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NMR Studies of the Tautomerism of Cyclo-tris(4-R-2,6-pyridylformamidine) in Solution and in the Solid State

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Abstract: Two novel cyclo-tris(4-R-2,6-pyridylformamidine)s (R = H, CH_3) have been studied by solution- and solid-state NMR. Both compounds show fast exchange of NH protons in dimethyl sulfoxide at room temperature. The *E-syn* configuration of the formamidine group with the NH protons in the outer ring position could be proved by low-temperature ^{1}H NMR experiments. The influence of deuteration of the NH group on the exchange rate has been demonstrated qualitatively. Proton exchange at the formamidine groups results in both a symmetric (**S**) and an asymmetric (**A**) isomer which could be spectroscopically identified and characterized at 193 K. Whereas two degenerate forms exist for **S**, six degenerate **A** forms can be distinguished. Prototropic tautomerism at one formamidine group results in exchange from **S** into **A**, whereas **A** is transformed to a degenerate **A** form or to **S**. It could be shown that some transitions between substructures are impossible by a single −N*H−CH═N−/−N*═CH−NH− exchange. The **S** isomer with three equivalent formamidine groups is the preferred isomer in solution as indicated by the **S**/**A** ratio at 193 K. From this result we conclude that in polyformamidines, ordered sequences of formamidine tautomers are also formed at low temperatures. Prototropic exchange was not observed in the solid state, neither by ^{13}C nor by ^{15}N solid-state NMR. For one trimer (R = CH_3), three molecules dimethyl sulfoxide per trimer molecule are within the lattice as could be proved by ^{13}C CPMAS NMR.

Introduction

The amidine substructure R−NH−C(R)═N−R with different substitution patterns is often a part of important chemical compounds with a large variety of properties.[1] Recently, new applications were found for well-defined polymeric structures containing a large number of amidine groups.[2] In the course of our investigations on polyamidines, we have synthesized and characterized a broad variety of polymers from aliphatic and aromatic diamines and different triethyl ortho esters.[3,4] They contain formamidine, acetamidine, or benzamidine groups which are linked by aliphatic or aromatic spacers. In solution, amidine groups can be involved in three isomerism processes—geometrical isomerism (Figure 1a), rotational isomerism (Figure 1b), and prototropic tautomerism (Figure 1c). The equilibria and the exchange rates depend both on the substituents of the amidine group and on the experimental conditions (solvent, concentration, temperature). Averaged NMR signals were often obtained in usual solvents at ambient temperature. Limbach and co-worker investigated such equilibria in detailed NMR studies on *N,N′*-bisarylformamidines in tetrahydrofuran.[5] Two conformers, *E-syn* and *E-anti*, were assigned which form a hydrogen bond to the solvent molecules at low concentration. *E-syn* is able to self-associate in cyclic hydrogen bonded dimers (Figure 1c). For this reason, the population of both forms is concentration dependent. Within these dimers of two *E-syn* isomers a double proton exchange takes place resulting in a change between tautomers *0* and *1*. The *E-anti* form is not able to exchange protons in a cyclic dimer. Intramolecular proton exchange was not observed. To obtain the best conditions for observation of both forms, the fast proton exchange and the fast rotation between *E-syn* and *E-anti* have to be slowed by low temperature. Furthermore, because of the occurrence of kinetic hydrogen/deuterium isotope effects, deuteration of the NH sites leads to a lowering of the pseudo-first-order rate constants and to an increase of the lifetimes of the tautomeric states. A similar effect is obtained by reduction of the concentrations. Finally, lower concentration also decreases the *E-syn*/*E-anti* ratio. The cyclic dimer can be formed because the

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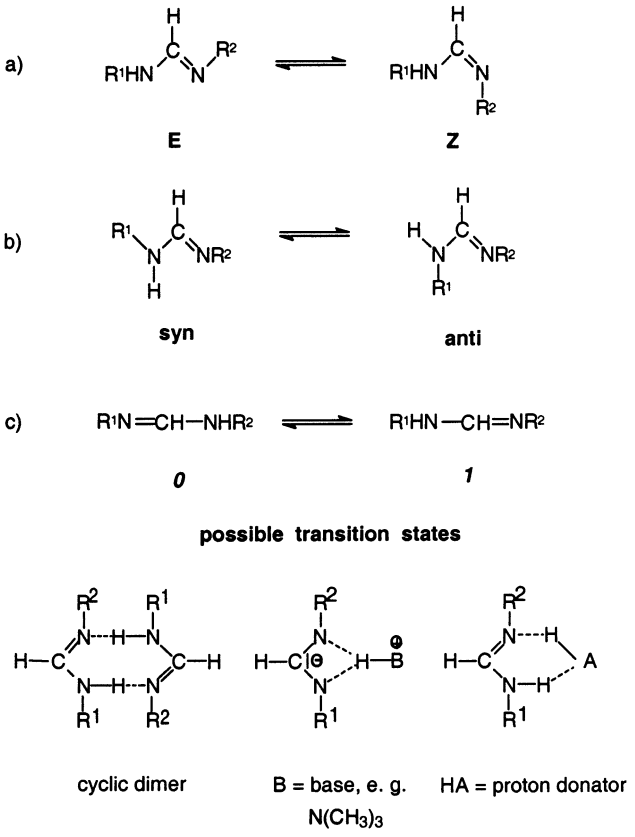

Figure 1. Geometric (a), rotational (b), and isomers from prototropic tautomerism (c) for formamidines $R^1-NH-CH=N-R^2$. Additionally, transition states were shown for proton exchange in a cyclic dimer, catalyzed by a base (here for triazene as reported in ref 6), and by a protic solvent.

Ar−N=CH−NH−Ar moiety is nonplanar in the liquid state. In contrast, for the structurally similar but planar 1,3-bis(4-fluorophenyl)triazene, the formation of cyclic dimers resulting in intermolecular proton transfer is prevented by intermolecular steric repulsion of the phenyl protons.[6] However, intramolecular proton-transfer catalyzed by a base which forms a contact ion pair with the triazene moiety (Figure 1c) could be proved by ^{1}H NMR on [1,3-^{15}N]-labeled triazene. A proton transfer can also occur due to a proton-transfer reaction in complexes with protic compounds (Figure 1c). In principle, intramolecular proton transfer seems also possible. Theoretical[7] and experimental[5] investigations showed that this process is less efficient compared with double-proton transfer in formamidine dimers or mixed dimers of formamidine and protic compounds. All these isomerism processes can take place for each amidine group within a polyamidine chain. It is of interest whether these processes take place independently or in a concerted way. Each isomerism process is characterized by two states (*E* or *Z*, *syn* or *anti*, *0* or *1*). Considering only the two tautomers (*0*, *1*), the polymer chain can be described by a sequence of tautomers of the amidine groups, which can be random (*..0101001110..*), alternating (*..0101010101..*) or blocky (*..0000111110..*). This is similar to the well-known situation of a copolymer from two monomers A and B or to the tacticity of a homopolymer expressed by the sequence of *meso* and *racemic* diads. NMR spectroscopy is a powerful method to determine such sequences.[8] With respect to a sequence of different states of amidine groups it can be expected that chemical shifts of the moiety between two amidine units are sensitive at least to the state of both neighboring units. In this way it should be possible to determine the content of *01* (*10*), *11*, and *00* sequences or diads. In fact, we have observed such amidine diads for a polyacetamidine derived from bis(4,4′-aminophenyl)methane.[9] The quantification indicates a random structure. A similar effect was observed for the trifluoroacetate of a polyacetamidine derived from decane-1,10-diamine.[4] The ^{13}C chemical shifts of the inner methylene groups of the alkyl spacer are sensitive to the configuration of both neighboring acetamidinium groups. The situation becomes more complicated when more than one isomerism process takes place. This is proved for several acet- and formamidines.[1,5,10] When, in addition to tautomerism, geometrical and rotational isomerism also have to be considered, the number of different diads increases drastically for a polyamidine. This strongly complicates the investigations on polymers. Short spacers between neighboring amidine groups should stimulate concerted isomerism processes within a sequence of amidine groups. Unfortunately, the reaction of ortho esters with diaminoethane or 1,3-diaminopropane do not result in polymers but in the corresponding five- and six-membered cyclic amidines.[4] For this reason, we started our investigations with a novel cyclotrimeric formamidine **I** containing a 4-R-2,6-pyridyl unit (**Ia**: R = H, **Ib**: R = CH_3) as spacer between the amidine groups (Figure 2).[11] These compounds constitute

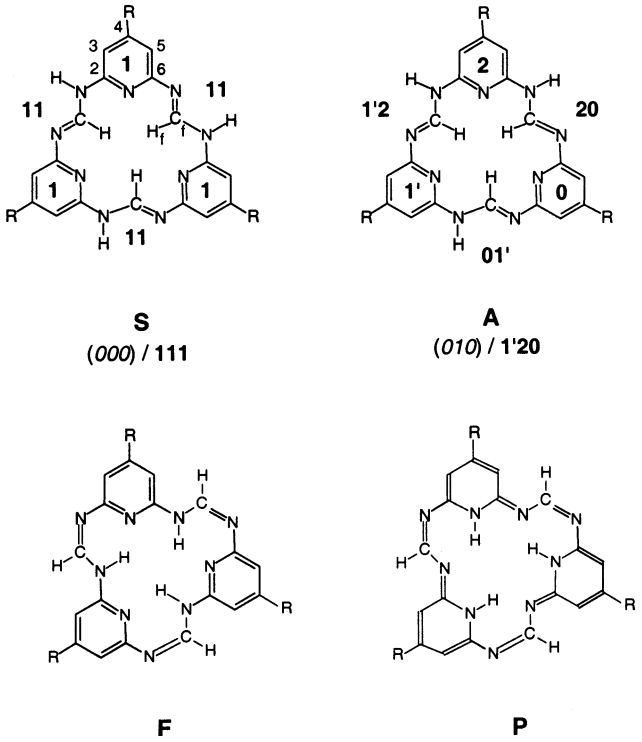

Figure 2. Possible structures for **I**, numbering of ring positions for NMR signal assignment, and introduction of the symbols and nomenclature used to describe the different moieties (**1**, **0**, **1′**, **2**) and formamidine groups (**11**, **01′**, **1′2**, **20**).

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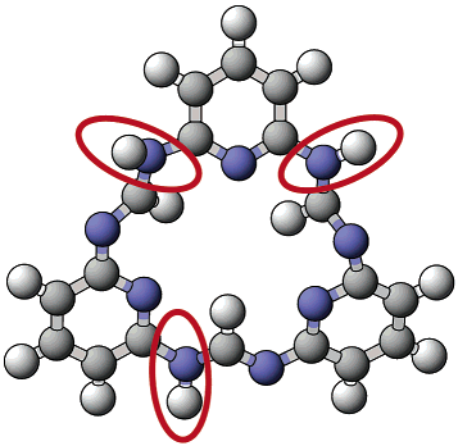

Figure 3. Crystallographic structure for **Ia**. The N−H bonds in the nonplanar **A**-like structure are indicated by ellipses.

an interesting model system to study the interactions between different formamidine groups, because three formamidine groups are separated only by a few bonds in a cyclic sequence. Furthermore, the geometry of the amidine group should be fixed for steric reasons. Several structures can be proposed for **I** with respect to the position of the formamidine CH proton (inside (**S**, **A**) or outside (**F**, **P**) the ring) and the arrangement of the NH proton (symmetric (**S**) or asymmetric (**A**) or bonded to pyridine nitrogen (**P**)). Some examples are given in Figure 2. For **Ia**, a structure analysis by combined X-ray powder diffraction and force-field-constrained Rietveld refinement proposed a nonplanar structure similar to **A** (Figure 3).[12] Structural similarities to porphyrins, phthalocyanines, porphyrenes, and tetraaza[14]annulenes are obvious. These compounds are characterized by intramolecular proton-transfer processes between different nitrogen positions inside the cyclic system.[13] Contrary to those compounds, the exchangeable NH protons of the formamidine groups of **Ia** are not located inside the cyclic system as indicated by the X-ray study. If this structure can also be confirmed for the solution state, proton exchange should occur only as an intermolecular process as expected for the corresponding polymers.

In this paper we determine the structure of **Ib** in solution. A further question addressed in this paper concerns the proton exchange processes. It is obvious that each amidine group of the trimer can exist in state *0* or *1* (Figure 1c). In this way eight structures can be realized (Figure 4). The two symmetric forms (*111*) and (*000*) are degenerated (**S**, **S***). Furthermore, six degenerate asymmetric (**A**) trimers exist which are characterized by occurrence of both the *0* and the *1* tautomer. Each **A** can be transformed into **S** or two alternative **A** forms. On the basis of this theoretical model, the proton exchange processes of **I** are investigated. The strategy involves low-temperature NMR measurements and partial deuteration[5] in order to reach the slow hydrogen exchange regime necessary to distinguish different tautomers. Two notations were used to describe the tautomers. A notation based on the active process (tautomerism) is used up to now to clarify the dynamic processes. To discuss the NMR results, a notation based on the different pyridine moieties is preferred which allows a better characterization of the overall structure (Figure 2). The pyridine moieties are characterized by the number of NH groups in 2- and 6-position (none: **0**, one: **1**/**1′**, two: **2**) and the amidine groups by the type of neighboring pyridine moieties. On the basis of molecule symmetry, **S** (**S***) are characterized by three equivalent pyridine moieties **1** and formamidine groups **11**, respectively. The isomer **A** contains the pyridine units **0**, **1′**, and **2** and the formamidine units **1′2**, **20**, and **01′**. We distinguish between **1** and **1′** because these pyridine moieties are in different sequences (**111** and **01′2**).

The novel cyclotrimeric structure of **I** with donor and acceptor groups also opens up further applications, for example in metalorganic and catalytic chemistry and in biochemistry. For example, they can be regarded as potential building units for supramolecular assemblies based on interactions of the three amidine groups with proton donors or metals ions. To obtain more information about the solid-state structure of **I**, ^{13}C and ^{15}N CPMAS NMR experiments were performed on **Ia** and **Ib**. The solid-state NMR results were also related to the X-ray structure analysis[12] and the solution state NMR investigations.

Experimental Section

General Procedures. 2,6-Diaminopyridine (Fluka), 2-aminopyridine (Fluka), and *N*,*N*-dimethylformamidine dimethyl acetal (Aldrich) were used as purchased. 2,6-Diamino-4-methylpyridine was synthesized from 2-amino-4-methylpyridine (Merck) and $NaNH_2$ (Fluka) according to a literature procedure.[14] Triethyl orthoformate (TEOF) (Fluka) and dimethyl sulfoxide (DMSO) (Fluka) were stored over molecular sieves and purified by distillation prior to use.

Synthesis of Cyclo-tris(2,6-pyridylformamidine) (Ia) and Cyclo-tris(4-methyl-2,6-pyridylformamidine) (Ib). For the preparation of the cyclic formamidines, the previously reported procedure[11] was slightly modified. An excess of 10 mol % TEOF (38.5 mmol) was added to a solution of 35.0 mmol of the respective diamine in 35 mL of DMSO under a slow nitrogen stream. The temperature of the reaction mixture was gradually raised to 140°C and maintained for 4 h. Ethanol formed during the reaction was distilled off. After cooling to room temperature, the precipitate was filtered, extracted with hot acetone, and dried in a vacuum at 90°C for 8 h. **Ia**: yield: 91%, sublimation at 288 °C, no melting until decomposition; **Ib**: yield: 74%, no melting until decomposition; NMR (DMSO-d_6, 303 K): **Ia** − ^1H: 6.58 (d, J = 7.6 Hz, $H_{3/5}$), 7.59 (t, H_4), 10.32 (H_f), 10.71 (NH); ^{13}C: 109.6 ($C_{3/5}$), 140.42 (C_4), 149.84 (C_f), 155.3 ($C_{2/6}$); **Ib** − ^1H: 2.22 (CH_3), 2.54 (CH_3 of three mol DMSO per mol **Ib**), 6.39 ($H_{3/5}$), 10.29 (H_f), 10.66 (NH); ^{13}C: 20.63 (CH_3), 40.45 (CH_3 of DMSO), 110.2 ($C_{3/5}$), 150.15 (C_f), 150.91 (C_4), 155.2 ($C_{2/6}$). ^{15}N CPMAS (solid, 303 K): **Ia** −248.6, −157.2, −154.1, −150.5, −149.1, −135.9, −129.6; **Ib** −251.4, −151.6, −148.8, −147.6, −146.7, −145.1, −143.8. Data from ^{13}C CPMAS NMR spectra are summarized in Table 2.

***N*,*N′*-Di(2-pyridyl)formamidine (2).** An excess of 50 mol % TEOF (70 mmol) was added to 79.0 mmol of 2-aminopyridine and refluxed at 146 °C under a low nitrogen stream for 9 h. Ethanol formed during the reaction was distilled off. Finally, the excess of TEOF was distilled off. The product was recrystallized from petroleum ether/toluene (1:1). Yield: 89%; mp 104−106 °C; NMR (DMSO-d_6, 303 K): ^1H: 7.00 (broad, H_3), 7.04 (t, H_5), 7.71 (t, H_4), 8.29 (d, H_6), 9.65 (H_f), 10.68 (NH); ^{13}C: 114.9 (C_3), 118.78 (C_5), 138.29 (C_4), 148.33 (C_6), 149.91 (C_f), 157.0 (C_2).

***N*,*N*-Dimethyl-*N′*-2-pyridylformamidine (3).** This model compound was synthesized from 2-aminopyridine (Fluka) and *N*,*N*-dimethylformamidine dimethyl acetal (Aldrich) as described by Cunningham et al.[15]

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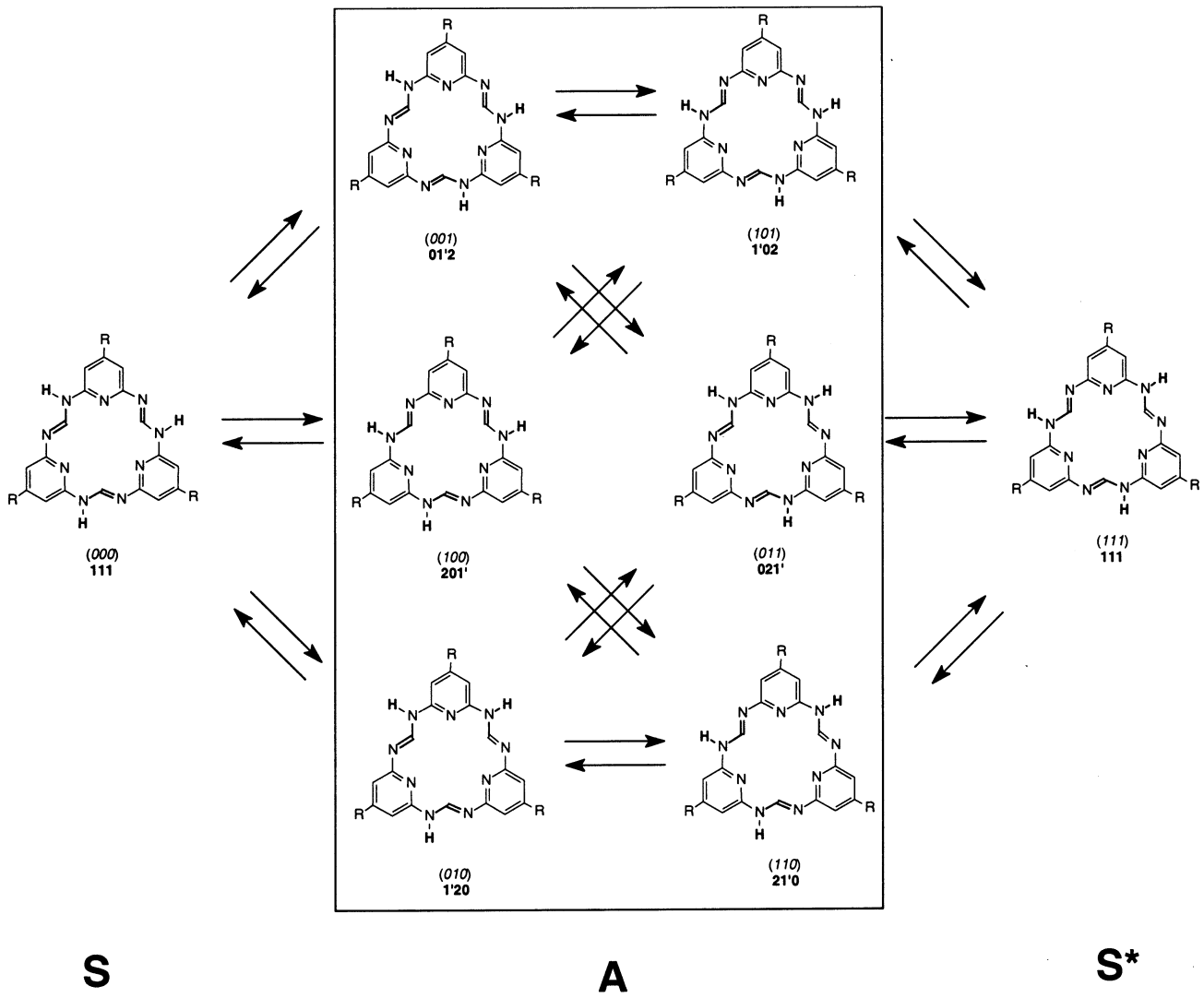

Figure 4. Relations between structures of **I** due to −N*=CH−NH−/−N*H−CH=N− (*0*/*1*) exchange at *one* of the three formamidine groups. The italic numbers in brackets describe the sequence of amidine groups and the bold numbers the sequence of different pyridine moieties (compare also Figure 2). The degenerate asymmetric structures **A** are within the frame. The symmetric structures **S** and **S*** also are degenerated.

Yield. 46%; mp 28−29 °C; NMR (DMSO-d_6, 303 K): ^{1}H: 2.96 (s, CH_3), 3.06 (s, CH_3), 6.50 (d, H_3), 6.86 (t, H_5), 7.55 (t, H_4), 8.17 (d, H_6), 8.46 (H_f), ^{13}C: 34.16 (CH_3), 40.01 (CH_3), 117.23 and 117.41 (C_3, C_5), 137.48 (C_4), 147.85 (C_6), 155.07 (C_f), 161.86 (C_2).

NMR Spectroscopy. The solution-state ^{1}H and ^{13}C NMR spectra were recorded on a Bruker spectrometer DRX 500 operating at 500.13 MHz for ^{1}H and 125.75 MHz for ^{13}C. The spectra in DMSO-d_6 were referenced on the solvent signal at 2.50 ppm (^{1}H) and 39.6 ppm (^{13}C), respectively. The low-temperature ^{1}H NMR experiments were carried out on a 4×10^{-3} M solution of **Ib** in a mixture of 80 μL of dried DMSO-d_6; 650 μL of dried THF-d_8, and 120 μL of $CD_3O(H/D)$ (isotopic enrichment of CD_3OD: 99.8 at. %). These spectra were referenced for all temperatures on internal TMS ($\delta = 0$ ppm). The transverse 2D rotating-frame Overhauser spectroscopy (T-ROESY) experiment uses $+x$ and $-x$ 180°-pulses for spin-lock.[16] The total duration of spin-lock was adjusted by a loop parameter $n = 600$ and a 90° pulse width of 105 μs to 252 ms. The ^{13}C and ^{15}N CPMAS measurements were performed on a Bruker spectrometer AMX 300 operating at 75.47 MHz for ^{13}C and 30.41 MHz for ^{15}N. The samples were spun at 4−4.5 kHz in a 7 mm CPMAS probe head from Bruker. The CP times were 1 ms for ^{13}C and 5 ms for ^{15}N, and the repetition times were 2 s for ^{13}C and 4 s for ^{15}N. The ^{15}N chemical shifts were referenced to external solid glycine located at −347 ppm from nitromethane.[17]

Results

Solution-State NMR. The solubility of **I** in common solvents is very low. It was found that dimethyl sulfoxide (DMSO) is the best solvent. Figure 5 shows the ^{1}H and ^{13}C NMR spectra of **Ia** which clearly indicate the equivalence of both the 2/6 and 3/5 ring positions. Line broadening points to dynamic processes which are fast enough to narrow the signal of $H_{3/5}$ to an extent which allows determination of $^3J_{HH}$ to H_4. The ^{1}H and ^{13}C NMR data for **Ia** and **Ib** in DMSO-d_6 at 303 K are given in the Experimental Section.

To investigate dynamic processes, measurements at low temperatures are necessary. For these experiments, a DMSO-d_6 solution of **Ib** was diluted with a nearly 10-fold excess of THF-d_8. In this way, ^{1}H NMR measurements down to 193 K without precipitation of **Ib** could be performed (Table 1). Partial deuteration of the NH function was achieved by adding a mixture of CD_3OH/CD_3OD to this solution.

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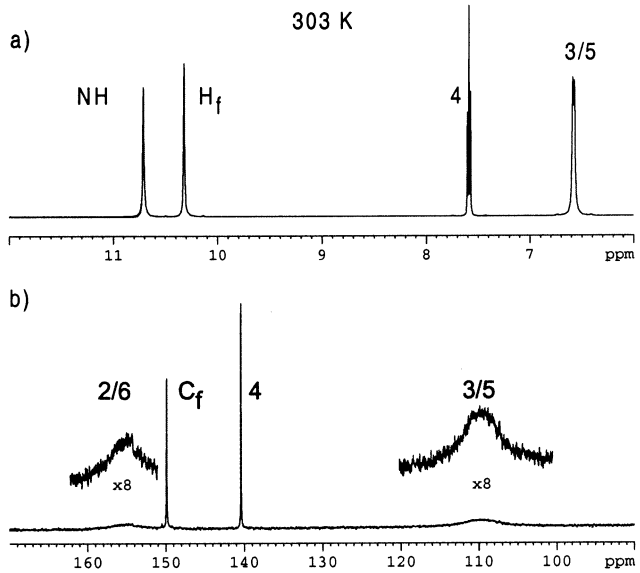

Figure 5. ^{1}H and ^{13}C NMR spectra of **Ia** at 303 K in DMSO-d_6 (signal numbering according Figure 2).

Table 1. ^{1}H NMR Signal Assignment (chemical shifts in ppm) for the Isomers **S** and **A** of **Ib** (deuterium fraction D = 0.48) at 193 K

	Ib (**S**)		**Ib** (**A**)	
pyridyl unit	1	1′	2	0
H_3	6.39	6.39	6.25	6.47
H_5	6.35	6.36	6.25	6.47
CH_3	2.16		2.18, 2.16, 2.14	

amidine unit	11	01′	20	1′2
NH	10.85	10.78	10.86	10.94
H_f	10.485	10.545	10.45	10.395
H_f (ND isotopomer)	10.48	10.54	10.445	10.390

Figure 6 shows the aromatic protons region of **Ib** obtained at 223 K with the same solvent composition except that the deuterium fraction of the NH group was adjusted to different values by changing the CD_3OH/CD_3OD ratio (1:0; 1:1; 0:1). Although in all spectra the slower dynamics result in a signal splitting, the largest effect is reached at the highest deuterium fraction (0.91, Figure 6c), indicating the isotope effect on the proton exchange rate. For a detailed spectroscopic analysis, the sample with the medium N−H deuterium fraction of 0.48 was used to benefit from the reduced exchange rate due to deuteration and the H−H couplings of the nondeuterated moieties. The NMR spectra are characterized by increasing signal splitting with decreasing temperature due to slowing of the dynamic processes. The proton chemical shifts of the signals and centers of signals groups, respectively, remain constant for H_f, H_3, H_5, and CH_3. A low-field shift is observed for the NH protons which appear at 10.22 ppm at 293 K. The ^{1}H NMR spectrum measured at 193 K is shown in Figure 7. From this spectrum a value of 10.7 Hz for the $^3J_{HH}$ couplings between NH and CH can be determined. This value is characteristic for a *trans*-coupling in a *syn*-arrangement.[5a,b] Each signal region shows three more or less well separated subregions with an intensity ratio of about 1:3:1. The spectral regions of the formamidine NH and CH protons reflect the partial deuteration of NH. The overall intensity of the NH region showing the doublets of the −NH−CH═N− groups is reduced. The small $^3J_{HD}$ coupling of the −ND−CH═N− groups results in broadened signals for

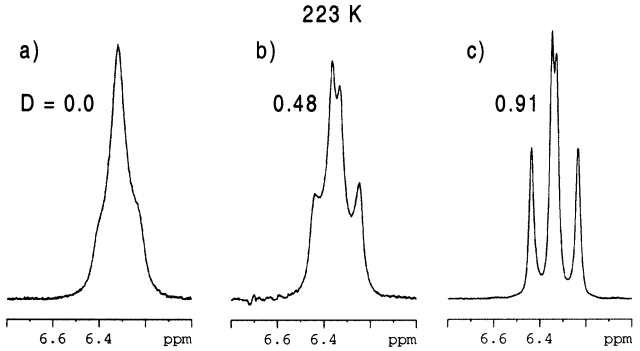

Figure 6. ^{1}H NMR spectra (aromatic protons region) of **Ib** at 223 K for different deuterium fractions D of the NH group: (a) 0, (b) 0.48, and (c) 0.91.

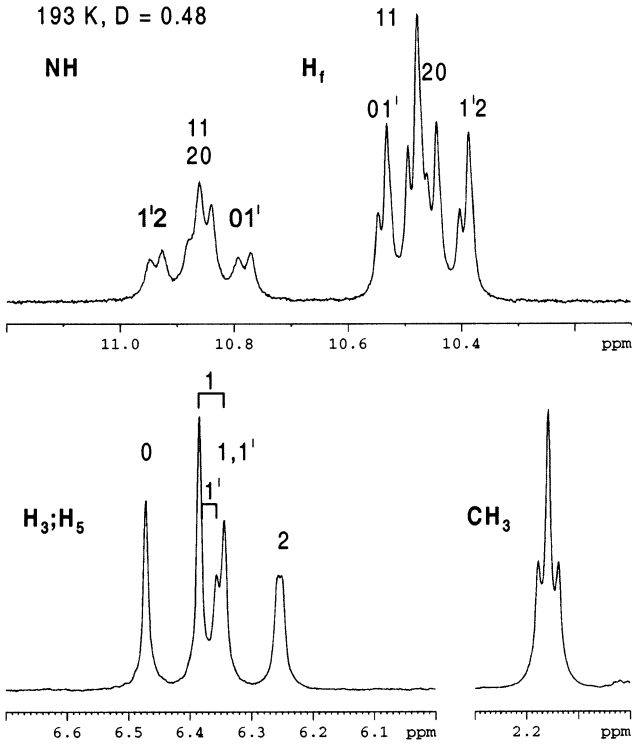

Figure 7. ^{1}H NMR spectrum of **Ib** (deuterium fraction D = 0.48) at 193 K with signal assignments according numbering and nomenclature in Figure 2. For more detailed assignment see Table 1.

this CH proton which are high-field-shifted with respect to the center of the doublets from the −NH−CH═N− groups due to the isotopic effect. In the aromatic proton region an isotopic effect cannot be observed. The transverse 2D rotating-frame Overhauser enhancement spectroscopy (T-ROESY) spectrum (Figure 8) shows ROE cross-relaxation between NH protons and aromatic protons which is only possible when the NH protons are located in the outer ring position. Finally, four different pairs of CH and NH protons belonging to different formamidine groups can be identified in a ^{1}H,^{1}H correlation spectroscopy (COSY) spectrum.

Solid-State NMR. Figure 9 depicts the ^{13}C CPMAS spectra of **Ia** and **Ib**. Carbons without directly attached protons were identified using the dipolar dephasing experiment.[18] Besides the signals of the cyclic structure, additional signals at about 40 ppm are observed in the spectrum of **Ib**. They can be assigned

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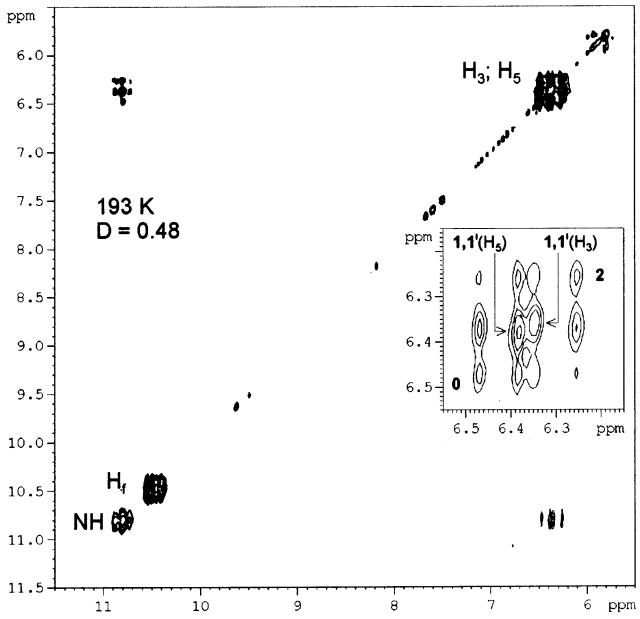

Figure 8. 2D T-ROESY spectrum of **Ib** (deuterium fraction D = 0.48) at 193 K showing the ROE cross-peaks between NH and aromatic protons and exchange correlations (insert: aromatic protons).

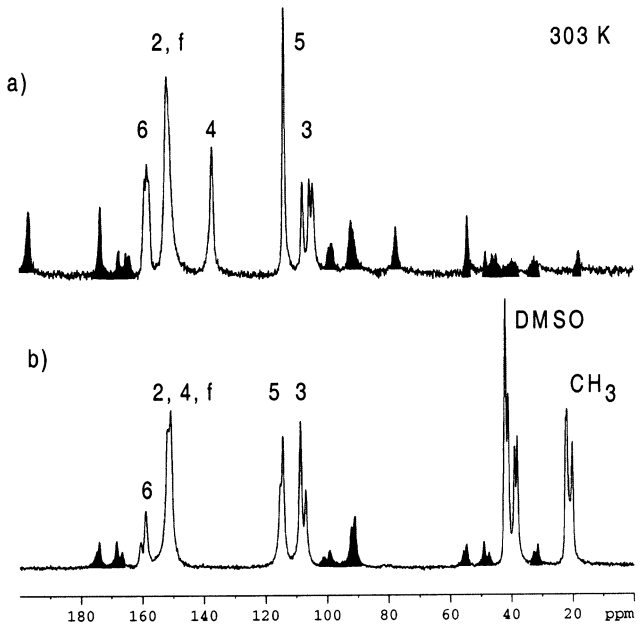

Figure 9. ^{13}C CPMAS spectra of (a) **Ia** and (b) **Ib**, recrystallized from DMSO (hashed: spinning sidebands).

to dimethyl sulfoxide, which was used to recrystallize this sample. The signal intensities and the shape of this signal group (compare, for example, with C_5 and CH_3) prove that three solvent molecules per molecule **Ib** are incorporated into the lattice. This is confirmed by signal integration in the ^{1}H NMR spectrum of the dissolved sample. Precipitation from a DMSO solution by , for example, acetone results in a DMSO-free product. Its ^{13}C CPMAS spectrum is characterized by signal shifts for the ring carbons compared with the DMSO containing sample. C_3 and C_5 result in a common signal at 112 ppm. The C_6 signal now appears at 157.9 ppm as a shoulder on the common signal of C_2, C_4, and C_f (152.6 ppm). To estimate the ^{13}C chemical shifts of isomers **S** and **A** in the absence of fast proton exchange, ^{13}C chemical shift increments for the

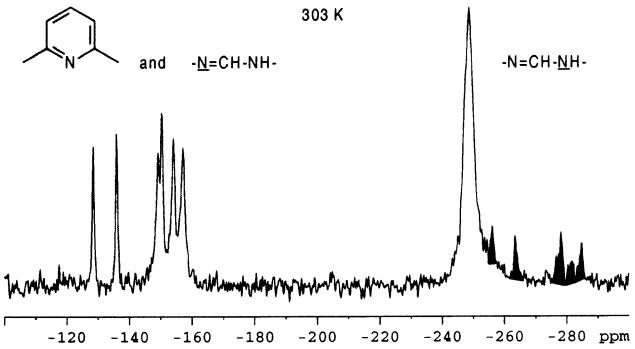

Figure 10. ^{15}N CPMAS spectrum of **Ia** (hashed: spinning sidebands).

Table 2. Comparison of Calculated and Experimental ^{13}C Chemical Shifts (in ppm) of **Ia** and **Ib** in the Solid State

	δ_{calcd} for **Ia(S)** and **1′** of **Ia(A)**[a]	δ_{calcd} for **0/2** of **Ia(A)**[a]	δ_{exp} for **Ia**	δ_{exp} for **Ib**
C_2	150.7	160.5/150.7	152.0	150. 8[c]
C_3	105.6	110.4/108.6	104.7, 105.7, 108.0[b]	107.0. 108.7[b]
C_4	140.4	138.8/142.0	137.3	151.7[c]
C_5	113.4	110.4/108.6	113.4[b]	114.3; 115.2[b]
C_6	160.5	160.5/150.7	157.7; 158.4; 159.1	158.8, 160.5
C_f			151.8[d]	151.3[d]
CH_3				20.1; 21.8; 22.1
DMSO				38.0; 38.9, 41.0; 41.9

[a] ^{13}C substituent effects Z_i (in ppm) on pyridine carbons i ($\delta_{2/6}$ = 149.7 ppm; $\delta_{3/5}$ = 124.2 ppm; δ_4 = 136.2 ppm) in DMSO-d_6 due to 2-substitution by −N=CH−N(CH$_3$)$_2$: Z_2 = +12.2; Z_3 = − 6.9, Z_4 = +1.3; Z_5 = − 6.9, Z_6 = −1.4 and −NH−CH=N−Py: Z_2 = +2.4; Z_3 = −11.7, Z_4 = +2.9; Z_5 = − 3.9, Z_6 = −1.4 (see also text). [b] Assignment for isomer **S**, the low-field signals cover C_3(**1′**) and $C_{3/5}$(**2**) and the high-field signals C_5(**1′**) and $C_{3/5}$(**0**) in case of isomer **A**. [c] Assignment possibly reversed. [d] Signal position determined from the difference spectrum of a CPMAS spectrum with and without nonquarternary carbon suppression by dipolar dephasing.[13]

−NH−CH=N−Py and −N=CH−NH−Py moieties were deduced from the solution spectra of two model compounds. *N*,*N*′-Di(2-pyridyl)formamidine (**II**) shows fast proton exchange in DMSO solution. Therefore, the observed ^{13}C chemical shift effects with regard to pyridine are mean values of the increments of the −NH−CH=N−Py and the −N=CH−NH−Py moiety. The increments of a −N=CH−N(CH$_3$)$_2$ moiety on pyridine were determined from *N*,*N*-dimethyl-*N*′-2-pyridylformamidine (**III**). Using these values as estimation for the −N=CH−NH−Py moiety, the −NH−CH=N−Py increments can be estimated from the aforementioned averaged increments determined from **II** (footnote in Table 2). The ^{15}N CPMAS spectra of both **Ia** and **Ib** (with DMSO) show six sharp signals for the sp^2-hybridized pyridine and imino nitrogens as well as a broad signal for the amino nitrogens of the formamidine groups (Figure 10). The broadening of the NH signal at −248.6 ppm is caused by residual dipolar coupling with the proton. Substitution of H_4 by a methyl group results in a high-field shift for the pyridine nitrogens.[19] This is observed for the signals at −129.6 and −135.9 ppm, which were assigned to two pyridine nitrogens of **Ia**. The third pyridine nitrogen is one of the four signals between −149.1 and −157.2 ppm. For **Ib**, all sp^2 nitrogen signals appear between −143.8 and −151.6 ppm. The chemical shift difference between amidine NH and =N− nitrogen of about 100 ppm corresponds with data given for *N*,*N*′-bisarylformamidines.[20] For both ^{13}C and ^{15}N CPMAS

(19) DiGioia, A. J.; Furst, G. T.; Psota, L.; Lichter, R. L. *J. Phys. Chem.* **1978**, *82*, 1644.

spectra, no signal coalescence or significant signal broadening was observed up to 343 K. This proves the absence or very low rate of proton exchange for **Ia** and **Ib** in the solid state.

Discussion

The results presented in the preceding section show clearly that prototropic tautomerism is the key in understanding the NMR spectroscopic results in solution. An intermolecular proton exchange takes place as can be concluded from the configuration of **I** determined from coupling constants and ROE correlations. The value of 10.7 Hz for the $^3J_{HH}$ couplings between NH and CH of the amidine group is in agreement with a *syn*-arrangement of this group. Therefore, structure **P** in Figure 2 can be ruled out. The ROE correlations observed between NH protons and pyridine ring protons prove an outer ring position for the NH protons in contrast to similar ring systems with intramolecular proton exchange (e.g. porphyrins). The CH of the amidine group protons has to occupy the center of the ring and so structure **F** in Figure 2 can be ruled out also. The neighborhood of the pyridine nitrogen and the CH proton as proved here was also found to be the preferred conformation for *N*,*N*-dimethyl-*N*′-2-pyridylformamidine.[21] This arrangement and *E-syn* conformation of the formamidine group allow us to conclude that the Py-N═CH−NH−Py moiety is more or less planar. This is assumed to be the major reason for cyclization during the reaction of 2,6-diaminopyridine with triethyl orthoformate.[22] In contrast, the phenyl rings are twisted with regard to the amidine plane in most Ar−N═CH−NH−Ar moieties due to steric interactions between the CH proton and *ortho*-ring protons.[20] Therefore, not cyclic compounds but polymeric structures were obtained from 2,6-diaminobenzene. All proton signals split into three subregions with only small chemical shift differences at slow proton exchange. Four different pairs of CH and NH protons could be assigned in the COSY spectrum. These findings can be explained by two isomers for **I** which differ in the arrangement of NH protons: one with a symmetric structure (**S**) and another one with an asymmetric structure (**A**) as shown in Figure 2. No evidence for geometric or rotational isomers was found. The three equivalent pyridine moieties **1** of **S** result in two signals for the ring protons H_3 and H_5 of **Ib** in the slow exchange regime. In contrast to this, isomer **A** of **Ib** results in four signals for these protons with an intensity ratio of 2:1:1:2 ($H_{3/5}$(**0**):H_3(**1′**):H_5(**1′**):$H_{3/5}$(**2**)). This is confirmed by the signal pattern of this signal region (Figure 7). Additionally, a small splitting of the signal at 6.25 ppm reflects the asymmetry of **A**. With regard to the formamidine groups only one type (**11**) is possible for **S**, but three different groups (**1′2**, **20**, and **01′**) can be distinguished for **A** (Figure 2) in accordance with the COSY results.

The 2D T-ROESY spectrum should allow the assignment of most of the aromatic and NH signals. The NH signal at 10.85 ppm shows an intense ROESY cross-peak to H_3 of **S** and is assigned to **11**. Cross-peaks to **1** and **11** signals, respectively, were found for all signals of **A**. As all substructures of **A** can be formed from **S** by a single proton exchange (Figure 4) and vice versa, these cross-peaks should be caused by exchange-relayed enhancements. If the longitudinal relaxation of the enhanced protons is slower than the rate of structural change between **S** and **A** due to proton exchange, remaining enhancement obtained, for example in **S** can be passed down to protons of **A** substructures formed after exchange. The aromatic protons of **2** and **0** can be distinguished by an absence of cross-peaks of the latter to NH protons. The proton signal at 6.25 ppm show cross-peaks to NH protons at 10.94 and 10.86 ppm and is assigned to the **2** unit located between the NH sites of two different formamidine groups (**1′2**, **20**). The signal at 6.47 ppm assigned to the **0** unit shows only the aforementioned correlation to NH at 10.85 ppm (**11**). Finally, the NH signal at 10.78 ppm belongs to the formamidine group **01′**. The COSY correlations give the corresponding formamidine CH protons. Table 1 summarizes all signal assignments for **Ib** (**S**, **A**) at 193 K. Several known mechanisms and transition states were presented for proton-transfer reactions in the Introduction (Figure 1c). We would exclude the intramolecular base-catalyzed proton transfer[6] because neither DMSO nor THF should act as catalytic base. The trimer structure of **I** suggests a planar arrangement with an optimized electronic coupling between the pyridyl and amidine π-systems. This would prevent the formation of cyclic dimers from formamidine groups of two trimers for steric reasons. However, from model considerations we cannot exclude conformational mobility allowing the formation of such dimers as a source of proton exchange. Small deviations from a planar ring were reported by Friedel et al. for **Ia** in the solid state.[12] A larger twist of the pyridine moieties out of the plane of the amidine groups seems possible in solution. Under the experimental conditions, however, interactions with the protic solvent CD_3O(H/D) should be the main source of −N*H−CH═N−/−N*═CH−NH− exchange. These proton-transfer reactions in an amidine−protic solvent complex (Figure 1c) result also in the observed deuteration of NH groups. The different mechanisms cannot be separated, as we are not able to use a pure aprotic solvent. The complex interactions between the dissolved compound and the quite different solvents prevent a reasonable analysis of the temperature-dependent spectra with respect to kinetic or thermodynamic data. Therefore, only the structural consequences of proton exchange reactions are discussed. A single −N*H−CH═N−/−N*═CH−NH− exchange within an amidine group of a symmetric form **S** results in each case in the asymmetric form **A**. Any exchange for **A** results with a *statistical* probability of 1/3 in the **S** form and with 2/3 in a degenerate **A** form. This can be illustrated as shown in Figure 4. Starting with **S**, a single −N*H−CH═N−/−N*═CH−NH− exchange (edge of the cube) results in an **A** form. Six degenerate permutations of substructures **1′** − **2** − **0** can be distinguished for **A** and two enantiomers exist also for **S**. They are placed in corners of the cube. Each **A** can be transformed into **S** or two alternative permutations. Further conclusions can be drawn from the representation in Figure 4 which help to understand the exchange pattern in the T-ROESY spectrum. The structural change from **S** to **A** or vice versa by a proton exchange results in a chemical shift change for the proton which is involved in this exchange but also for the other protons of **I** (Table 1). These chemical shift changes may result in exchange cross-peaks in the T-ROESY spectrum between signals which are related by this exchange. The insert in Figure 8 shows the enlarged exchange cross-peak region for the aromatic protons

(20) Anulewicz, R.; Wawer, I.; Krygowski, T. M.; Männle, F.; Limbach, H.-H. *J. Am. Chem. Soc.* **1997**, *119*, 12223.
(21) Cunningham, I. D.; Llor, J.; Munoz, L. *J. Chem. Soc., Perkin Trans. 2* **1992**, 2253.
(22) Böhme, F.; Kunert, C.; Klinger, C.; Komber, H. *Macromol. Symp.* **1998**, *128*, 183.

H_3 and H_5 of **Ib** and is to be discussed in the following in more detail. It is obvious from Figure 4, that some conversions of substructures are not possible by single NH exchange processes. So, **2** cannot directly be converted into **0** by a single −N*H−CH═N−/−N*═CH−NH− exchange and vice versa. Consequently, only aromatic protons $H_{3/5}$ of a **1** or **1′** substructure can be converted to $H_{3/5}$ protons of **2** and **0** substructures by amidine proton exchange. The "forbidden" ROESY peak between $H_{3/5}$ of **2** and **0** is of much lower intensity than the other ones and is possibly caused by two simultaneous NH exchange processes. Furthermore, the exchange peak pattern seems to confirm that H_3 and H_5 in substructure **1** or **1′** cannot interchange their chemical surrounding by a single NH exchange, i.e. H_3 of **1** cannot be converted directly to H_5 of **1**. All other proton positions are connected by a single NH exchange in accordance with Figure 4. The forbidden **2**/**0** conversion also means that a formamidine unit **1′2** cannot be converted directly into a formamidine unit **01′**. This is in accordance with the missing exchange signal between the NH signals at 10.78 and 10.94 ppm assigned to these formamidine groups.

Finally, the ratio of both isomers of **Ib** can be calculated from the intensities of the three subregions in the ^{1}H NMR spectrum at slow exchange. A **S**/**A** ratio of 0.25:0.75 is expected assuming the same energy for both isomers. The experimental value is about 0.40:0.60 at 193 K. That means, the symmetric form is energetically preferred. Obviously, the exchange probability at an individual formamidine group of **I** is influenced by the overall structure of the isomer. Not all exchange reactions within Figure 4 are energetically equivalent but the formation of **S** from **A** is preferential compared to the transfer to a degenerate **A** form. This result helps to answer the original question whether the sequence of tautomers of the amidine groups in a polyformamidine should be random or shows any degree of order. Obviously, sequences of same orientation of the amidine tautomers (*0* or *1*) are energetically preferred. Despite the peculiarities of cyclic systems, we propose a blocky sequence of such tautomers, e.g. ...*00011110000*..., in polyformamidines. The degree of blockiness should depend on the spacer between the amidine groups. A low number of bonds between neighboring amidine groups (e.g. 1,2-, 1,3-, or 1,4-diamidine substituted aromatic compounds) ensuring π-conjugation between successive amidine π-systems should promote blocky structures. Correlation effects between amidine group tautomers separated, for example, by longer alkyl spacers or 4,4′-disubstituted diphenylenemethane should be low and result in random sequences.[9] It seems that blocky structures are only feasible at low temperatures. Although the temperature dependence of the **S**/**A** equilibrium could not be determined, the slight preference of **S** at 193 K suggests that both isomers should be nearly equal populated at room temperature. For this reason, it is expected that at higher temperatures ordered structures would only be available if the preference of **S** could be increased, for example by introduction of special spacers between the amidine groups, or by reduction of randomization if fast proton exchange could be slowed. This seems to be difficult for formamidines, but at least the exchange rate can be drastically reduced if the formamidine proton H_f is substituted by aryl or alkyl groups. Acyl- and arylamidines prefer the *E-anti* form (Figure 1) which is not able to exchange protons in a cyclic dimer.[1,5,9,23]

In contrast to solution, the solid-state NMR results prove the absence or very low rate of tautomerism for the solid samples. Both ^{13}C and ^{15}N CPMAS spectra at 303 and 343 K are identical. Furthermore, a ^{15}N chemical shift difference between NH and N of the amidine group of about 100 ppm also at 343 K is characteristic for absence of tautomerism.[20] The absence of proton exchange in the solid-state is in accordance with a largely planar structure of **I**. Anulewicz et al. have evidenced for solid *N*,*N*′-bisarylformamidines that proton transfer and hydrogen bonding in cyclic dimers of formamidine groups are controlled by the molecular structure.[20] It was shown that two bisarylformamidines cannot approach each other to form a cyclic dimer able to proton exchange when the aryl groups were not significantly twisted from the amidine plane. A similar situation is realized for **I** because a large twist of the pyridine rings from the amidine plane is unlikely in the solid state. Only a minor but significant deviation from a planar structure was found for **Ia** in the X-ray study (Figure 3).[12] The absence of intermolecular proton exchange in the solid state refer also to the role of the protic solvent as proton transmitter in solution. The signals observed seem to represent only one isomer. This raises the question whether the NMR data can be used to identify its structure. Using the estimated increments for the −NH−CH═N−Py and −N═CH−NH−Py moiety, the ^{13}C chemical shifts of the different pyridine units of isomers **S** and **A** were calculated (Table 2). The calculated values correspond well with the signal regions observed for **Ia** (Table 2). Unfortunately, the chemical shift differences between signal regions of substructure **1** of **S** and units **0**, **1′**, and **2** of **A** are not large enough for an unique structure assignment, taking into account both that −N═CH−N$(CH_3)_2$ was used to estimate the effect of −N═CH−NH−Py and that the increments were determined in solution. The experimental values correspond best with the calculated values for the **S** form. However, the splitting of several signals which is also observed in the ^{15}N spectra is in contradiction with a highly symmetric structure. It can be explained by disturbed 3-fold symmetry of **S** in the crystalline state but most probably it reflects the asymmetric structure of form **A**, which was proposed for **Ia** in the X-ray study.[12] The authors obtained the best fitting of rotating-crystal and powder diffraction measurements to a structural model when water molecules were additionally packed into the unit cell of **Ia**. The evidence of solvent incorporation into the crystal structure could directly be provided for **Ib** by our ^{13}C CPMAS measurements. The 1:3 molar ratio of trimer and dimethyl sulfoxide may indicate that the NH proton of each amidine unit is in interaction with the oxygen of a DMSO molecule. The additional 4-methyl substitution compared with **Ia** should result in significant voids between trimer molecules which can be filled by solvent incorporation. Nevertheless, also a DMSO-free sample has been obtained as could be proved by ^{13}C CPMAS.

Conclusions

^{1}H NMR studies on novel cyclo-tris(4-R-2,6-pyridylformamidine)s (R = H, CH_3) prove fast intermolecular proton exchange between amidine groups in solution at room temperature. By low-temperature measurements an equilibrium of a symmetric and asymmetric tautomer could be evidenced. Both tautomers have the same *E-syn* arrangement of the Py-NH−CH═N−Py moieties with the CH protons inside the

(23) Komber, H.; Klinger, C.; Böhme, F. *Macromolecules* **1997**, *30*, 8066.

ring. They differ in the positions of amino and amido nitrogens of amidine groups and may interconvert by intermolecular proton exchange on one amidine group. For this reason, **I** constitutes an interesting model system to study the interactions between different formamidine groups. It could be shown that the symmetric tautomer **S** of **Ib** with a ordered sequence of amidine group orientations (*000*) is preferred at 193 K. Therefore, also for noncyclic polyformamidines with short spacers between amidine groups a structure with blocky ordered amidine group orientations is proposed (e.g. ...*000011111000*....) at least at low temperatures. Precise selection of spacers and slow of proton exchange by choosing acyl- or arylamidines instead of formamidines could possibly preserve this effect also at higher temperatures.

A proton exchange could not be proved in the solid-state by ^{13}C and ^{15}N CPMAS measurements up to 343 K. Obviously, only one tautomer exists, and steric hindrance prevents the formation of cylic dimers of amidine groups which are able to undergo intermolecular proton exchange. Significant spacings between trimer molecules may be the reason for incorporation of solvent molecules into the crystal as could be proved for the 4-methyl derivative **Ib**. Whether the symmetric or asymmetric tautomer exists in the solid-state cannot be stated unequivocally. However, signal splitting in the ^{13}C and ^{15}N CPMAS spectra indicates a nonsymmetric structure. Both a nonplanar symmetric and the asymmetric structure may be the reason. Taking the results of a recent X-ray study[12] into account, the spectra should reflect a solid-state structure similar to the isomer **A**.

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