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In references *Advances in Polymer Science* is abbreviated *Adv Polym Sci* and is cited as a journal.

Springer WWW home page: springer.com
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Library of Congress Control Number: 2006934209

ISSN 0065-3195
ISBN 978-3-540-46829-5 Springer Berlin Heidelberg New York
DOI 10.1007/978-3-540-46830-1

Springer is a part of Springer Science+Business Media

springer.com

Cover design: WMXDesign GmbH, Heidelberg
Typesetting and Production: LE-TEX Jelonek, Schmidt & Vöckler GbR, Leipzig

Printed on acid-free paper 02/3100 YL – 5 4 3 2 1 0

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Adv Polym Sci (2007) 206: 1–29
DOI 10.1007/12_092

Published online: 10 June 2006

Enforced Folding of Unnatural Oligomers: Creating Hollow Helices with Nanosized Pores

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Abstract This article reviews the progress made during the last several years on developing folding helical oligomers consisting of aromatic residues based on a backbone-rigidification strategy. In this approach, rigid, planar, aromatic residues are linked by planar linkers such as amide and urea functionalities. Folding into helical conformations is realized based on the incorporation of localized intramolecular hydrogen bonds that limit the rotational freedom of the backbones, and through the introduction of backbone curvature by linking the aromatic residues in a nonlinear fashion. As a result, the corresponding oligomers are forced to adopt well-defined helical conformations containing interior cavities. Changing the backbone curvature leads to the tuning of the cavity sizes. Such enforced folding based on a "tying up" leads to stable helical backbones that are independent of side chain substitution, which offers a variety of robust helical scaffolds for presenting functional groups. The pore-containing helices combine the feature of secondary and tertiary structures, a feature seen in few other natural or unnatural folding

systems. Such an enforced folding approach should provide a simple, predictable strategy for developing a new class of nanoporous structures with predictable dimensions.

Keywords Aromatic oligoamides · Foldamer · Folding · Helix · Nanoporous

Abbreviations

AFM	Atomic force microscopy
CD	Circular dichroism
1D	One-dimensional
2D	Two-dimensional
DCC	Dicyclohexylcarbodiimide
DMF	*N*,*N*-Dimethylformamide
DMSO	Dimethyl sulfoxide
DNA	Deoxyribonucleic acid
EDC	1-Ethyl-3-(3-dimethylaminopropyl) carbodiimide
ESI	Electrospray ionization
GPC	Gel-permeation chromatography
HATU	1-[Bis(dimethylamino)methylene]-1*H*-1,2,3-triazolo[4,5-*b*]pyridinium-3-oxide hexafluorophosphate
IR	Infrared
MALDI	Matrix-assisted laser desorption/ionization
NMR	Nuclear magnetic resonance
NOE	Nuclear Overhauser enhancement
NOESY	Nuclear Overhauser enhancement (effect) spectroscopy
PE	Phenylene ethynylene
m-PEs	*meta*-Phenylene ethynylenes
TFA	Trifluoroacetyl
T_m	Melting temperature of DNA
UV	Ultraviolet

1 Introduction

During the last 10 years there has been increasing interest in the design and synthesis of both oligomeric and polymeric systems that fold into well-defined secondary structures [1–10]. Foldamer research is the culmination of efforts beginning in the early twentieth century at the advent of synthetic polymer chemistry and the growth of fields such as molecular biology and supramolecular biology [4]. The amalgamation of these fields has led to the development of unnatural folding systems.

The field of unnatural folding oligomers (aka foldamers) was pioneered by the research groups of Gellman and Seebach, from the studies of secondary structural properties of β-peptides [11–23]. A foldamer, as defined by Moore, is "any oligomer that folds into a conformationally ordered state in solution, the structures of which are stabilized by a collection of noncovalent inter-

actions between nonadjacent monomer units" [4]. More simply, a foldamer can be expressed as an unnatural system that adopts a well-defined secondary structure [2].

Numerous unnatural oligomers that fold into these well-defined secondary structures (foldamers) have been reported since the pioneering work of Gellman and Seebach [11, 19–21]. Recent progress has been made in designing pseudo-biological oligomers (or polymers) that fold predictably. Major systems involve those developed in the laboratories of Iverson [23–26], Lehn [27–30], Moore [31–47], Gong [48–55], and Huc [56–65]. Indeed, since the mid-1990s a veritable explosion in the development of novel folding systems has opened the door to wide-ranging biological and materials science applications. Unnatural foldamers are being developed to answer whether nature has the monopoly on folded structures, to mimic the functions of biomacromolecules, to test if new functions not seen in nature can be developed, and finally, to probe whether diverse chemical challenges can be met [2].

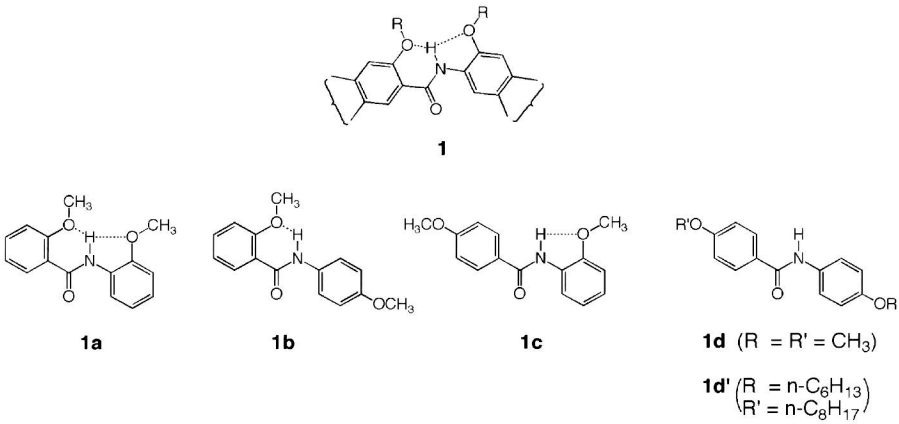
Among reported foldamer systems, those consisting of flat, rigid, aromatic residues constitute a significant percentage [8, 9]. Most of these oligomers fold into various helical conformations. This review summarizes the progress made in recent years on designing and preparing porous structures based on a backbone-rigidification strategy that enforces crescent or helical conformations on aromatic oligoamides and related oligomers. Our own effort along this direction has led to foldamers with enforced, well-defined helical conformations containing cavities of adjustable sizes. Recently, the enforced folding of precursor oligomers was also found to facilitate highly efficient macrocyclization processes, leading to shape-persistent macrocycles with large interior cavities [66].

2
Backbone-Rigidified Folding Oligoamides with Tunable Cavity Sizes

2.1
A Novel Three-Center Hydrogen Bond

We have developed a general strategy for achieving a folded conformation based on the rigidification of the backbones of aromatic oligoamides. The key to the success of this approach is a three-center hydrogen bond consisting of the five- and six-membered hydrogen-bonded rings as shown by the general structure **1**. We extensively investigated the stability of this previously unknown three-center hydrogen bond using both theoretical [49, 67, 68] and experimental [48–52, 66] methods.

Amide **1a** and its structural isomers **1b–d** were studied using the Gaussian 98 program, X-ray crystallography, and IR and ^{1}H NMR spectroscopies. The obtained results clearly revealed *positive cooperativity* between the two-



center hydrogen-bonding components, i.e., the two two-center components of the three-center hydrogen bond reinforce each other.

The calculated and experimental results, shown in Table 1, closely follow the same trend. The cooperative effects are demonstrated by the N – H stretching frequencies. Relative to **1d**, ab initio calculation indicates that the formation of a two-center H-bond in a five-membered ring in **1c** produces a small blueshift of the N – H stretching frequency, indicating the weakness of this two-center H-bond which alone does not have the strength to produce the expected redshift. IR experiment showed that the N – H stretching fre-

Table 1 Calculated and measured parameters for the N – H bonds of **1a–d** [a]

Compd	υ_{NH} (calcd) [b] (cm^{-1})	υ_{NH} (obsd) (cm^{-1})	δ_{NH} (calcd) [c] (ppm)	δ_{NH} (obsd) [c] (ppm)	r_{NH} (calcd) (Å)	r_{NH} (obsd) (Å)
1a	3423	3340	10.43	10.61	1.013	0.91 ± 0.02
	(– 57)	(– 104)	(3.16)	(3.00)	(0.005)	
1b	3437	3372	9.80	9.61	1.011	0.86 ± 0.02
	(– 43)	(– 72)	(2.53)	(2.00)	(0.003)	
1c	3485	3433	8.46	8.50	1.009	0.85 ± 0.02
	(+ 5)	(– 11)	(1.19)	(0.90)	(0.001)	
1d [d]	3480	3444	7.27	7.61	1.008	–
	(0)	(0)	(0.00)	(0.00)	(0.000)	

[a] Values in parentheses relative to **1d'**. IR and NMR measurements carried out at 1 mM of sample concentration

[b] Frequencies scaled by 0.9613

[c] Values of chemical shifts relative to that of TMS (calculated value = 31.91 ppm)

[d] Calculation based on **1d**; IR and NMR measurements based on **1d'**

quency of **1c** did show a small but clearly discernable redshift of 11 cm^{-1}. In sharp contrast, the cooperative action of the two two-center components in **1a** leads to a much larger redshift in the N – H stretching frequency of **1a** than the two-center bond in **1b** or **1c**. The sizable redshift value clearly indicates nonpairwise effects.

Cooperative effects are also manifested by the ^1H NMR signals of the amide protons, as indicated by results from both computational and experimental studies. There is a shift to lower field upon formation of an H-bond. The shift is larger for the two-center H-bond of **1b** than for that of **1c**, and is the largest upon forming the three-center H-bond in **1a**, indicating the energetic superiority of the three-center H-bonding over the two-center H-bonding.

Ab initio calculation indicated that the donor N – H bonds of amides **1a–c** were all elongated upon formation of intramolecular H-bonds relative to **1d**. The formation of a three-center H-bond in **1a** leads to the largest increase of its N – H bond length among amides **1–3**. In contrast, the N – H bond of **1c** shows the smallest increase in its length, indicating that the two-center H-bond in **1c** is the weakest. The measured N – H bond lengths of **1a**, **1b**, and **1c** based on their crystal structures are consistent with the ab initio results.

The enhanced stability of the three-center hydrogen bond was further confirmed by rates of hydrogen–deuterium (H-D) exchange involving the amide protons. As shown in Fig. 1, compared to those of **1b** and **1c**, the amide proton of **1a** exhibits a long half-life of H-D exchange, suggesting a very slow exchange reaction. Such a result implies that the enforced conformation of **1a** is quite robust, undergoing slow interconversion between conformations.

The intramolecular three-center H-bonding interaction also persists in the solid state. As shown in Fig. 2, in the crystal structure of **1a**, the NH group is involved in both a five-membered ring H-bond and a six-membered ring H-bond, leading to a planar molecule reminiscent of a typical three-center H-bond [70]. The six-membered ring H-bond in **1b** is preserved in its solid-state structure. Amide **1b** adopts a nearly flat conformation due to the presence of this two-center intramolecular H-bond. The five-membered ring H-bond in **1c**, which persists in solution as indicated by IR and NMR

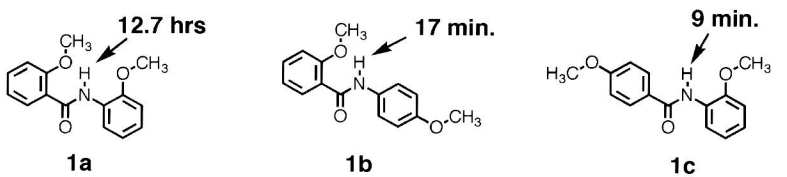


Fig. 1 The half-lives of amide proton–deuterium exchange of amides **1a–c** based on 1D NMR experiments (500 MHz, $CDCl_3$: DMSO-d_7 : D_2O = 2 : 19 : 19)

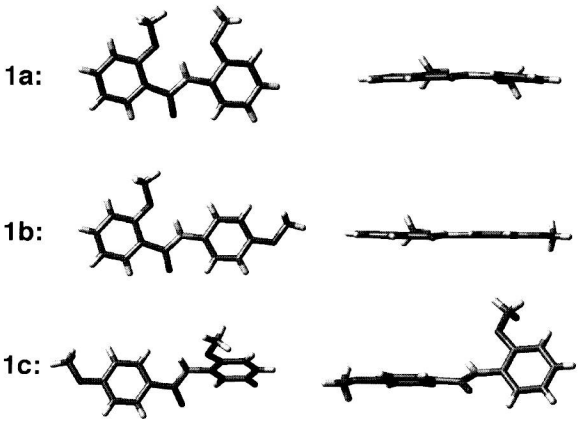


Fig. 2 The crystal structures of amides **1a–c** as viewed from the front (*left*) and side (*right*)

data, is disrupted in the solid state. Instead of forming an intramolecular H-bond, the NH of **1c** is involved in intermolecular H-bonding, indicating the marginal stability of the five-membered ring H-bond observed in solution. Positive cooperativity in the three-center H-bonding in **1a** is clearly indicated by these results; the presence of the six-membered ring component helps the formation of the five-membered ring component which would otherwise be disrupted, as shown by the solid-state structure of **1c**.

The extraordinary stability of the hydrogen-bonded diarylamide structure was further demonstrated by the nuclear Overhauser enhancement spec-

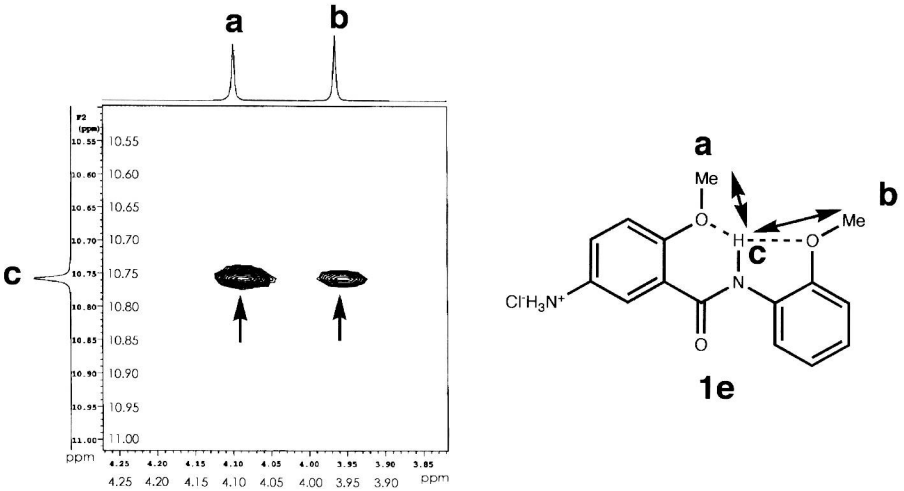


Fig. 3 NOEs observed in the NOESY spectrum of **1e** (6 mM) in 50% DMSO-d_6/50% H_2O (500 MHz, mixing time 0.5 s, 298 K)

troscopy (NOESY) spectrum of the water-soluble amide **1e** recorded in 1 : 1 D_2O and DMSO-d_6 (Fig. 3). The persistence of the three-center hydrogen bond was revealed by two strong NOEs corresponding to contacts between the amide proton and those of the two adjacent methoxy groups. Even in the presence of 50% D_2O, the amide proton of **1e** underwent very slow exchange, which allowed the NOEs involving the amide proton to be recorded. The high stability of the three-center H-bonds in longer oligomers was also demonstrated by the half-lives of amide H-D exchange, ranging from days to too long to be measurable [48, 52].

2.2 Crescent Oligoamides

We designed a series of short aromatic oligoamides with enforced, crescent backbones. Figure 4 shows the crystal structures of a dimer, a trimer, and a tetramer, which are the nitro oligomer intermediates for preparing longer oligomers. The backbones of these short oligomers are almost completely planar due to the presence of the three-center hydrogen bonds. The folded conformations were indicated by the strong amide–side chain NOEs that were detected by NOE difference and NOESY spectra in $CDCl_3$ [48–50, 52]. Each of the amide protons shows the expected NOEs with the protons of the methyl or α- and β-methylene groups of its two adjacent side chains. These amide–side chain NOEs were detected in a variety of solvents with oligomers of different lengths. Their consistent presence has served as a convenient indi-

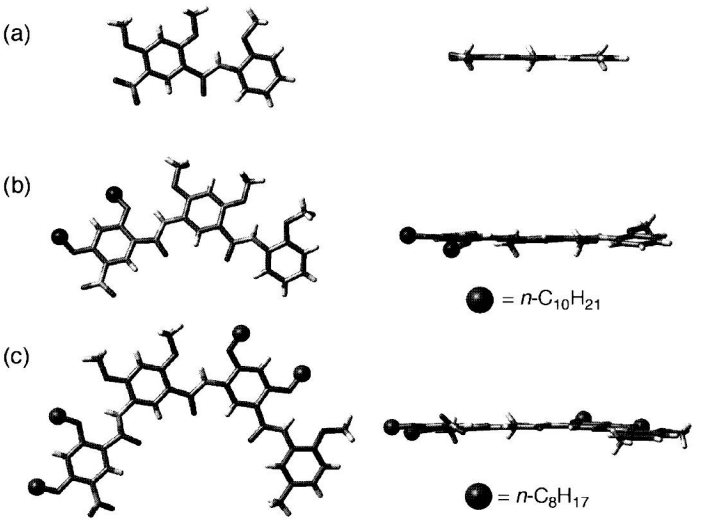


Fig. 4 The crystal structures of **a** a dimer, **b** trimer, and **c** a tetramer, as viewed from front (*left*) and side (*right*)

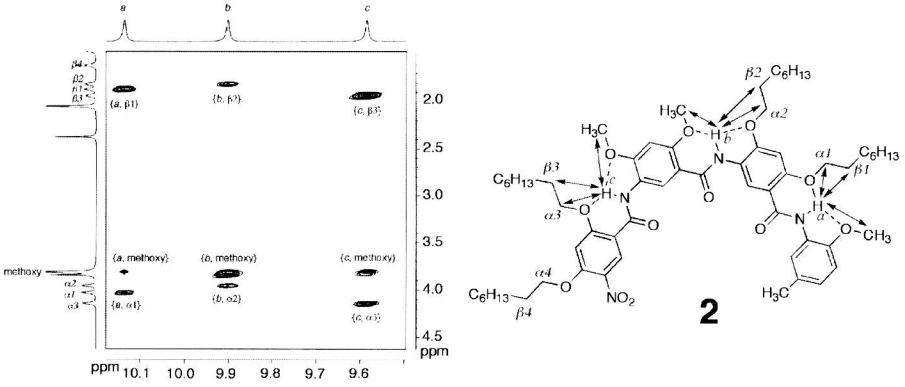


Fig. 5 Expanded plot of the NOESY spectrum of **2** in $CDCl_3$ (50 mM, 800 MHz, 300 K, mixing time: 0.3 s) showing the NOEs between the amide proton and the protons of the side chains

cator of the presence of the three-center H-bonds, and thus for the folding of these crescent-shaped short oligoamides. For example, the NOESY spectrum of tetramer **2** shows three cross peaks for each of the amide protons, corresponding to contacts with protons of the side chains (Fig. 5).

Similar NOESY studies in water (90% H_2O, 10% D_2O) on water-soluble tetramer **3** showed the same amide–side chain NOEs (Fig. 6), suggesting that these foldamers are stably folded in water. These oligoamides, with rigidified backbones and persistent shape, possess large, amide oxygen-decorated cavities that should serve as hosts for large cations and polar organic molecules.

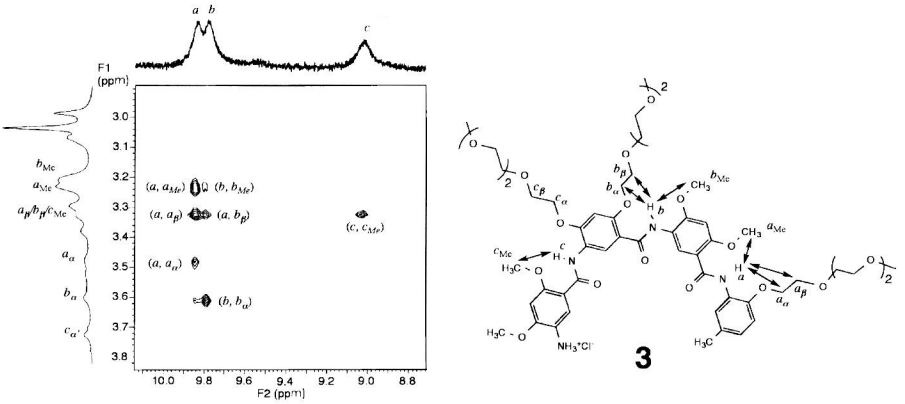


Fig. 6 Partial NOESY spectrum of tetramer **3** in water containing 5% D_2O (10 mM, 500 MHz, 297 K, mixing time: 0.5 s). The NOEs between the protons of the amide groups and those of the adjacent side chains are indicated by *arrows*