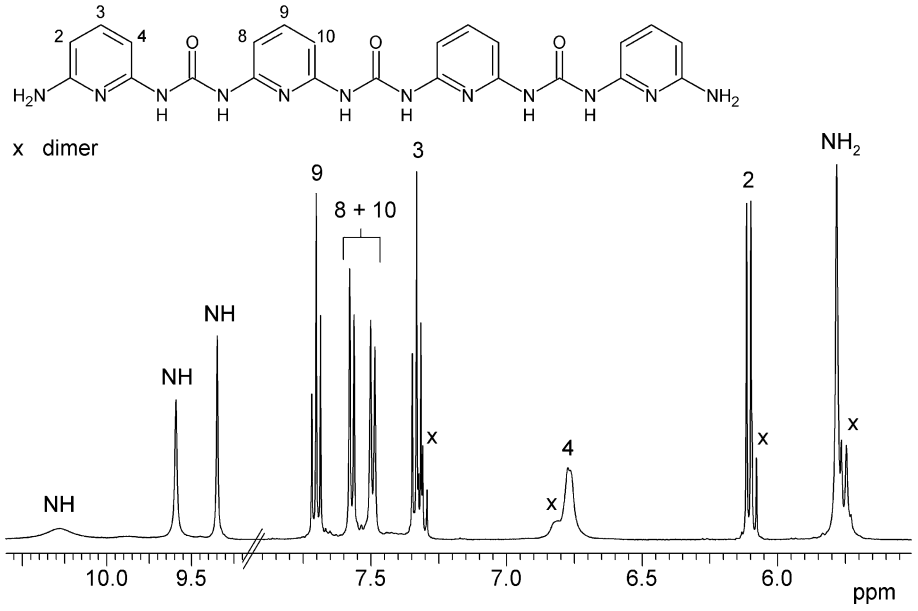
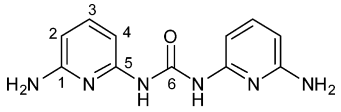


Figure 7. ^{1}H NMR spectrum of the linear tetramer (solvent: DMSO-d_6).

At lower temperature and in less polar solvents, exchange reactions are distinctly reduced. The reaction in acetone under reflux (56 °C) rendered primarily even-numbered linear oligomers, albeit the yield was relatively low. Beside the linear tetramer as the major component, linear oligomers up to the dodecamer were evidenced. We regard the linear tetramer as a potential building block for polymers with structure variable chain segments. We intend to spend more time on its separation and utilization in polymer synthesis.

EXPERIMENTAL SECTION

1,3-Bis-(6-amino-pyridin-2-yl)-urea 1.

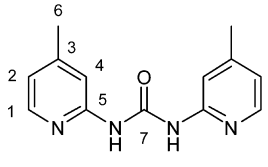


1

2,6-Diaminopyridine (15.0 g, 137.5 mmol) and *N*,*N*′-carbonyldiimidazole (CDI, 10.14 g, 62.5 mmol) were stirred in THF (230 mL) overnight at room temperature under a low nitrogen stream. The resulting precipitate was filtered off, washed with small amounts of THF, and dried under vacuum (at 40 °C). After recrystallization in THF, **1** was obtained as pale gray crystals. Yield: 6.4 g (42%).

^{1}H NMR (DMSO-d_6): δ (ppm) = 9.86 (br, 2H, NH), 7.31 (t, 2H, H_3), 6.82 (d, 2H, H_4), 6.08 (d, 2H, H_2), 5.74 (s, 4H, NH_2). ^{13}C NMR (DMSO-d_6): δ (ppm) = 158.1 (C_1), 151.8 (C_6), 151.1 (C_5), 139.09 (C_3), 101.6 (C_2), 99.33 (C_4). Anal. Calcd for $C_{11}H_{12}N_6O$: C, 54.09; H, 4.95; N, 34.41. Found: C, 53.87; H, 5.06; N, 34.17. Mp 218 °C; solidification after melting; lit.[26] mp, no melting observed.

1,3-Bis-(4-methyl-pyridin-2-yl)-urea 2.

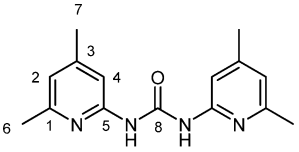


2

2-Amino-4-methylpyridine (0.79 g, 7.28 mmol) and CDI (0.54 g, 3.31 mmol) were dissolved in 21 mL of THF. The resulting reaction mixture was stirred at room temperature overnight under a nitrogen atmosphere. The precipitate was filtered off, washed with THF, and dried under vacuum (40 °C). White crystals were obtained. Yield: 0.52 g (59%).

^{1}H NMR (DMSO-d_6): δ (ppm) = 10.55 (br, 2H, NH), 8.14 (d, 2H, H_1), 7.53 (s, 2H, H_4), 6.89 (d, 2H, H_2), 2.31 (s, 6H, H_6). ^{13}C NMR (DMSO-d_6): δ (ppm) = 152.6 (C_5), 152.0 (C_7), 149.2 (C_3), 146.95 (C_1), 119.3 (C_2), 112.61 (C_4), 20.9 (C_6). Anal. Calcd for $C_{13}H_{14}N_4O$: C, 64.45; H, 5.82; N, 23.13. Found: C, 64.18; H, 5.85; N, 22.85. Mp 228 °C; lit.[27] mp 228 °C.

1,3-Bis-(4,6-dimethyl-pyridin-2-yl)-urea 3.



3

2-Amino-4,6-dimethylpyridine (0.50 g, 4.09 mmol) and CDI (0.30 g, 1.86 mmol) were stirred in 10 mL of THF at room temperature under nitrogen. After 4 h the precipitate was filtered off, washed with THF, and dried under vacuum (40 °C). White crystals were obtained. Yield: 0.28 (52.3%).

^{1}H NMR (DMSO-d_6): δ (ppm) = 10.40 (br, 2H, NH), 7.35 (s, 2H, H_4), 6.74 (s, 2H, H_2), 2.37 (s, 6H, H_6), 2.25 (s, 6H, H_7). ^{13}C NMR (DMSO-d_6): δ (ppm) = 155.5 (C_1), 152.0 (C_8), 149.3 (C_3), 118.3 (C_2), 109.5 (C_4), 23.6 (C_6), 20.8 (C_7). Anal. Calcd for $C_{15}H_{18}N_4O$: C, 66.64; H, 6.71; N, 20.73. Found: C, 66.66; H, 6.65; N, 20.68. Mp 242 °C; lit.[27] mp 240 °C.

Condensation Reactions. 2,6-Diaminopyridine or dimer **1**, respectively, was converted with CDI in DMSO at different temperatures (80−180 °C). The procedure is described exemplarily for the conversion of **1** at 80 °C: An excess of 10 mol % of CDI (1.43 g, 8.8 mmol) was added to a solution of **1** (1.95 g, 8 mmol) in 8 mL of DMSO. The reaction mixture was heated at 80 °C for 4 h under a low nitrogen stream. After being cooled to room temperature, the precipitate was filtered off, washed with DMSO, and dried under vacuum (80 °C, 8 h). A grayish powder-like solid was obtained, which does not melt up to 320 °C. Yield: 2.07 g (96%).

Mixtures of two cyclic trimers (**M2**, **M3**) and one cyclic tetramer (**M1**) were obtained. **M3** has proved to be insoluble in DMSO, whereas **M1** and **M2** were soluble. The whole reaction product was soluble in deuterated trifuoroacetic acid (TFA-*d*). Assignment of ^{1}H NMR signals was performed according to our previous publication.[23]

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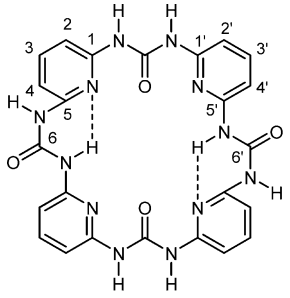
^{1}H NMR (TFA-d): δ (ppm) = 8.29 (3t, H_a of **M1**, **M2**, and **M3**), 7.46 (d, J = 8.4 Hz, H_b of **M3**), 7.26 (d, J = 8.4 Hz, H_b of **M2**), 7.22 (d, J = 8.4 Hz, H_b of **M1**).

M1 with small amounts of **M2** (ca. 3%) was isolated from the mixture by repeated extraction with DMSO at 40 °C.

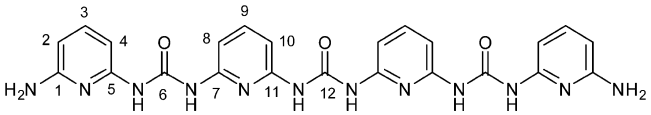


M1

^{1}H NMR (DMSO-d_6): δ (ppm) = 12.50 (s, 2H, NH at 1′), 9.92 (s, 2H, NH at 1 or 5′), 9.73 (s, 2H, NH at 1 or 5′), 8.61 (s, 2H, NH at 5), 7.76 (4H, H_3 and $H_{3'}$), 7.49 (6H, H_2, $H_{2'}$ and H_4), 6.65 (2H, $H_{4'}$). ^{13}C NMR (DMSO-d_6): δ (ppm) = 151.7, 150.6, 150.5, and 148.7 (C_1, $C_{1'}$, C_5, $C_{5'}$), 151.4 and 150.8 (C_6 and $C_{6'}$), 141.3 and 140.8 (C_3 and $C_{3'}$), 106.0 and 104.4 (C_2, $C_{2'}$, C_4 and $C_{4'}$). ESI−MS m/z 541.3 $[MH]^+$. Anal. Calcd for $C_{24}H_{20}N_{12}O_4$: C, 53,33; H, 3.73; N, 31.10. Found: 53,40; H, 3.69; N, 30.94. Mp 242 °C. The grayish powder-like compound does not melt up to 320 °C.

Condensation Reaction in THF (R15). An excess of 10 mol % of CDI (0.36 g, 2.25 mmol) was added to a solution of **1** (0.5 g, 2.05 mmol) in 25 mL of THF. The reaction mixture was kept at 20 °C for 28 d under a low nitrogen stream. The precipitate was filtered off and rejected. The filtrate was concentrated by evaporation of the solvent under reduced pressure. The obtained solid was extracted with acetone and dried under vacuum at 40 °C. According to ^{1}H NMR analysis, the sample (**R15**) has proved to be a mixture of 80 mol % of linear tetramer and 20 mol % of dimer **1**. Yield: 0.014 g (2.5%).

Signal assignment of the linear tetramer (see Figure 7):



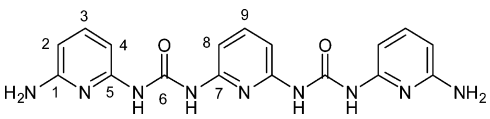
^{1}H NMR (DMSO-d_6): δ (ppm) = 10.5 (s, 2H, NH at 5), 9.59 (s, 2H, NH at 7), 9.35 (s, 2H, NH at 11), 7.70 (t, J = 7.9 Hz, 2H, H_9), 7.57 (d, J = 7.9 Hz, 2H, H_8 or H_{10}), 7.49 (d, J = 7.9 Hz, 2H, H_8 or H_{10}), 7.33 (t, J = 7.9 Hz, 2H, H_3), 6.77 (br, 2H, H_4), 6.11 (d, J = 7.9 Hz, 2H, H_2), 5.79 (s, 4H, NH_2). ^{13}C NMR (DMSO-d_6): δ (ppm) = 158.1 (C_1), 151.8 (C_6), 151.6 (C_{12}), 151.0 (C_5), 150.9 (C_7), 150.7 (C_{11}), 140.2 (C_9), 139.3 (C_3), 106.5 (C_8 or C_{10}), 106.4 (C_8 or C_{10}), 101.8 (C_2), 99.3 (C_4). ESI−MS m/z 245.0 $[MH]^+$ (dimer), 515.2 $[MH]^+$ (tetramer). Sample **R15** does not melt up to 320 °C.

Heating Experiments in DMSO. A mixture of **2** (0.19 g, 0.8 mmol) and **3** (0.22 g, 0.8 mmol) was stirred in 8 mL of DMSO at 180 °C for 8 h. No precipitate was formed during the reaction. The solvent was removed at 50 °C under vacuum.

The same procedure was performed on a mixture of **2** (0.19 g, 0.8 mmol) and 2,6-diaminopyridine (0.09 g, 0.8 mmol) at 100, 120, and 180 °C, respectively.

Furthermore, compound **1** (0.5 g, 2.05 mmol) was heated in 20 mL of DMSO at 100, 120, and 180 °C, respectively, for 4 h under a low nitrogen stream. After being cooled to room temperature, the precipitate was filtered off and the filtrate was evaporated at 50 °C under vacuum. Mixtures of unconverted compound **1**, cyclic trimer **M2** (precipitate), 2,6-diaminopyridine, as well as open trimers and tetramers were obtained (^{1}H NMR spectrum, see Figure 4).

Signal assignment of the linear trimer (not isolated):



^{1}H NMR (DMSO-d_6): δ (ppm) = 10.5 (br, 2H, NH at 5), 9.45 (s, 2H, NH at 7), 7.68 (t, 1H, H_9), 7.52 (d, 2H, H_8), 7.34 (t, 2H, H_3), 6.71 (br, 2H, H_4), 6.12 (d, 2H, H_2), 5.84 (s, 4H, NH_2). ^{13}C NMR (DMSO-d_6): δ (ppm) = 158.1 (C_1), 151.9 (C_6), 151.08 (C_5), 150.9 (C_7), 140.1 (C_9), 139.3 (C_3), 106.5 (C_8), 101.8 (C_2), 99.3 (C_4).

Instruments. ^{1}H and ^{13}C NMR measurements were performed at 500.13 MHz (^{1}H) and 125.74 MHz (^{13}C), respectively. DMSO-d_6 (δ (^{1}H) = 2.50 ppm; δ (^{13}C) = 39.60 ppm) and TFA-d_1 were used as solvents. For measurements in trifluoroacetic acid-d, sodium 3-(trimethylsilyl)-3,3,2,2-d_4-propionic acid was used as internal standard (δ (^{1}H) = 0 ppm). 2D spectra (gsCOSY, gsHSQC, and gsHMBC) were recorded to verify the signal assignments using the pulse sequences included in the Bruker TOPSPIN 2.1 software package.

MALDI-TOF MS spectra were recorded in reflector mode and positive polarity. The samples were exposed to desorption/ionization processes by a smart beam II laser and accelerated and reflected by electric fields. Dihydroxy benzoic acid (DHB) was used as matrix. The mass spectra represent the accumulation of about 1000 single-laser-shot spectra. The calibration of the measurements was performed by using PMMA standards.

Molecular Modeling. The most probable conformation of the urea linkage between two pyridyl moieties was concluded from ab initio quantum mechanical calculations. For this, the geometry of the respective subunits 1,3-di(pyridin-2-yl)urea and 1,1′-(pyridine-2,6-diyl)diurea was optimized with the program package GAMESS using the atomic orbital basis set 6-31G.[28] The calculations were performed for an isolated molecule in an ideal gas under zero point energy conditions (0 K; pressure: 0 N/m^2). On the basis of the optimized geometries, a linear tetramer and cyclic trimers were constructed by using an in-house developed program.[29] The corresponding energies were minimized by the program package GAMASS under the same conditions as mentioned above. The optimized structure is shown in Scheme 3.

■ ASSOCIATED CONTENT

Supporting Information

^{1}H and ^{13}C NMR spectra of **1**-**3**, **M1**, and **R15** in DMSO, ^{1}H NMR spectra of **R1**-**R14** in TFA. Quantum mechanical calculations of the structure shown in Scheme 3. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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