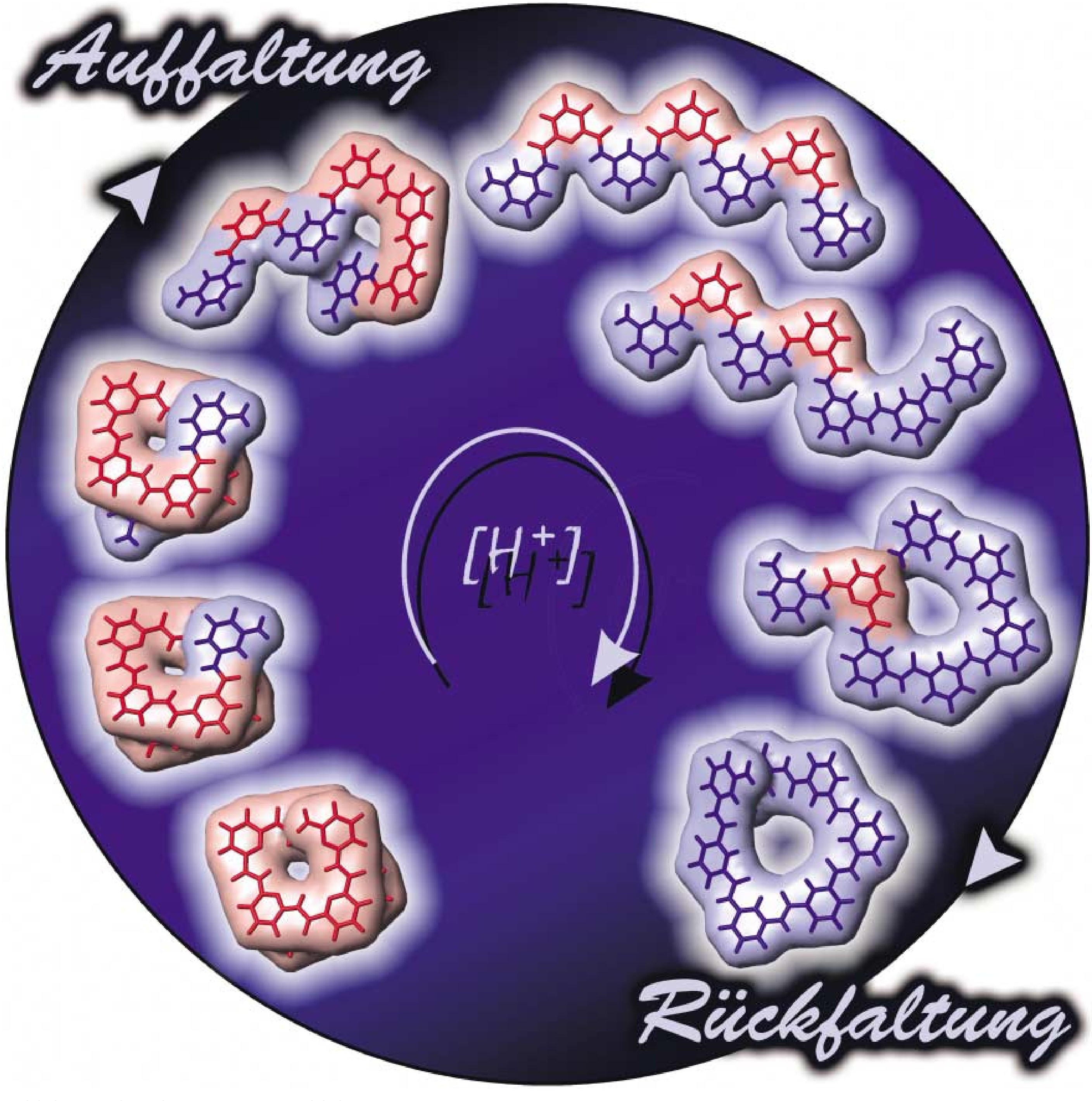
Zuschriften



Molekulare Maschinen können Energie in molekulare Bewegungen von großer Amplitude umwandeln. Die selektive Protonierung eines Oligoamid-Stranges führt zu einer Auffaltung der helicalen Konformation zu einer linearen Struktur, die nachfolgend in eine andere Helix zurückfaltet. Mehr dazu finden Sie in der Zuschrift von I. Huc et al. auf den folgenden Seiten.

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pH-Induced Changes in Conformation

Protonation-Induced Transition between Two Distinct Helical Conformations of a Synthetic Oligomer via a Linear Intermediate**

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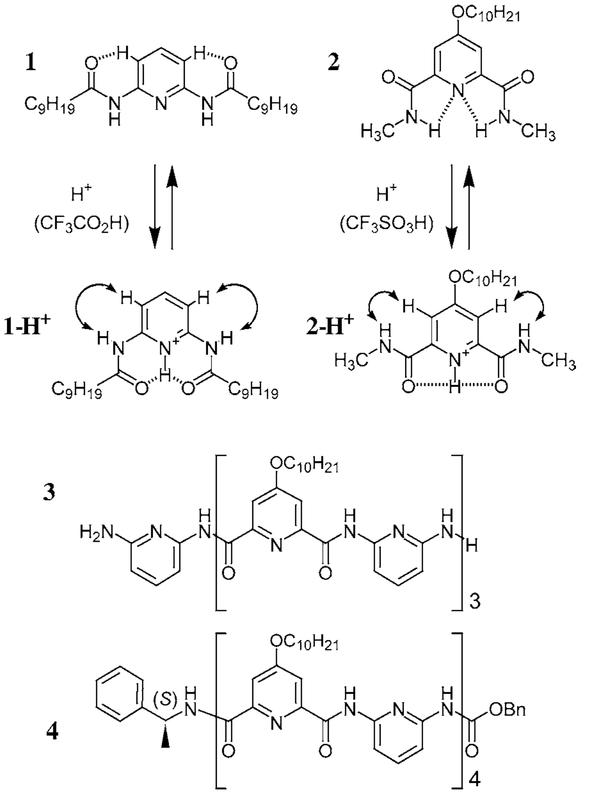
Dedicated to Dr. Christian Rolando

Designed molecular and supramolecular structures held together by noncovalent interactions have been increasing in size and complexity.[1] They provide frames within which or between which controlled dynamic structural changes of large amplitude (molecular motions) can be envisaged such as rotations and translations or combinations thereof.[2] Interest in these so-called molecular machines is fueled by their relation to important natural phenomena and by the prospect of elaborating useful chemical devices. Molecular motions can be triggered by various means (e.g., ion binding, electron transfer, and light excitation) and can often be reverted by simply removing or reversing the triggering stimuli.[2] Here, we present an original system in which a large conformational change caused by protonation is formally reverted not only upon deprotonation but also upon further protonation: helical oligopyridine–dicarboxamide strands unfold to an extended linear conformation upon partial protonation,[3] which upon full protonation refolds to a helix related to (though distinct from) the initial state.

Oligoamides prepared from 2,6-pyridinedicarboxylic acids and 2,6-diaminopyridines adopt stable helical conformations in the solid state as well as in solution in organic solvents and in water.[4–6] The bending of the strands into helices arises from the strongly preferred conformations of 2,6-bis(carbonylamino)pyridine units and 2,6-pyridinedicarboxamide units, which are both stabilized by intramolecular hydrogen bonds as in **1** and **2** (Scheme 1).



Scheme 1. Changes in the conformations of **1** and **2** upon protonation to give **1**-H^+ and **2**-H^+, respectively, and structures of **3** and **4**. The double-headed arrows indicate relevant NOE correlations seen in the ^1H NMR spectra of **1**-H^+ and **2**-H^+.

We speculated that protonation at the pyridine nitrogen of these units should affect their conformational preferences and investigated their behavior in the presence of acids of various strengths: CF_3CO_2H (TFA, $pK_a = 0$), CH_3SO_3H (MsOH, $pK_a = -2$), and CF_3SO_3H (TfOH, $pK_a = -16$). When 1 equiv MsOH is added to a solution of **1** in $CDCl_3$, protonation is shown to occur quantitatively, leading to the conformation shown in Scheme 1, in which the carbonyl groups form hydrogen bonds with the pyridinium N^+H and not with H^3 aryl protons. The following observations support for this conformation: 1) A sharp signal for the pyridinium N^+H is observed at very low field ($\delta = 17$ ppm); 2) Protonation causes downfield shifts of the NMR signals of H^4 and NH protons and an upfield shift of the signal of H^3 as the neighboring carbonyl oxygen moves farther away; 3) NOE experiments with **1**-H^+ reveal a strong correlation between the amide proton and the adjacent aromatic proton, and no correlation with the pyridinium N^+H;[7] 4) The proposed conformation is also adopted in the solid by all four 2,6-bis(carbonylamino)pyridinium derivatives listed in the CCDB.[8]

When TFA is used instead of MsOH, **1** is also protonated but roughly four equivalents of acid are needed.[7] On the other hand, pyridinedicarboxamide **2** is not protonated by TFA[7] and only partially by MsOH.[9] The electron-withdrawing effect of the carbonyl groups and the intramolecular hydrogen bonds apparently decrease the basicity of the pyridine nitrogen. Quantitative protonation of **2** is achieved upon adding TfOH, which results in an upfield shift of the signals of aromatic and amide protons, and the development of a pyridinium signal. NOE experiments with **2**-H^+ show a correlation between the amide proton and the neighbor aryl proton.[7] Again, this indicates a 180° rotation about the aryl-amide linkages, presumably caused by the larger strength of a $N^+H\cdots OC$ hydrogen bond with respect to a $CH^3\cdots OC$ hydrogen bond (Figure 1).

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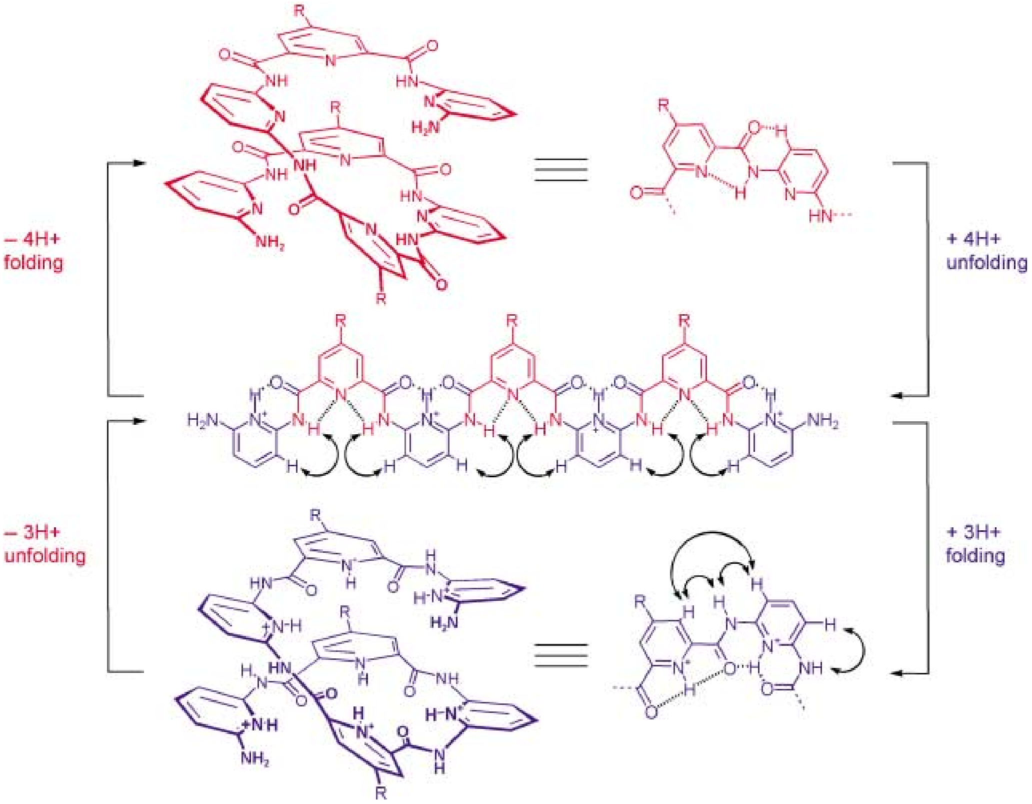
In oligomeric strands **3** and **4**, protonation at each pyridine site is expected to cause local conformational changes that may cooperatively affect the structure of the whole molecule. According to the behavior of **1** and **2**, TFA should protonate all four diaminopyridine units of **3** and only them, giving rise to an extended linear conformation (Scheme 2). When a 1 mM solution of **3** in $CDCl_3$ is titrated with TFA, the initial sharp ^1H NMR spectrum of the single helix broadens extensively as partially protonated species equilibrate and sharpens again when saturation is reached (20 equiv TFA).[7,10] The linear conformation of **3**-$(H^+)_4$ is demonstrated by NOESY spectra which show that each amide proton correlates with only one proton: the H^3 proton of the neighbor aminopyridine ring (Scheme 2 and Figure 1 a).

The conformational preferences of **1**-H^+ and **2**-H^+ led us to speculate that the protonation of **3**-$(H^+)_4$ to give **3**-$(H^+)_7$ may result in the folding of the linear extended strand into a helix (Scheme 2). Heptaprotonation was achieved by treating **3** with an excess of TfOH. The ^1H NMR spectrum shows the signals of the expected four different pyridinium protons at $\delta = 15.5$, 14.9, 11.6, and 11.5 ppm, which can be assigned unambiguously.[11] The signals of the amide protons are found at $\delta = 10.1$, 9.6 and 9.7 ppm and partly overlap with the signal of TfOH. In NOESY experiments each amide signal shows two correlations: one with the H^3 proton of the neighbor diaminopyridine ring, and one with the H^3 proton of the neighbor pyridinedicarbonyl ring (Scheme 2 and Figure 1 b). Moreover, these two aromatic protons also directly correlate. No correlation is observed between the amides and the pyridiniums, which is consistent with the helical structure proposed for **3**-$(H^+)_7$.

Circular dichroism (CD) measurements of **4** were performed to corroborate the NMR data obtained with **3**. The terminal chiral (*S*)-(1-phenyl)ethylamino group of **4** shifts the equilibrium between the right- and left-handed helical conformations, which gives rise to a CD signal in the absorption region of the oligoamide associated with its helical conformation. Upon addition of TFA, this signal progressively disappears (Figure 2 a) and is restored upon neutralization with excess Et_3N. This is consistent with the proposed transition from the helical conformation to the linear strand for **4**-$(H^+)_4$. No chiral induction is possible in the latter, and only the CD bands belonging to the chiral terminal group are observed ($\lambda < 280$ nm).

Titration of **4** with TfOH initially results in a similar decrease of CD intensity as the diaminopyridine units are protonated, but it is then followed by the appearance of a new signal in the absorption region of the pyridinium chromophores as the pyridinedicarbonyl units are protonated as well (Figure 2 b).[12] The oligomeric sequence of **4**-$(H^+)_8$ therefore adopts a chiral conformation, in agreement with the helix proposed on the basis of NMR data.

In summary, the conformational preferences of **1**, **2**, **1**-H^+, and **2**-H^+, on the one hand, and the large difference in pK_{BH^+} between **1**-H^+ and **2**-H^+, on the other hand, translate into selective protonations and conformational changes in oligoamides such as **3** and **4** that give rise to an unprecedented pH-controlled equilibrium between a nonprotonated helix, a



Scheme 2. The equilibria between the helical conformation of **3** (top), the linear conformation of **3**-$(H^+)_4$ (middle), and the helical conformation of **3**-$(H^+)_7$ (bottom) Protonated units are represented in blue and nonprotonated units are in red. The double-headed arrows indicate relevant observed NOE correlations.

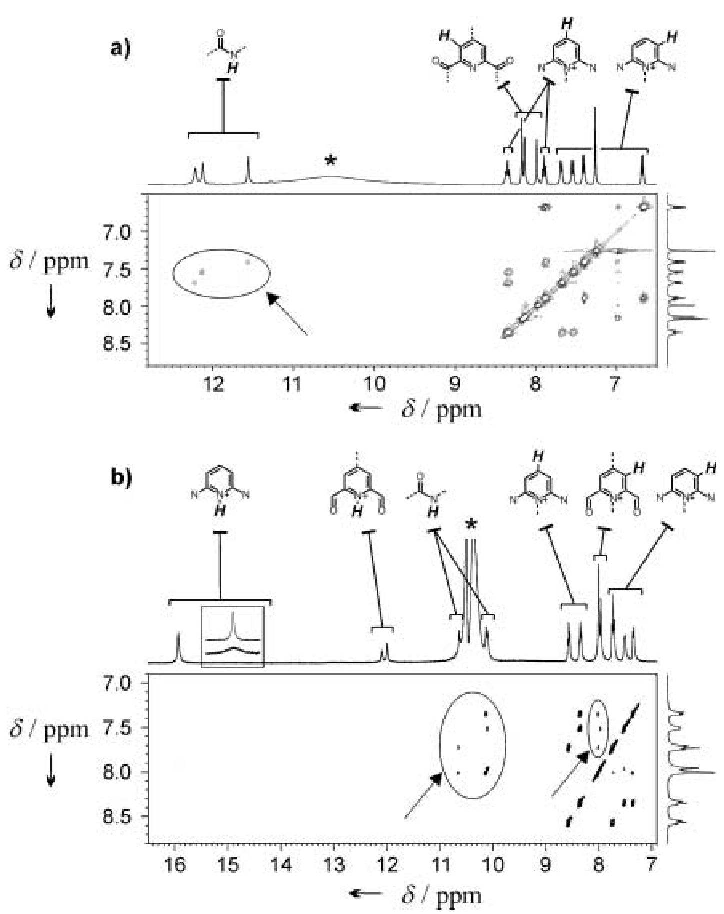


Figure 1. 400 MHz ^{1}H NMR NOESY spectra at 298 K of a) **3**-$(H^+)_4(CF_3CO_2^-)_4$ (20 mM in $CDCl_3$ in the presence of 20 equiv TFA); the asterisk marks the signal of CF_3CO_2H, the arrow marks relevant correlations; b) **3**-$(H^+)_7(CF_3SO_3^-)_4$ (20 mM in TfOH); the asterisk marks the residual signal of CF_3SO_3H after presaturation, arrows mark relevant correlations. Because of exchange phenomena, the presaturation causes the disappearance of the terminal pyridinium signal at $\delta = 14.9$ ppm. If the signal is not presaturated, it is broad at 298 K and sharp at 273 K (inset).

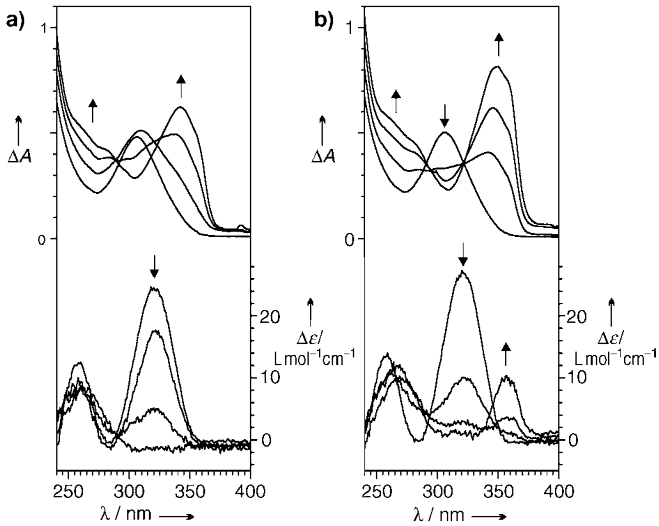


Figure 2. UV/Vis absorption (top) and CD (bottom) spectra of (*S*)-**4** (1 mM in $CHCl_3$ at −10 °C in a 0.1-mm cell) in the presence of acids. The arrows indicate the evolution of the spectra in the presence of a) 0, 30, 50, and 80 equiv TFA and b) 0, 2, 4, and 15 equiv TfOH.

partially protonated linear strand, and a fully protonated helix distinct from the nonprotonated helix. This system may be considered as an "or" logic gate, which gives a CD signal in neutral or very acidic media but not in slightly acid medium. Upon tuning the pK_a of the pyridine nitrogens, using for example electron-donating or -withdrawing groups in position 4, one can hope to combine protonated and nonprotonated pyridine units in even more complex structural patterns and molecular motions.

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Keywords: chirality · conformation analysis · helical structures · hydrogen bonds · supramolecular chemistry

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[1] J.-M. Lehn, *Supramolecular Chemistry–Concepts and Perspectives*, VCH, Weinheim, **1995**.

[2] For reviews: *Special Issue on Molecular Machines* (Ed.: J. F. Stoddart), *Acc. Chem. Res.* **2001**, *34*, 409; V. Balzani, F. Credi, M. Raymo, J. F. Stoddart, *Angew. Chem.* **2000**, *112*, 3484; *Angew. Chem. Int. Ed.* **2000**, *39*, 3348.

[3] For related examples of unfolding of bent or helical conformers: P. S. Corbin, S. C. Zimmermann, *J. Am. Chem. Soc.* **2000**, *122*, 3779; M. Barboiu, J.-M. Lehn, *Proc. Natl. Acad. Sci. USA* **2002**, *99*, 5201; H. Nakako, R. Nomura, T. Masuda, *Macromolecules* **2001**, *34*, 1496; M. Fujiki, *J. Am. Chem. Soc.* **2000**, *122*, 3336; J. Lie, G. B. Schuster, K.-P. Cheon, M. M. Green, J. V. Selinger, *J. Am. Chem. Soc.* **2000**, *122*, 2603.

[4] For a recent and extensive review on the folding properties of synthetic molecular strands see: D. J. Hill, M. J. Mio, R. B. Prince, T. S. Hughes, J. S. Moore, *Chem. Rev.* **2001**, *101*, 3893.

[5] N. C. Singha, D. N. Sathyanarayana, *J. Mol. Struct.* **1997**, *403*, 123; V. Berl, I. Huc, R. G. Khoury, J.-M. Lehn, *Chem. Eur. J.* **2001**, *7*, 2798; I. Huc, V. Maurizot, H. Gornitzka, J.-M. Léger, *J. Chem. Soc. Chem. Commun.* **2002**, 578.

[6] For related systems see: B. Gong, *Chem. Eur. J.* **2001**, *7*, 4337, and references therein; Y. Hamuro, S. J. Geib, A. D. Hamilton, *J. Am. Chem. Soc.* **1997**, *119*, 10587.

[7] See supporting information.

[8] S. J. Geib, S. C. Hirst, C. Vicent, A. D. Hamilton, *J. Chem. Soc. Chem. Commun.* **1991**, 197; R. P. Dixon, S. J. Geib. , A. D. Hamilton, *J. Am. Chem. Soc.* **1992**, *114*, 365; R. Ostaszewski, Z. Urbanczyk-Lipkowska, *J. Mol. Struct.* **1999**, *474*, 197.

[9] The data cannot be interpreted unambiguously. The addition of MsOH causes some variations in chemical shifts, which suggests that protonation occurs, but no pyridinium signal is observed. The titrations are complicated by the poor miscibility of $CDCl_3$ and MsOH, and cosolvents interfere with the protonation.

[10] Protonation also causes the dissociation of the double helices formed by these oligomers, see: V. Berl, I. Huc, R. G. Khoury, M. J. Krische, J.-M. Lehn, *Nature* **2000**, *407*, 720; V. Berl, I. Huc, R. G. Khoury, J.-M. Lehn, *Chem. Eur. J.* **2001**, *7*, 2810.

[11] The assignment is based on the comparison of this spectrum to the spectra of shorter oligomers, and on the integration and the values of the chemical shifts of these signals: the signals at higher field belong to the pyridinedicarbonyl units, and the signals at lower field belong to the diaminopyridine units; the less deshielded and broader signal at $\delta = 14.9$ ppm is assigned to the terminal pyridinium unit, which can form a hydrogen bond with only one carbonyl group.

[12] The band induced in the pyridinium chromophores becomes faint at very high TfOH concentration (above 30 equiv) or in the presence of MeOH, presumably because of a weaker induction in protic medium.