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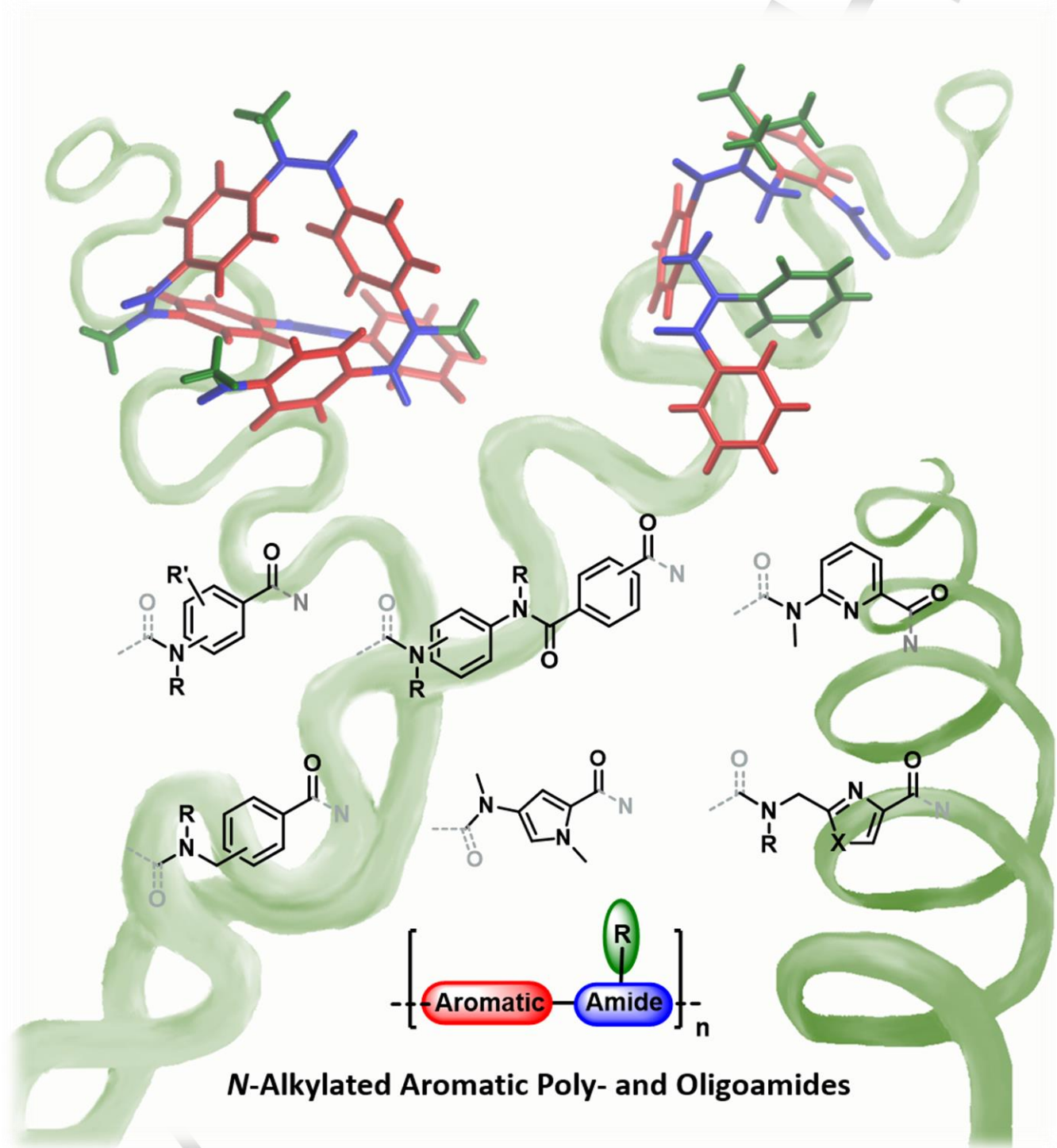
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## N-Alkylated Aromatic Poly- and Oligoamides

Ayman Akhdar,<sup>[a]</sup> Dr. Arnaud Gautier,<sup>[a]</sup> Dr. Thomas Hjelmgaard,<sup>\*[b]</sup> and Dr. Sophie Faure<sup>\*[a]</sup>



# N-Alkylated Aromatic Poly- and Oligoamides

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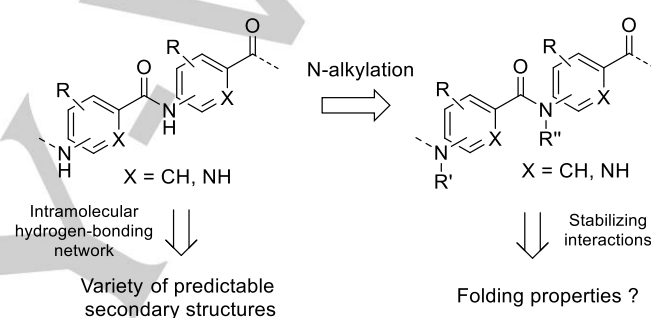
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**Abstract:** *N*-alkylated aromatic poly- and oligoamides are a particular class of abiotic foldamers that is deprived of the capability of forming intramolecular hydrogen-bonding networks to stabilize their tri-dimensional structure. The alkylation of the backbone amide nitrogen atoms greatly increases the chemical diversity accessible for aromatic poly- and oligoamides. However, the nature and the conformational preferences of the *N,N*-disubstituted amides profoundly modify the folding properties of these aromatic poly- and oligoamides. In this review, representative members of this class of aromatic poly- and oligoamides will be highlighted, among them *N*-alkylated phenylene terephthalamides, benzamides, pyridylamides and aminomethyl benzamide oligomers. The principal synthetic pathways to the main classes of *N*-alkylated aromatic polyamides with narrow to broad molecular-weight distribution, or oligoamides with specific sequences, will be detailed and their foldameric properties will be discussed. The review will end with describing the few applications reported to date and the future prospects.

## 1. Introduction

Aromatic oligoamides constitute a particularly important class of abiotic foldamers with a high propensity to adopt well-defined conformations.<sup>[1]</sup> Many types have been designed that fold into secondary as well as tertiary structures owing to their highly constrained backbones. The most studied are oligoamides comprising benzene, pyridine and/or quinoline scaffolds with the amide connections arranged in either a “one-way sequence” manner using amino acid building blocks or in a symmetric manner using a combination of diamine and diacid building blocks (Figure 1). These oligoamides quickly proved to be highly conformationally stable, predictable and modular foldamers.<sup>[2]</sup> Their well-defined conformations arise from intramolecular hydrogen-bonding networks, restricted rotation about the aryl-amide bonds and the intrinsic rigidity and planarity of the aromatic units.<sup>[1a]</sup> The high predictability and the robustness of their tridimensional structuration have made aromatic oligoamides promising unnatural oligomers for applications in biological and material sciences. For example,  $\alpha$ -helix or  $\beta$ -sheet-like foldamers exhibiting tailored functions have been designed to mimic or bind to protein surfaces.<sup>[3]</sup> Although the aromatic oligoamide backbones are inherently only distantly related to the parent peptides and proteins, the aim is still to mimic the side chain presentation of these biopolymers. To address this challenge, it is therefore necessary to increase the tunability of aromatic oligoamides. To introduce further chemical diversity, substitution of the aromatic entities was studied extensively but the synthetic access to the required diversely functionalized building blocks is

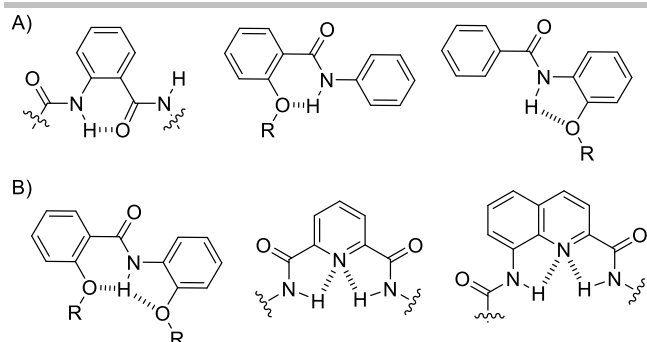
time-consuming and can sometimes be particularly challenging.<sup>[1]</sup> Given that most of the aromatic oligoamides such as benzamide and pyridylamide oligomers are deprived of aliphatic carbons in their backbone, the remaining way to further enhance chemical diversity is alkylation of the backbone amide nitrogen (Figure 1).



**Figure 1.** Schematic representation of aromatic oligoamides and their *N*-alkylated counterparts.

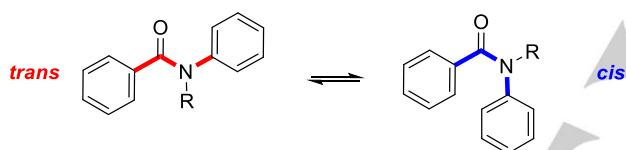
This strategy appears particularly appealing considering the large variety of side chains potentially accessible. However, the stabilizing interactions involving the amide protons that serve to restrict the rotation about the NHCO-aryl bond will unfortunately no longer be available. Indeed, local hydrogen bonding represents the most versatile means to block rotation about the CONH-aryl and NHCO-aryl bonds and lead to robust, well-defined secondary structures such as crescents and helices (Figure 2). For example, in *ortho*-connected benzamide oligomers, intramolecular hydrogen bonds between adjacent amide-NH and CO groups lead to a planar arrangement of the substituents and formation of a linear strand structure of oligoanthranilamides as demonstrated by Hamilton and coll.<sup>[4]</sup> An exocyclic hydrogen-bond acceptor (such as an alkoxy group) at the *ortho* position on the aryl group was found to stabilize the anti-conformation through a six- or five-membered hydrogen-bonded ring.<sup>[5]</sup> This strategy was particularly efficient for the design of  $\alpha$ -helix proteomimetics.<sup>[6]</sup> Based on the same principle, Gong and co-workers showed that a three-center hydrogen bonding system can exist and totally block rotation around the amide linkage.<sup>[7]</sup> Repetition of this motif into *meta*- and/or *para*-benzamide oligomers gave rise to rigid crescent and pseudo-cyclic structures with various curvatures. In aza-aromatic oligoamides such as pyridine and quinolone amide oligomers, three-center hydrogen bonding systems are also the key of their robust and predictable secondary structures.<sup>[1]</sup>

## MINIREVIEW



**Figure 2.** Examples of hydrogen bonding systems: A) two-center hydrogen bonding systems; B) three-center hydrogen bonding systems found in aromatic and aza-aromatic amide oligomers.

These examples show that the absence of the amide-NH group will considerably alter the foldameric properties of aromatic oligoamides. Besides this, *N*-alkylated aromatic oligoamides also have to deal with another major feature of the *N,N*-disubstituted amides; the low-energy rotameric *cis/trans* barrier.<sup>[8]</sup> Thus, while most secondary aromatic amides exhibit a *trans* conformation, *N,N*-disubstituted amides are prone to *cis/trans* isomerism (Figure 3). The preferred conformation depends on various steric and/or electronic interactions that take place between the backbone and the side chain on the nitrogen.



**Figure 3.** *Cis/trans* isomerism of *N*-alkylated aryl amides.

**Thomas Hjelmgard**, obtained his PhD in total synthesis from the Technical University of Denmark (Prof. D. Tanner, 2005). He then continued as postdoctoral fellow within total synthesis (Prof. J. Nielsen, 2005), linear and macrocyclic peptides (Prof. D. J. Aitken, 2006), linear and macrocyclic peptoids (Prof. C. Taillefumier, 2008), and arylopeptoids (Prof. J. Nielsen). In 2012, he became assistant professor at the University of Copenhagen, working on arylopeptoid constructs. In 2013, Thomas moved to an R&D position at Rockwool International, focusing on research within green chemistry.



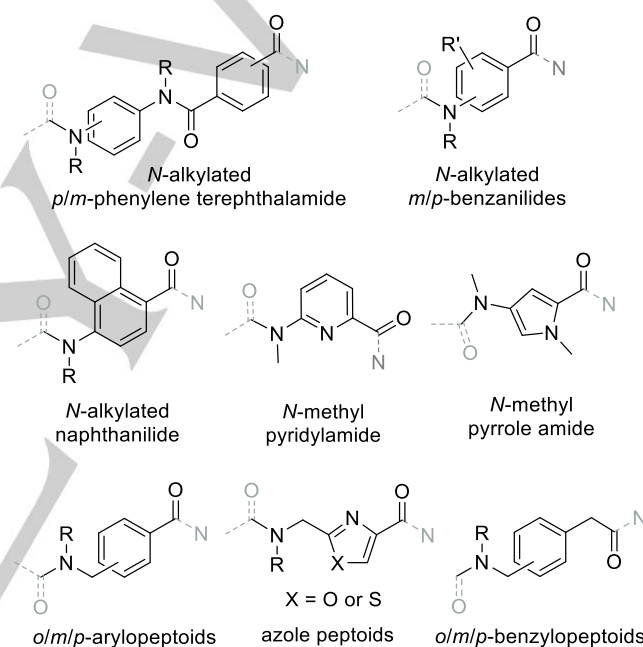
**Sophie Faure**, studied chemistry at the University of Reims-Champagne-Ardennes where she received her PhD in organic photochemistry in 1999. As postdoctoral fellow, she worked with Prof. D. Enders in Aachen and at the faculty of pharmacy Paris-Descartes. She joined the CNRS in 2002 as Chargé de Recherche to work on natural macrocyclic peptides with Prof. D. J. Aitken. In 2007, she turned her interest towards the synthesis and study of the foldameric properties of  $\alpha$ -peptoid oligomers and related family members such as  $\beta$ -peptoids and arylopeptoids.



This review will focus on *N*-alkylated poly- and oligoamides. The main type of *N*-alkylated aromatic poly- and oligoamides developed to date will be reviewed. The various synthetic strategies used to access either polymers or oligomers will then be detailed, followed by the foldameric properties. At the end of the review, the applications reported in the literature and the future prospects will be discussed.

## 2. Classes of *N*-alkylated aromatic oligoamides

The *N*-alkylated aromatic poly- or oligoamides developed to date can be divided into different classes depending on the backbone aromatic or heteroaromatic ring nature, the mono- or bi-directional amide arrangement and the presence or absence of aliphatic carbons in the backbone (Figure 4).



**Figure 4.** Some classes of *N*-alkylated oligoamides developed in the literature.

The first example of *N*-substituted aromatic amide repeating sequences appeared back in the 1980s in the polymer field with the study of poly(*m*- or *p*-phenylene terephthalamide) derivatives to modulate the physical properties of Kevlar® (poly(*p*-phenylene terephthalamide, PPTA) and Nomex® (poly(*m*-phenylene terephthalamide, MPDI), and in particular in an attempt to increase the solubility of these types of polymers.<sup>[9]</sup> *N*-substituted PPTA and MPDI are composed of alternating symmetric aryl diacid and aryl diamine residues with *para* and *meta* substitution patterns, respectively (Figure 4), and can be obtained by direct polymerization of secondary aromatic diamines and terephthaloyl chloride or by alkylation of the formed PPTA (section 3.1). Introduced ten years later by Shudo and co-workers,<sup>[10]</sup> *N*-alkylated benzamides represent one of the most studied type of *N*-substituted aromatic oligoamides (Figure 4). Various *meta*-<sup>[11]</sup> and *para*-oligobenzamides<sup>[10]</sup> were studied, including mixed backbones.<sup>[12]</sup> Although more difficult to obtain, the conformational preference of *ortho*-connected benzanilides have been studied by the Clayden group.<sup>[13]</sup> However, the synthetic



## MINIREVIEW

methods developed to access these oligobenzamides in general do not allow for the preparation of chemically defined oligomers. In spite of the wide structural diversity that is potentially available by the introduction of various side chains on the nitrogen of the backbone amides, this approach is thus far less exploited than for other classes of *N*-alkylated oligoamides such as peptoids (*i.e.* oligomeric or *N*-substituted glycines).<sup>[14]</sup> Indeed, mainly homooligomers have been studied and only scarce examples of heterooligomers have been reported.<sup>[15]</sup> The secondary structures adopted by these oligomers have been studied in detail and some of them were shown to exhibit helical conformations (section 4.2).<sup>[16]</sup> Among anilide-type oligomers, the more hindered *N*-alkylated oligo-1,4-naphthanilide have also briefly been addressed but a preferred structuration could not be evidenced (Figure 4).<sup>[16b]</sup> Pyridine-containing *N*-methyl heteroaromatic amides were studied by Okamoto and co-workers. The hydrogen bond acceptor ability of the pyridine ring was exploited to design aromatic oligoamides that were conformationally switchable under exposure to external stimuli (section 5).<sup>[17]</sup> Inspired by the structure of natural oligoamides, netropsin and distamycin A that bind in the minor groove of DNA,<sup>[18]</sup> polyamides containing *N*-methylpyrrole amino acids were also studied.<sup>[19]</sup> Tanatani and co-workers have recently explored the conformational preferences of the *N*-alkylated amide bonds on the pyrrole group in heterooligomers containing both pyrrole and arene rings.<sup>[20]</sup> More related to *N*-alkylated benzamides, oligomeric *N*-substituted aminomethyl benzamides, or arylopeptoids, possess a backbone-methylene group adjacent to the phenyl ring. In connection with their pioneering work on peptoids,<sup>[14]</sup> Zuckermann and co-workers briefly mentioned the synthesis of such oligomers in few patents back in the 1990's,<sup>[21]</sup> but arylopeptoids were further developed by other groups taking advantages of the great chemical diversity available by variation of the substituents on the nitrogen.<sup>[22]</sup> The replacement of the phenyl group by heteroaromatic rings such as thiazole and oxazole led to azole peptoid-type oligomers.<sup>[23]</sup> The addition of a second backbone-methylene between the aromatic and the acid function resulted in benzylopeptoids which were briefly studied by De Riccardis and co-workers to access macrocycles with complexing properties.<sup>[24]</sup>

### 3. Synthesis of *N*-alkylated aromatic poly- and oligoamides

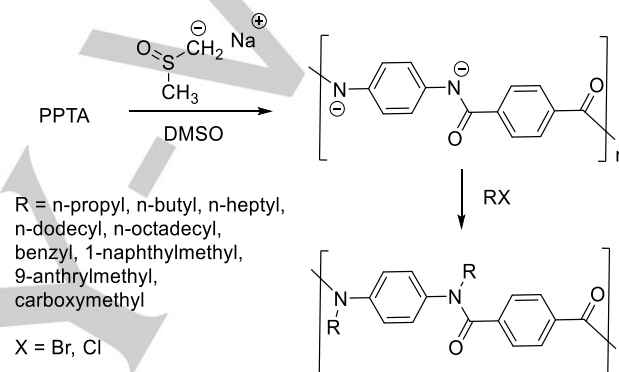
This section describes the principal synthetic pathways to the main classes of *N*-alkylated aromatic poly- or oligoamides.

The synthetic approaches leading to polymers with broad to narrow molecular-weight distribution are detailed in section 3.1 (Alkylation of polyamides and direct polymerization) and those leading to oligoamides with precise and defined sequences are detailed in sections 3.2 (Monomer synthesis) and 3.3 (Submonomer synthesis).

#### 3.1. Alkylation of polyamides and direct polymerization

*N*-substituted poly(*m*-phenylene terephthalamide) were originally prepared by polycondensation of symmetrical *N,N'*-disubstituted diamines and arylene diacid chlorides but suffer from the poor solubility of the formed polymers and the lability of the secondary diamines at high temperature leading to polyamides with broad molecular-weight distribution.<sup>[9b]</sup> This method was rapidly

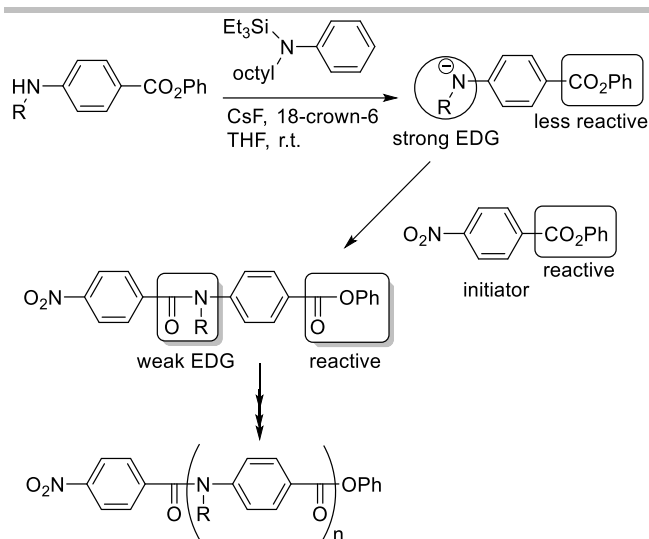
replaced by alkylation of poly(*p*-phenylene terephthalamide) (PPTA) or poly(*m*-phenylene terephthalamide) (MDPI) with a selected alkyl or aryl halide *via* a metalation reaction.<sup>[9a]</sup> However, the major issue is achieving full completion of the reaction in order to obtain homogeneous *N*-substituted polymers.<sup>[25]</sup> A high degree of alkylation and aralkylation could be obtained by using sodium methylsulfinylmethylide in dimethyl sulfoxide as solvent, improving the solubility of the *N*-metalated PPTA compared to sodium in liquid ammonia (Scheme 1).<sup>[9a]</sup> Applying these conditions, a panel of alkyl or aryl halides, bromo acetic acid, propylene oxide and acrylonitrile were used as reagents for the *N*-alkylation reaction.<sup>[9a], [26]</sup> A high degree of substitution (86 to 100%) was observed for PPTA polymers with both low and high average molecular weights (4100 and 24 000 g.mol<sup>-1</sup>), except for 9-anthrylmethyl and carboxymethyl substituents. However, this method of access could not provide polyamides with narrow polydispersity.



**Scheme 1.** Alkylation of poly(*p*-phenylene terephthalamide).

To access polymers of *N*-alkylated benzamides with a polydispersity ( $M_w/M_n$ ) close to 1, Yokozawa and co-workers have developed a chain-growth polycondensation process<sup>[27]</sup> using phenyl aminobenzoate derivatives.<sup>[28]</sup> To provide aromatic polybenzamides having precisely controlled molecular weights and quite narrow molecular weight distributions (MWD), the process relies on the use of a small amount of reactive initiator and the formation of a polymer with more reactive end groups than the monomer to avoid step-growth polycondensation. Thus, an *N*-alkylated *p*-benzamide polymer with high molecular weight ( $M_n = 10\,000\text{ g.mol}^{-1}$ ) and narrow distribution ( $M_w/M_n = 1.12$ ) was synthesized using *N*-triethylsilyl-*N*-octyl aniline in presence of cesium fluoride as base to deprotonate the phenyl 4-(alkylamino)benzoate building blocks. A highly reactive anilide anion is then formed while the ester group in the *para* position undergoes a strong deactivating effect (Scheme 2).<sup>[29]</sup> Phenyl 4-nitrobenzoate as initiator is therefore required to enable the formation of the first amide bond. The propagation is then ensured by reaction of the reactive monomer with the ester of the growing chain. Shortly thereafter, Ueda and co-workers reported a similar polycondensation process with the metal amide anion of 4-(*N*-octylamino)benzoylbenzoxazolin-2-thione generated using EtMgBr in the presence of LiCl and *p*-nitrobenzoyl chloride as initiator.<sup>[30]</sup> *N*-octyl *p*-benzamide polymers with  $M_n$  ranging from 4 700 to 20 100 g.mol<sup>-1</sup> were prepared using this new protocol with narrow distributions ( $M_w/M_n = 1.13\text{-}1.17$ ).

## MINIREVIEW

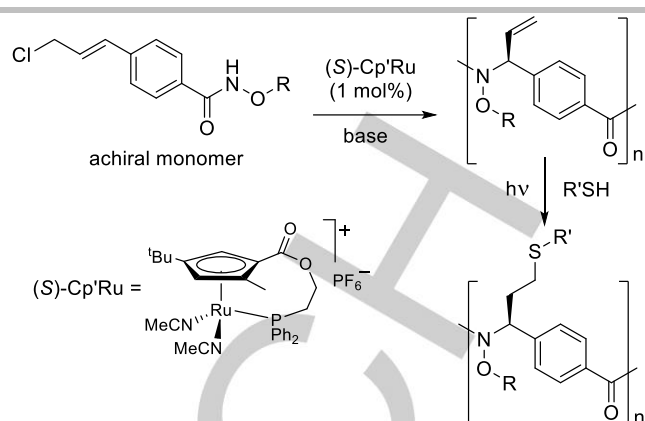


R = octyl, 4-octyloxybenzyl, (S)-2-(methoxyethoxyethoxy)propyl  
EDG = electron donating group

**Scheme 2.** Chain-growth polycondensation to access *N*-alkylated poly(*p*-benzamides).

The same methodology is applicable to access poly(benzamides) of the *meta*-series since the inductive effect of the nucleophilic site is enough strong to deactivate the electrophilic site at the *meta* position of the monomer.<sup>[31]</sup> Nevertheless the use of a lithium amide base having bulky alkyl substituents (LiHMDS) was necessary in order to obtain polymers with narrow molecular weight distribution ( $M_n = 4\,380\text{ g}\cdot\text{mol}^{-1}$ ;  $M_w/M_n = 1.27$ ). The inclusion of a coordinating additive such as *N,N,N',N'*-tetramethylethylenediamine (TMEDA) could furthermore be beneficial.<sup>[31b],[32]</sup> This type of polycondensation enables the synthesis of well-defined block copolyamides having different aminoalkyl side chains or different aryl substitution patterns (*meta/para*)<sup>[31a], [33]</sup> as well as telechelic poly(*p*-benzamide)s (*i.e.* reactive polymers possessing reactive functional groups at the chain ends)<sup>[34]</sup> and cross-linked star polymers with aromatic polyamide arms.<sup>[35]</sup> It is worth noting that this type of polycondensation in the absence of an initiator was efficiently applied to access aromatic oligoamide macrocycles such as calix[3]amides.<sup>[36]</sup> One drawback of the chain-growth polymerization is the difficulty of accessing high molecular weight polymers since only polyaramides up to  $24\,000\text{ g}\cdot\text{mol}^{-1}$  could be formed. To this end, Kilbinger and coworkers have studied a modified procedure using highly reactive pentafluorophenol esters in a step-growth manner, enabling the preparation of polyaramides of up to  $M_n\ 50\,000\text{ g}\cdot\text{mol}^{-1}$  but with higher polydispersity ( $M_w/M_n = 2-3$ ).<sup>[37]</sup>

A particularly appealing asymmetric polymerization catalyzed by planar-chiral cyclopentadienyl ruthenium complexes (I) followed by thiol-ene post-modification or ring-closing metathesis was developed by Onitsuka and co-workers to access optically active poly-*N*-alkoxyamides.<sup>[38]</sup> These are closely related to *N*-substituted poly(aminomethyl benzamide)s with one asymmetric center on the backbone (Scheme 3). However, conformational properties of these poly-*N*-alkoxyamides were not studied and the *N*-alkoxyamide groups were readily transformed to secondary amide groups by the reductive cleavage of N–O bonds.<sup>[39]</sup>

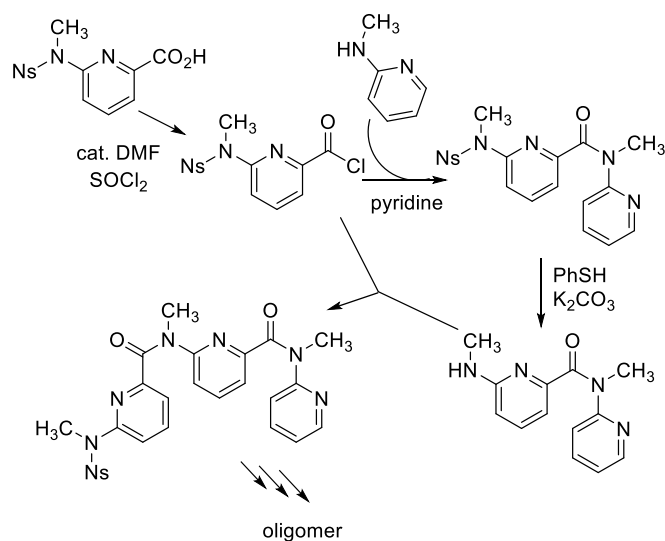


**Scheme 3.** Asymmetric polymerisation to access optically active poly-*N*-alkoxyamides.

Even though the chain-growth polymerization process has proven to be efficient to access *N*-alkylated polyamides with narrow polydispersity, only polyamides carrying one type of side chain or at the best two types of side chains in the case of block copolymers, can be obtained. The development of other synthetic pathways was necessary to prepare oligoamides with specific sequences and lengths.

### 3.2. Monomer synthesis

Short *N*-alkylated aromatic oligoamides with specific sequences were synthesized in solution by the successive introduction of selected monomers in a mono-directional manner. This was mostly achieved using *N*-protected *N*-alkylated monomeric aromatic derivatives, activating the carboxylic acid as the corresponding acid chloride prior to the coupling step. Various *N*-protecting groups were employed, comprising for example trifluoroacetate<sup>[40]</sup> and *o*- or *p*-nitrobenzenesulfonyl (nosyl) to access oligo(*p*-benzamide)s<sup>[41]</sup> and oligo(pyridyl amide)s (Scheme 4).<sup>[42]</sup>



**Scheme 4.** Solution phase synthesis of a *N*-methyl oligoamide bearing pyridine 2-carboxamide.

## MINIREVIEW

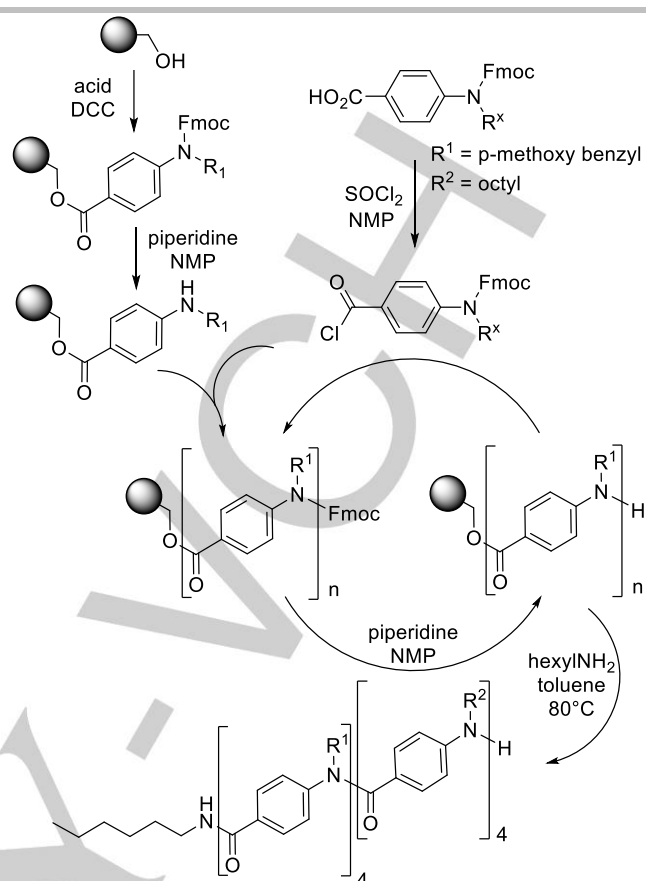
The latter could also serve for the synthesis of secondary amines by means of Fukuyama's nosyl methodology.<sup>[41],[43]</sup> Even though this synthetic pathway is theoretically applicable to a wide variety of monomers, only a few side-chains have been studied and essentially only homooligomers have been prepared. A few groups have opted for the coupling of a primary amine usually obtained by reduction of nitroarene derivative, followed by alkylation using a selected alkyl halide. Using this approach, Clayden and co-workers have synthesized short oligomers of *o*-, *m*- and *p*-linked benzamides as well as of 1,4-naphthanilides with good to excellent yield for each step.<sup>[16b]</sup> This methodology was also employed by Tanatani to prepare *N*-methyl oligoamides with alternating arene and pyrrole rings but was less efficient.<sup>[20]</sup> Again, only one type of side chain was used to prepare the oligomer. To access longer oligomers, an efficient block-coupling approach was preferred as illustrated by Ueda and co-workers in the preparation of *N*-alkylated oligo(*p*-benzamide)s comprising up to sixteen residues.<sup>[40]</sup>

The monomer synthesis using acid chloride derivatives was also performed in a bi-directional manner to access symmetrical pyridine-containing *N*-methyl aromatic oligoamides<sup>[17c]</sup> and unsymmetrical *N*-methyl aromatic amide oligomers.<sup>[12a]</sup>

Kilbinger and coworkers were the first to describe the solid-phase synthesis of *N*-substituted oligo(*p*-benzamide)s up to decamer length using a Wang resin support and a Fmoc-based strategy. This strategy involves the acylation of a secondary aromatic amine by *N*-Fmoc- and *N*-PMB-protected *p*-amino benzoyl chloride or *N*-Fmoc-protected *N*-alkyl *p*-amino benzoyl chloride (Scheme 5).<sup>[15a]</sup> This methodology was used to access homooligomers and heterooligomers with, at best, two types of side chains.

Except for the first residue attachment, peptide-type coupling reagents proved to be inefficient even when using coupling reagents employed for the synthesis of aromatic amides (DBOP, TPP). Instead, activation of the acid as the corresponding acid chloride was achieved using thionyl chloride in NMP (Scheme 5).<sup>[15a]</sup> At the end of the iterative process, the oligomer was obtained by nucleophilic cleavage from the resin using hexylamine in toluene without loss of *p*-methoxy benzyl groups. The yield of the solid-phase synthesis was, however, not reported. A slightly modified methodology in which the acid chloride derivative was generated using bis(trichloromethyl)carbonate (triphosgene) instead of thionyl chloride was automatized using a commercial peptide synthesizer to access up to a 15-mer heterooligoamide in 54% overall yield (30 synthetic steps).<sup>[44]</sup>

A solid-phase strategy was also used to access series of *p*-benzamide trimers carrying various substituents on the nitrogen and also on the aryl ring.<sup>[15b,c]</sup> For the first time, the accessibility to diverse side chains was exploited. In these publications, the acid chloride was generated using 1-chloro-*N,N*,2-trimethyl-1-propenylamine (Ghosez's reagent)<sup>[45]</sup> in chloroform followed by addition of *N*-methylimidazole as base prior to the ensuing reaction. This solid-phase methodology was adapted to the use of a microwave assisted peptide synthesizer, allowing facile library generation of functionalized oligomers in excellent yield and good purity for a panel of hydrophobic side chains but an incompatibility of some side chains was observed.<sup>[46]</sup>



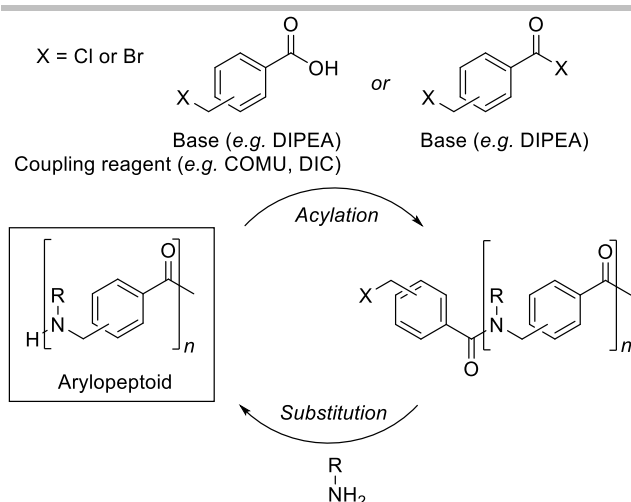
**Scheme 5.** Solid-phase synthesis of heterooligomers of *N*-substituted *p*-benzamides carrying two types of *N*-substituents.

To the best of our knowledge, synthesis on solid-support of *N*-alkylated *o*- or *m*-benzamide, naphthanilide, pyridylamide, pyrrole amide oligomers have not been reported in the literature. By contrast with other classes of *N*-alkyl aromatic oligoamides, classical Fmoc-based solid-phase peptide synthesis (SPPS) using HATU as coupling reagent could efficiently be performed to access benzyloptoid trimers and tetramers on a 2-chlorotrityl chloride resin with yields ranging from 60 to 84%, prior to macrocyclisation to access cyclic compounds.<sup>[24]</sup> Monomer synthesis has not been applied to the preparation of aryloptoids since the submonomer approach appears much more convenient as will be discussed in the following section.

### 3.3. Submonomer synthesis

The backbone structure of oligomeric *N*-substituted aminomethyl benzamides, or aryloptoids, allow for their synthesis *via* a unique "submonomer" method wherein each of the aromatic amide residues can be created in two steps directly on the growing chain (Scheme 6). This convenient iterative cycle comprises an acylation reaction with an activated chloro- or bromomethyl benzoic acid followed by a substitution reaction with a primary amine. The submonomer method thus enables complete control over the backbone sequence, and potentially provides access to highly diverse structures.

## MINIREVIEW



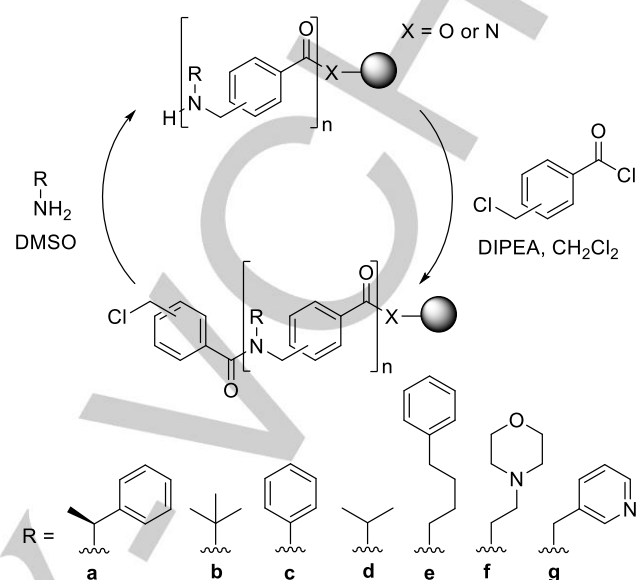
**Scheme 6.** Acylation and substitution steps in "submonomer" synthesis of arylopeptoids.

As previously mentioned, the first disclosure of arylopeptoids appeared in a series of patents in the mid to late 1990's.<sup>[21]</sup> A few pentameric *para*-arylopeptoids were synthesized on solid phase using the above submonomer method wherein 0.5 equiv. of *N,N'*-diisopropylcarbodiimide (DIC) was employed to activate the benzoic acid building blocks as their corresponding anhydrides. In 2007, Lokey and Combs disclosed the solid phase synthesis of a limited number of short oligomers (tetra- and pentamers) of *para*- and *meta*-arylopeptoids, activating the bromomethyl benzoic acid building blocks with 1.0 equiv. DIC.<sup>[22a]</sup> In 2011, the first solution phase synthesis of trimeric *para*- and *meta*-arylopeptoids was reported, using bromomethyl benzoyl bromides as the aromatic building blocks.<sup>[22b]</sup> Each acylation-substitution cycle was carried out in a one-pot procedure and the method is adaptable to gram-scale synthesis. Furthermore, head-to-tail coupling of suitably deprotected trimers in the presence of 1-Cyano-2-ethoxy-2-oxoethylideneaminoxydimethyl amino-morpholino-carbenium (COMU) as coupling agent gave access to arylopeptoid hexamers and nonamers.

After studying a range of conventional peptide coupling reagents, COMU was also found to be the most efficient reagent for submonomer synthesis of arylopeptoids on solid phase.<sup>[47]</sup> Both *para*- and *meta*-arylopeptoids with acid or amide groups at the C-terminus were synthesized, and the efficiency of the method was demonstrated by the synthesis of two model hetero-dodecamer arylopeptoids in 25-27% yield and >99% purity (58-62% crude purity). Although generally broadly applicable, this method proved inadequate for the incorporation of very bulky side chains such as *tert*-butyl and for the use of the less reactive anilines. This was later solved in 2012 by using chloromethyl benzoyl chlorides in the acylation step (Scheme 7).<sup>[48]</sup> This modification not only allowed for installation of previously inaccessible side chains but generally provided higher crude purities (59-99% for hexamer synthesis) and purified yields (23-69% of hexamers with HPLC purity >99%) than the previous methods.

The following year, the synthesis of the first arylopeptoids with *ortho*-backbones was then reported.<sup>[49]</sup> Examples of such *ortho*-linked "one-way sequence" aromatic oligoamides remain very rare. Nonetheless, the efficient synthesis of a wide variety of *ortho*-arylopeptoids both in solution and on solid phase was

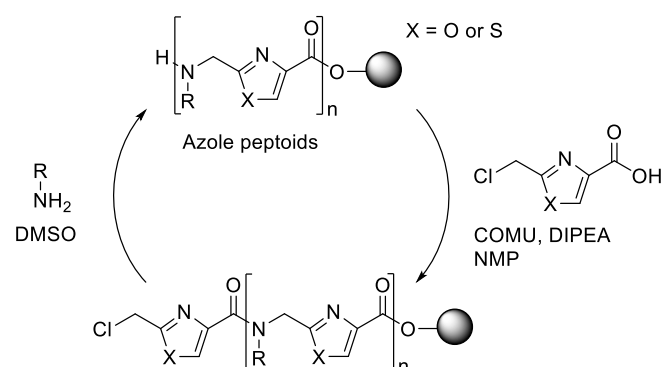
demonstrated. On solid phase, activation of the aromatic building block as the corresponding acid chloride was in this case found to be considerably more efficient than using the free acid in combination with a peptide coupling reagent. This is presumably due to the increased steric hindrance.



**Scheme 7.** Improved solid-phase synthesis of arylopeptoids and some of the side chain diversity available.

The solid phase methodology based on the use of chloromethyl benzoyl chlorides in the acylation step has furthermore been adapted to semi-automated microwave synthesis.<sup>[50]</sup> Strongly reduced reaction times were achieved in this way and the synthesis of a model arylopeptoid nonamer with alternating *ortho*-, *meta*-, and *para*-substituted backbone pattern carrying very challenging side chains was demonstrated.

Intriguingly, the submonomer method may also be adapted for installation of heteroaromatics such as furanes, pyrazines, oxazoles and thiazoles in the aromatic oligoamide backbone.<sup>[23]</sup> Thus, various trimeric azole peptoids (or heteroarylopeptoids) with oxazoles or thiazoles in the backbone were efficiently synthesized with isolated yields ranging from 13 to 63% via the submonomer method using free acids activated with COMU in the acylation steps (Scheme 8).<sup>[23b]</sup>

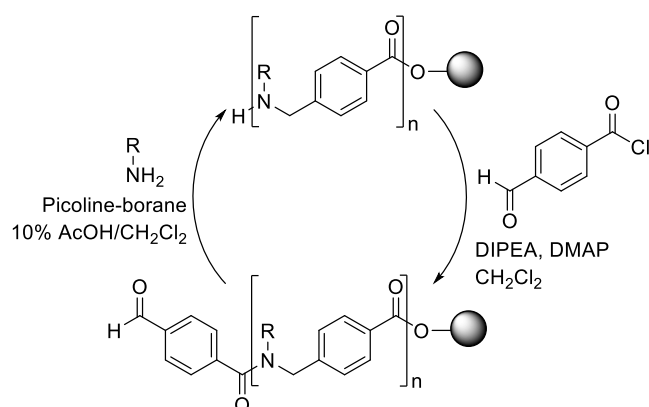


**Scheme 8.** Submonomer synthesis of azole peptoids.



## MINIREVIEW

The synthetic methodology of the submonomer method for the solid-phase synthesis of arylopeptoid architectures was furthermore recently broadened by the development of an iterative cycle based on acylation – reductive amination rather than the above acylation – substitution cycle (Scheme 9).<sup>[22c],[51]</sup> In this technique, formylbenzoyl chloride was used in the acylation step and the installation of the side chain was then achieved by reaction with an amine in the presence of picoline-borane. Only introduction of phenyl and 4-methoxyphenyl side chains have been studied. This alternative method allows for using a smaller excess of reagent when using aromatic amines in the second step of the iterative cycle.



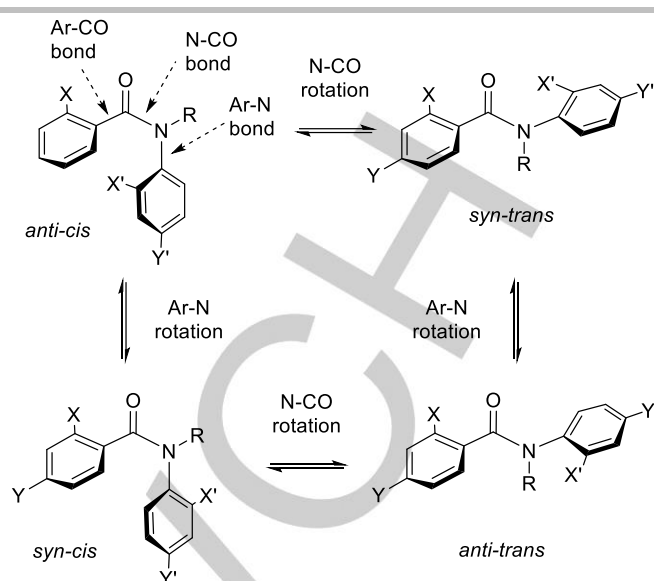
**Scheme 9.** Submonomer synthesis of arylopeptoids using an alternative acylation – reductive amination cycle.

## 4. Foldameric properties

The folding properties of *N*-alkylated aromatic poly- and oligoamides have been studied in solution by NMR and circular dichroism analysis, as well as by X-ray crystallography in the solid-state. The conformational behavior of the oligomers primarily depends on the *cis/trans* conformational preference of the *N,N*-disubstituted amides and the *syn/anti* arrangement of the arene rings. These local preferences may then act cooperatively along the backbone to induce well-defined secondary structures.

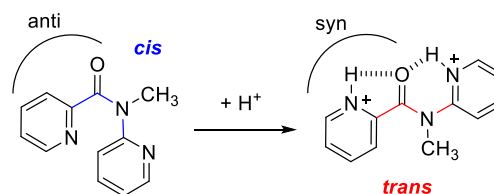
### 4.1. Local conformational preferences of *N,N*-disubstituted amides

For aromatic amides, the local possible conformations result from rotation about the Ar–N, Ar–CO and N–CO bonds. Depending on the *N*-substituents and aryl substitution, one conformation may be privileged (Figure 5). The preference for *cis* amide conformation (formally *E*) of *N*-methylbenzanilide monomer in solution in aprotic and protic organic solvents and in the solid-state was early shown by Shudo and co-workers.<sup>[52]</sup> They thoroughly investigated the *cis*-amide preference of *N*-methylanilides by means of crystallography and NMR<sup>[8a]</sup> as well as by theoretical studies.<sup>[53]</sup> Recently, the conformational preferences of *N*-alkyl anilides were thoroughly reinvestigated by Bloomfield using density functional theory (DFT) and NBO deletion strategies to discriminate energy differences due to orbital mixing from those due to steric strain.<sup>[8c]</sup> The *N*-alkyl *N*-aryl amide conformation appears to be governed by an interplay of steric and orbital delocalization effects.



**Figure 5.** Different conformations accessible by rotation about the Ar–N, Ar–CO and N–CO bonds

In the *cis* conformation, allylic strain ( $A^{1,3}$ ) between the aryl and the *N*-alkyl groups causes the aryl substituent to rotate out of the amide plane and the *trans* conformation is destabilized by a repulsive effect between the  $\pi$  system of the aromatic moiety and the lone pairs on the oxygen atom of the carbonyl. The *cis* conformation is even more stable for electron-rich arenes (for example  $Y'=\text{OCH}_3$ ), leading to an increase in the interaction with the carbonyl oxygen, and a higher repulsive effect due to the increased electron density in the  $\pi$  system. The conformation ratio may be modified by the presence of *ortho*-substituent(s) on the arene ( $X$  and/or  $X' = \text{I}, \text{CH}_3$ ) or a bulky substituent  $R$  on the nitrogen.<sup>[13]</sup> The proportion of *cis* and *trans* conformers may often be determined by NMR since the rotation about the C–N amide-bond of *N,N*-disubstituted amides is hindered and at the NMR time scale, two resonance peaks will often be observed for the protons adjacent to the amide, even at low to ambient temperature.<sup>[54]</sup> Similarly to *N*-methyl benzanilide, *N*-methyl-*N*-phenyl pyrrole 2-carboxamide exhibits predominantly the *cis* conformation but the proportion of *cis* conformer decreases in *N*-methyl-*N*-(4-pyrrole) benzamide as demonstrated by  $^1\text{H}$  NMR at low temperature in  $\text{CD}_2\text{Cl}_2$ .<sup>[20]</sup> A *cis* to *trans* switching effect induced by an environmental change (solvent or pH) was demonstrated by Okamoto and co-workers for *N*-methyl aromatic amides containing 2,6-disubstituted pyridine (Figure 6).<sup>[17]</sup>

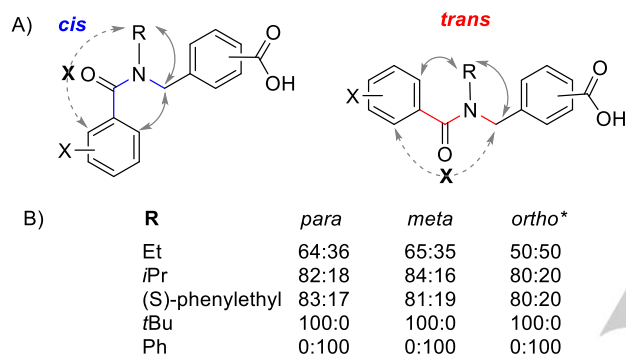


**Figure 6.** Acid-induced *cis-trans* switching of *N*-methyl-*N*-(2-pyridyl)-pyridine-2-carboxamide.

## MINIREVIEW

The protonation of the pyridyl ring under acidic conditions leads to a pyridinium core which is able to stabilize the *trans* conformation through the establishment of hydrogen-bonding with the oxygen of the adjacent carbonyl group. This conformational switch was evidenced by  $^1\text{H}$  NMR in  $\text{CD}_3\text{CN}$  upon addition of TFA-d or  $\text{DClO}_4$ .

*Cis-trans* amide isomerism in arylo- and benzyloleptoids was found to be more side chain specific due to the presence of the backbone-methylene. Indeed, the study of the *cis/trans* ratio in *meta*-, *para*- and *ortho*-aryloleptoid monomeric models carrying various side-chains showed conformational preferences similar to those of peptoid-type amides (Figure 7).<sup>[22b],[48],[49]</sup> As expected with *N*-phenyl substitution, exclusively the *trans* amide is observed. With aliphatic side chains, an equilibrium between *cis* and *trans* takes place, with the *cis* conformation being increasingly favored with increasing bulk of the side chain. The *tert*-butyl group thus results in a 100% *cis* conformation.



**Figure 7.** A) Representation of *cis* and *trans* amides in aryloleptoids and main NOESY correlations observed for amide conformation attribution; B) *cis/trans* proportion determined by NMR at 278K or 293K\* in  $\text{CDCl}_3$ .

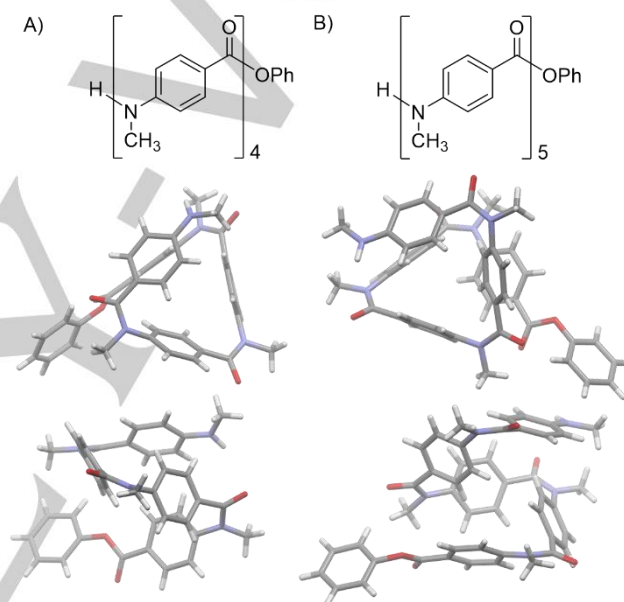
X-ray crystallographic studies of two aryloleptoid dimers recrystallized from chloroform containing a few drops of methanol, confirmed the *trans* and *cis*-directing effects of the phenyl and *tert*-butyl groups, respectively.<sup>[55]</sup> The phenyl side chain resulted in a more open, extended backbone structure, where the phenyl side chain points inwards into the twist created by the backbone. Conversely, the *tert*-butyl side chain resulted in a more packed structure where the *tert*-butyl group points outwards from the twist created by the backbone aromatic rings.

These studies of *N*-alkylated aromatic amide models show that good to high degrees of conformational control may be obtained around the aromatic amide. However, in order to construct oligomers with well-defined secondary structures, these conformational restrictions observed locally should act cooperatively to stabilize one preferred overall conformation.

#### 4.2. Secondary structures

*N*-unsubstituted aromatic polyamides such as poly(*p*-phenylene terephthalamide) and poly(*p*-benzamide) display extended rodlike structures due to their *trans*-amide conformation and intermolecular hydrogen bonding between polymer chains.<sup>[56]</sup> Despite their higher flexibility compared to aromatic oligoamides with free amide protons on the backbone, *N*-alkylated poly(*para*-

benzamide)s with narrow polydispersity ( $M_w/M_n < 1$ ) were shown to form helical conformations in solution and solid-state.<sup>[16a]</sup> Well-defined poly(*para*-benzamide)s with hydrophilic chiral oligo(ethylene glycol) *N*-side chains exhibited chain length dependent circular dichroism (CD) spectra in acetonitrile or chloroform, indicative of a chiral conformation. However, the high temperature dependency indicated thermodynamic control of the conformation. X-ray crystallographic analysis of *N*-methyl *para*-benzamide tetramers and pentamers, whose single crystals were obtained by recrystallization from  $\text{CCl}_4$  and ethyl acetate, respectively, revealed a helical conformation in solid-state with three monomer units per turn, *cis* conformation of the amide bonds and a *syn* arrangement of the benzene rings (Figure 8). Supported by these results, a helical conformation in solution was assigned and the helicity was deduced from inspection of the CD spectra and exciton model analysis of the absorption.

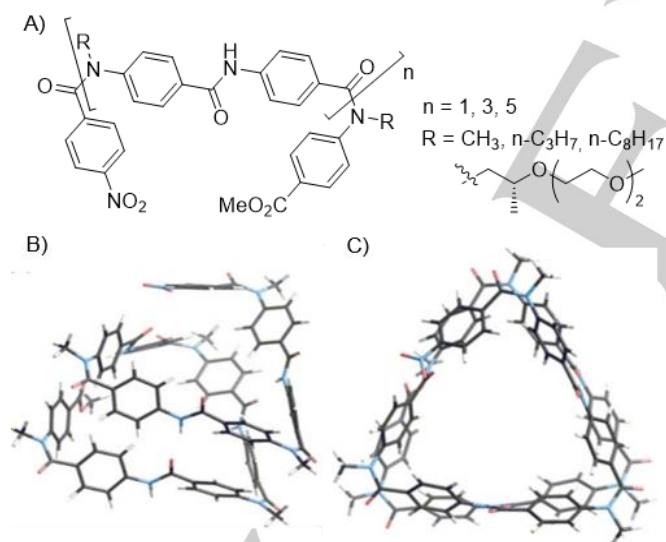


**Figure 8.** The crystal structures of 4-(methylamino)benzoic acid oligomers: A) a tetramer (top and side views) and B) a pentamer (top and side views). (adapted from reference [16a] with permission from American Chemical Society)

Induction of a one-handed helical chirality on the otherwise achiral *N*-methyl oligo(*para*-benzamide)s was performed *via* a domino effect based on the planar-axial-helical chirality relay caused by an (*S*)-*N,N*-methylphenyl-2-iodoferroceneamide transition-metal complex introduced at the *N*-terminal position of the oligobenzamide.<sup>[57]</sup> According to CD analysis performed in chloroform, the chiral induction led to a one-handed helix for a trimer but the screw-sense preference appeared less marked for longer oligomers. However, in absence of a marker that acts as a diastereotopic probe at the other terminal,<sup>[58]</sup> it was difficult to evaluate the chiral transmission in solution of these systems. Conformational analysis of *N*-alkylated poly(*meta*-benzamide)s was also performed by Yokozawa and co-workers.<sup>[31b]</sup> As for the *para* series, CD studies in protic or aprotic solvents of *N*-substituted poly(*meta*-benzamide)s carrying chiral aliphatic side chains showed a Cotton effect not due to the intrinsic chirality of the monomer units. The highly temperature dependent CD

## MINIREVIEW

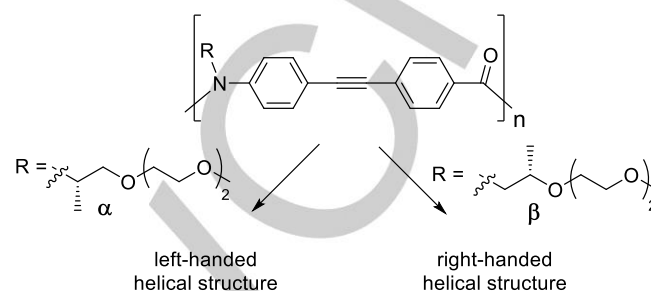
spectra were indicative of a chiral conformation of the polymer gradually becoming disordered with increasing temperature. The preferred conformation could not be determined since even if only *cis* conformation of amide bonds was observed, different conformations could arise from the variation of the dihedral angles between the amide linkages and benzene units (*syn* and *anti* arrangements) as previously observed for short *N*-methyl aromatic amide oligomers by Yashima and co-workers.<sup>[59]</sup> Clayden and co-workers have studied the conformational behaviour in different solvents of series of *ortho*-, *meta*- and *para*-linked oligobenzamides as well as hybrid *ortho/meta* or *para/meta* oligomers and oligo-1,4-naphthanilides by NMR.<sup>[13],[60]</sup> The evidence of a single conformation or dynamic mixtures of conformers was difficult to establish. In these studies, substituents were introduced on aromatic ring to slow down rotation about the Ar-CO and Ar-N axis. However, despite conformational restriction observed on dimers and trimers, the degree of control degraded significantly in longer oligomers. Tanatani and co-workers have taken advantage of the *cis*- or *trans*-conformation preference of tertiary and secondary amides to build a helical structure with a large cavity that could host guest molecules having a suitable molecular shape and size.<sup>[41]</sup> This helical construct was made from alternately *N*-alkylated and non-alkylated *para*-benzamides. NMR, UV, CD studies in polar aprotic solvents and theoretical analysis showed a helical conformation in solution with a cavity size of approximately 9 Å and stabilization through intramolecular hydrogen bond interactions of secondary amides (Figure 9).



**Figure 9.** A) Structure of alternating *N*-alkylated and non-alkylated *para*-benzamides and B) side-view and C) top-view conformation of a *N*-methylated pentamer obtained by DFT geometry optimization at the RI-B3LYP/def-SV(P) level based on the crystal structure of (*cis*, *trans*, *cis*) form monomer (adapted from reference [41] with permission from American Chemical Society).

This type of helical structure with a large cavity was also accessible from polyamides with a diphenylacetylene backbone bearing (*S*)- $\alpha$ - and (*S*)- $\beta$  methyl-substituted triethyleneglycol (TEG) side chains on the amide nitrogens (Scheme 10).<sup>[61]</sup> The large triangular cavity was first evidenced by X-ray analysis of a single crystal of a cyclic triamide, obtained by recrystallization from  $\text{CH}_3\text{CN}/\text{CH}_2\text{Cl}_2$ .<sup>[62]</sup> A polyamide ( $M_n = 14200$ ,  $M_w/M_n = 1.31$ )

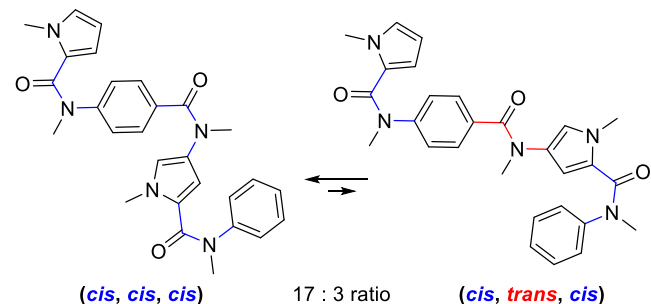
and oligoamides (5- to 7-mers) carrying the (*S*)- $\beta$  methyl-substituted triethyleneglycol side chain were found to exhibit similar CD curves in chloroform with a negative Cotton effect at 305-310 nm and a positive one at 350 nm. Polyamides *N*-substituted with  $\alpha$ - or  $\beta$ -chiral side chains were found to adopt a left- or right-handed helical structure, respectively, according to CD analysis in various solvents at 0°C and theoretical study.<sup>[61]</sup>



**Scheme 10.** Structure of diphenylacetylene-based oligoamide and chain-dependent helical folding.

Some reports from Wilson and Barnard suggested that short *N*-alkylated *para*-oligobenzamides, especially those bearing an *ortho*-substituent on the aromatic rings, might also, under certain conditions, be able to adopt extended conformations with *trans* amide bonds in solution.<sup>[15b,c]</sup> Up to now, this type of conformation has not been evidenced though. However, it should be noted that a crystallographic structure exhibiting *N*-alkylated benzamides in the *trans* form and a fully extended conformation, was obtained from DMSO- $d_6$  for a hybrid *N*-alkylated and non-alkylated *para*-benzamide trimer.<sup>[41]</sup>

Interesting features were also obtained when combining pyrrole and phenyl rings in *N*-methyl aromatic oligoamides.<sup>[20]</sup> NMR studies in  $\text{CD}_2\text{Cl}_2$  showed that the *N*-methylated amide attached at the 2-position of the pyrrole ring predominantly adopted the *cis* conformation, while the *cis/trans* ratio decreased when the *N*-methylated amide bond was at the 4-position of the pyrrole ring (Scheme 11). Chain-length and solvent dependent CD spectra reflected different folding properties than *N*-alkylated *para*-oligobenzamides, suggesting the presence of a combination of *cis*-amide bonds with an *anti/syn* conformational preference but this unique conformation has not yet been confirmed.



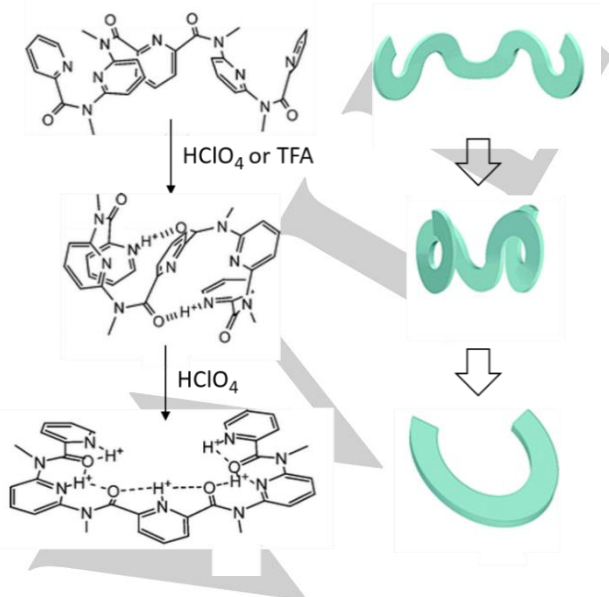
**Scheme 11.** Proportion of conformers observed by NMR in  $\text{CD}_2\text{Cl}_2$  at 233K.



## MINIREVIEW

The identification of the folding behaviour of oligomeric *N*-substituted aminomethyl benzamides (arylopeptoids) proved to be difficult since the amide conformation preference was markedly less pronounced in these oligoamides due to the additional backbone-methylene group. Some particular side chains, *i.e.* *tert*-butyl and aryl groups, inducing complete control of the *cis* or *trans* conformation, respectively, were identified (section 4.1) but their achiral nature made studies by circular dichroism impossible. Attempts to evidence a privileged conformation by CD was then performed using the (*S*)-*N*-(1-phenylethyl) (*spe*) side chain which has been used extensively in the conformational studies of peptoids.<sup>[14b]</sup> However, the control of this side chain on the *cis*-amide conformation is not total, inducing additional flexibility to the system. This made NMR and circular dichroism analysis difficult.<sup>[48]</sup> Efforts thus still need to be made to better understand conformational preferences of arylopeptoids.

Another area of interest in the field of foldamers is the development of oligomers exhibiting external stimuli responsive structures.<sup>[63]</sup> Many examples of anion- or ligand-responsive folding/unfolding systems have been described but far less foldamers whose conformational preference depends on acid-base stimuli. To this end, Okamoto and co-workers have developed pH-responsive conformation-switching foldamers based on the particular properties of the pyridine ring under acidic conditions (section 4.1).<sup>[17c],[42]</sup> Symmetrical *N*-methyl oligoamides, made from 2,6-disubstituted pyridines, were able to switch from a layered to a spiral form upon addition of TFA or a small amount of perchloric acid which protonate only the terminal mono-substituted pyridines. This was observed by NMR in CD<sub>3</sub>CN upon addition of TFA-*d* or DClO<sub>4</sub> and confirmed by the crystal structure of a perchlorate salt obtained from the studied oligomer and two equivalents of perchloric acid. Protonation of inner pyridine rings occurs upon further addition of perchloric acid which leads to a flat form with all *N*-methyl amides in a *trans* configuration according to the correlations observed between the *N*-methyl and pyridine protons in NOESY experiments (Scheme 12).



**Scheme 12.** Acid-responsive conformations of an *N*-methyl aromatic oligoamide made from 2,6-disubstituted pyridines (adapted from reference [17c] with permission from American Chemical Society).

The nature of the interactions involved in the folding of *N*-alkylated oligoamides combined with the low energy barrier of the *cis/trans* isomerism of *N,N*-disubstituted amides are responsible for the dynamic character of their secondary structures. In many cases, circular dichroism studies highlighted temperature-dependent folding but the privileged conformation in solution was difficult to assign by classical techniques such as NMR due to the absence of stabilizing hydrogen bonding and dynamic exchange of conformers. Fortunately, solid-state structures could be resolved in some cases which has assisted in the identification of the conformation in solution. The different conformational behaviours of *N*-substituted aromatic oligoamides compared to the parent non-substituted oligomers confers them unique properties that may be exploited for various applications.

## 5. Applications

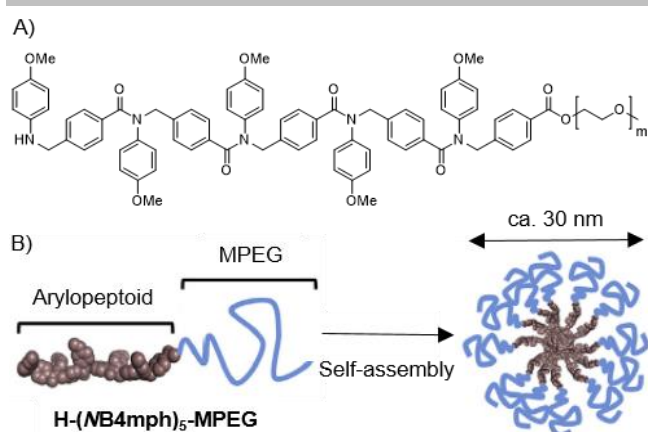
In material sciences, the unique properties of *N*-substituted poly(benzamide)s have allowed for the preparation of a number of polymers and co-polymers intended for use in the fabrication of self-assembled architectures. Indeed, one of their important properties is a good solubility in organic solvents which has greatly facilitated the preparation of well-defined polymers and co-polymers. To this end, the 4-(octyloxy)benzyl (OOB) or *N*-*p*-methoxybenzyl (PMB) groups were efficiently used as *N*-substituents to prevent aggregation during oligomer synthesis and to facilitate purification.<sup>[35],[44]</sup> The protecting groups could then be removed to obtain highly interesting shape-persistent materials. This strategy has for example led to the development of strongly aggregating poly(benzamide)s with a rod-like conformation or rod-coil conformation when associated with PEG coil block polymers.<sup>[44a]</sup> In addition, the well-controlled chain-growth polycondensation developed by Yokosawa and co-workers for the synthesis of poly(benzamide)s with narrow polydispersity,<sup>[27]</sup> has allowed for the access to a wide range of polymer and copolymer architectures: star-shaped polymers with a porphyrin core<sup>[64]</sup> or a microgel core made from diacrylamides,<sup>[35]</sup> tadpole-shaped dendrimers<sup>[40]</sup> and hyperbranched polymers.<sup>[65]</sup>

The optical properties of oligothiophenes attached to cyclic *meta*- or *para*-benzamides trimers and polymers were studied by Takagi and co-workers.<sup>[32],[36a]</sup> The alignment of the  $\pi$ -conjugated oligothiophene chromophores in a controlled fashion is particularly important in the context of development of active materials for optoelectronic devices.

Ikeda and co-workers have shown that an *N*-(4-methoxy)phenyl-substituted arylopeptoid pentamer featuring *all-trans* amide bonds, linked to a polyethylene glycol monomethyl ether (MPEG) polymer can self-assemble to form spherical-shaped nanostructures in aqueous media (10 mM HEPES at pH 7.4) (Figure 10).<sup>[51]</sup> This first report on the self-assembling ability of hydrophobic arylopeptoids bearing hydrophilic polymers lends promise of access to nanostructures with various shapes and functions which may for example be used in the development of drug carriers.



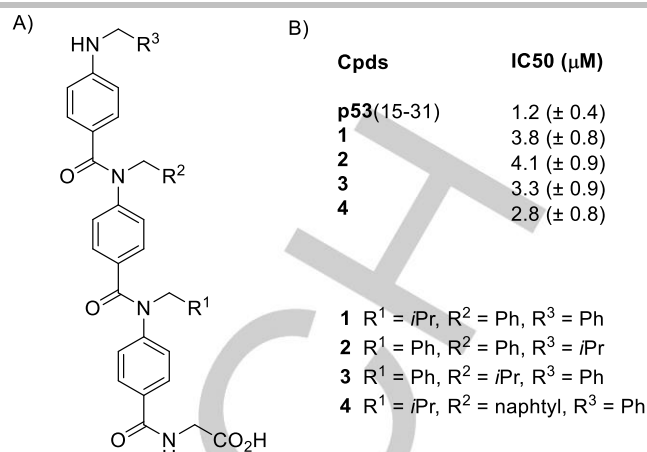
## MINIREVIEW



**Figure 10.** A) Structure of the arylopeptoid pentamer H-(NB4mph)<sub>5</sub>-MPEG; B) Schematic illustration of the formation of self-assembled nanostructures from H-(NB4mph)<sub>5</sub>-MPEG (adapted from reference [51] with permission from American Chemical Society).

The robustness of the methodologies developed for the submonomer synthesis of arylopeptoids make these types of *N*-alkylated aromatic oligomers highly suitable for educational purposes.<sup>[66]</sup> In the context of the Distributed Drug Discovery (D3) program,<sup>[67]</sup> a library of arylopeptoid dimers was screened to evaluate their activity on bacteria and yeasts.<sup>[66c]</sup> One dimer was found “partially active” on *Cryptococcus neoformans*. Nielsen and co-workers have also developed short arylopeptoids as agonists of the peroxisome proliferator-activated receptor  $\gamma$  (PPAR $\gamma$ ) involved in metabolic disorders.<sup>[68]</sup> However, these agonists were designed as small molecule ligands by analogy with existing PPAR $\gamma$  agonists rather than as proteomimetics.

By contrast, *N*-alkylated oligobenzanilides were used as proteomimetics to target protein-protein interactions. By analogy with the parent oligobenzanilides,<sup>[1c],[3a],[69]</sup> they have been developed as  $\alpha$ -helix mimics by Wilson and Barnard with interesting features such as amenability to library construction with high diversity and also to multifacial mimicry by the introduction of *O*-substituents on the backbone aromatic rings.<sup>[15c]</sup> Even though the *cis*-amide conformation of *N*-alkyl benzanilide is not favorable for the formation of extended conformations able to mimic one face of an  $\alpha$ -helix, trimeric *N*-alkylated benzanilides carrying hydrophobic side chains, developed by Wilson and co-workers were found to be potent inhibitors of the p53–hDM2 interaction (Figure 11).<sup>[15b]</sup> According to the <sup>1</sup>H–<sup>15</sup>N HSQC chemical shift perturbations observed, and a mapping onto the crystal structure of p53–hDM2, an extended conformation of the aromatic benzanilides appears to interact with the hydrophobic groove of p53 protein, even though this is not the preferred arrangement in solution. In addition, the all-*trans* conformation enables a side chain arrangement that match the spatial presentation of side chains located at the *i*, *i* + 4 and *i* + 7 positions of an  $\alpha$ -helix. Further studies are necessary to better understand the conformational behavior and interactions involved in this context. Compared to non-alkylated benzamides, these oligomers thus possess a certain degree of plasticity that may be beneficial for protein-surface recognition. Resolution of the structure of proteomimetic-protein complexes would be of high interest to further understand these interactions.



**Figure 11.** A) Proteomimetics of hDM2 binding domain; B) IC<sub>50</sub> values determined by fluorescence anisotropy competition assay for inhibition of the p53–hDM2 interaction.

In the pursuit of new oligoamide biomimetic scaffolds capable of transition metal binding, Fuller and co-workers have studied the ability of a thiazole-based aromatic oligoamide bearing a terpyridine group to bind Zn<sup>2+</sup> by UV analysis of a trimeric arylopeptoid in aqueous buffer upon addition of ZnCl<sub>2</sub>.<sup>[23b]</sup> The authors speculated that a distorted octahedral complex with two oligomers bound to one metal cation was formed. However, the conformational change upon metal coordination was difficult to evaluate due to the conformational heterogeneity of the thiazole-based oligomers. Changes in folding behavior upon binding were easier to evaluate on more highly-structured aromatic oligoamides such as arylopeptoid and benzylopeptoid macrocycles.<sup>[70],[24]</sup> These few studies have shown the promising binding potential of these types of macrocyclic oligoamides.

## 6. Summary and Outlook

*N*-alkylated aromatic poly- and oligoamides have so far been by less studied than aromatic foldamers built from secondary amides. Nevertheless, very efficient pathways for their synthesis have been developed both in solution-phase and on solid support. Notable highlights comprise the chain-growth polycondensation to access aromatic poly(*para*- and *meta*-benzamide)s with narrow polydispersity and the solid-phase submonomer synthesis to prepare arylopeptoids and azole peptoids with a large diversity of side chains. Although, convenient processes are thus in place, the level of accessible chemical diversity has not yet been fully exploited to design specific sequences directed to a particular application. Due to the inherent properties of the *N,N*-substituted amides, the studied *N*-alkylated aromatic oligoamides have revealed dynamic conformational preferences. The *para*-benzamide polymers bearing *N*-chiral aliphatic side-chains were found to adopt helical structure and pyridyl oligoamides have pH-responsive conformation. Nevertheless, further studies need to be carried out in order to increase the understanding of the interactions involved in the folding processes and to identify the preferred conformation of most oligoamides discussed herein. A number of polymer and co-polymer architectures with various shapes have been efficiently prepared owing to the good

## MINIREVIEW

organosolubility of these polymers. However, the self-assembling properties of this class of aromatic foldamers remains under explored despite a promising potential. More attention should be paid towards their ability to form supramolecular edifices. The application of *N*-alkylated aromatic oligoamides as proteomimetic foldamers is still at an early development stage. Although their conformational behaviors can be difficult to establish, the modularity and adaptability of this type of oligomers represent tremendous opportunities for application within a plethora of areas as outlined above. There is no doubt that further studies in this area of research will emerge in the coming years.

## Acknowledgements

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**Keywords:** aromatic oligoamides • conformational preferences • foldamers • helical structures • proteomimetics

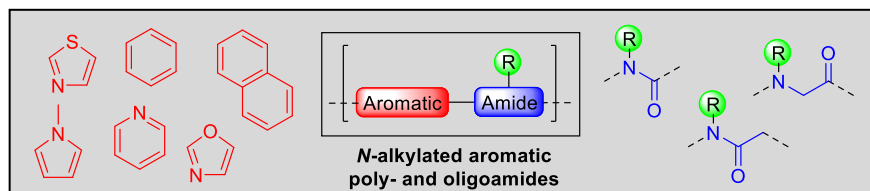
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*N*-alkylated aromatic poly- and oligoamides are abiotic foldamers incorporating *N,N*-disubstituted amides and aromatic rings in their backbones. The nature and the conformational preferences of *N,N*-disubstituted amides profoundly influence the folding properties of these poly- and oligomers, since intramolecular hydrogen-bonding networks could not operate to stabilize their tri-dimensional structure.