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Hairpin versus Extended DNA Binding of a Substituted β-Alanine Linked Polyamide

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Abstract: A series of α-substituted β-alanine (β*) linked polyamides (DbaPyPyPy-β*-PyPyPy) were prepared and examined. This resulted in the observation that while most substituents disrupt DNA binding, (*R*)-α-methoxy-β-alanine ($\beta^{(R)-OMe}$) maintains strong binding affinity and preferentially adopts a hairpin versus extended binding mode, providing an alternative hairpin linker to γ-aminobutyric acid (γ). A generalized variant of a fluorescent intercalator displacement assay conducted on a series of hairpin deoxyoligonucleotides containing a systematically varied A/T-rich binding site size was developed to distinguish between the extended binding of the parent β-alanine **1** (DbaPyPyPy-β-PyPyPy) and the hairpin binding of **3** (DbaPyPyPy-$\beta^{(R)-OMe}$-PyPyPy).

Introduction

Polyamides composed of *N*-methylpyrrole (Py), *N*-methylimidazole (Im), and a growing set of structural analogues bind in the DNA minor groove with predictable sequence selectivity and high affinities.[1−4] The linkage of such polyamides with γ-aminobutyric acid (γ) has been shown to provide hairpin polyamides that mimic the 2:1 side-by-side antiparallel binding of the unlinked polyamides, enhance the binding affinity 10^2−10^4 fold, and improve the binding selectivity.[5] In contrast, polyamides incorporating a one carbon shorter linker, β-alanine (β), have been shown to bind preferentially in an extended mode.[5,6] Moreover, the incorporation of the flexible β-alanine subunit into γ-hairpin polyamides has been shown to be required for binding to DNA sequences longer than seven base pairs (bp), permitting the readjustment of the registry of the polyamides to match that of the DNA minor groove.[5,7] In such hairpins, the β-alanine subunit binds in an extended mode, and the β/β pair binds to A−T and T−A in preference to C−G and G−C.[8]

Herein we report the synthesis and evaluation of the series of Py polyamides **1**−**9** linked using a central β-alanine subunit, Figure 1. Addition of substituents to this central β-alanine linker was used to probe their impact on binding and resulted in the discovery that while most substituents disrupt DNA binding, (*R*)-α-methoxy-β-alanine ($\beta^{(R)-OMe}$) maintains strong binding affinity and preferentially adopts a hairpin versus extended binding mode providing an alternative hairpin linker to γ-aminobutyric acid (γ). Models of the bound conformation identify structural features responsible for this behavior, provide a general solution to enhancing adoption of β-hairpin conformations potentially extendable to γ-hairpins, and suggest modifications that may provide further improvements.

Just as importantly, we employed a generalizable variant of our recently disclosed fluorescent intercalator displacement (FID) assay[9−11] to study the DNA binding properties of **1**−**9**, Figure 1. Thus, the hairpin bound conformation of **3** (DbaPyPyPy-$\beta^{(R)-OMe}$-PyPyPy) versus the extended bound conformation of the parent β-alanine **1** (DbaPyPyPy-β-PyPyPy) could be distinguished by analysis[12−14] of FID titrations of hairpin deoxyoligonucleotides containing a systematically varied A/T-rich binding site size. Complementary assessments using a combination of footprinting and affinity cleavage techniques[15−21] are technically more demanding, require the separate preparation

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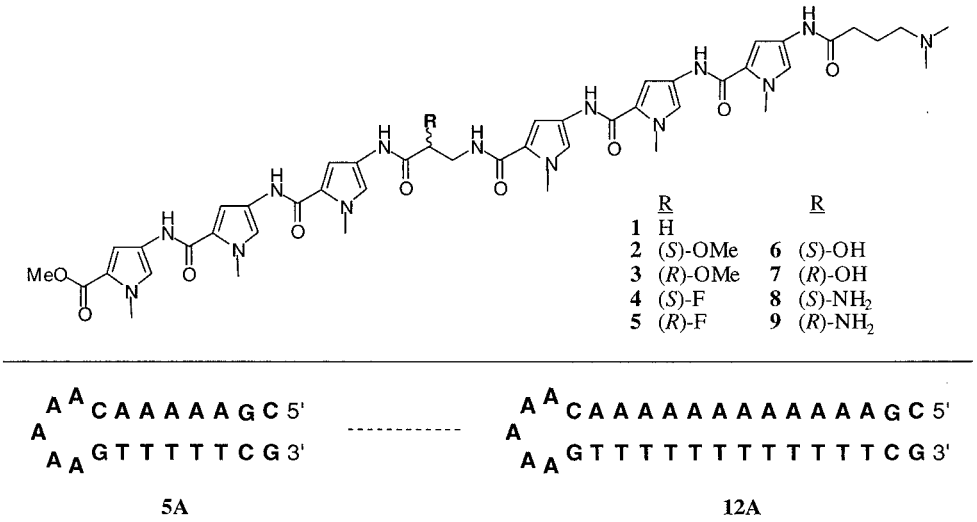
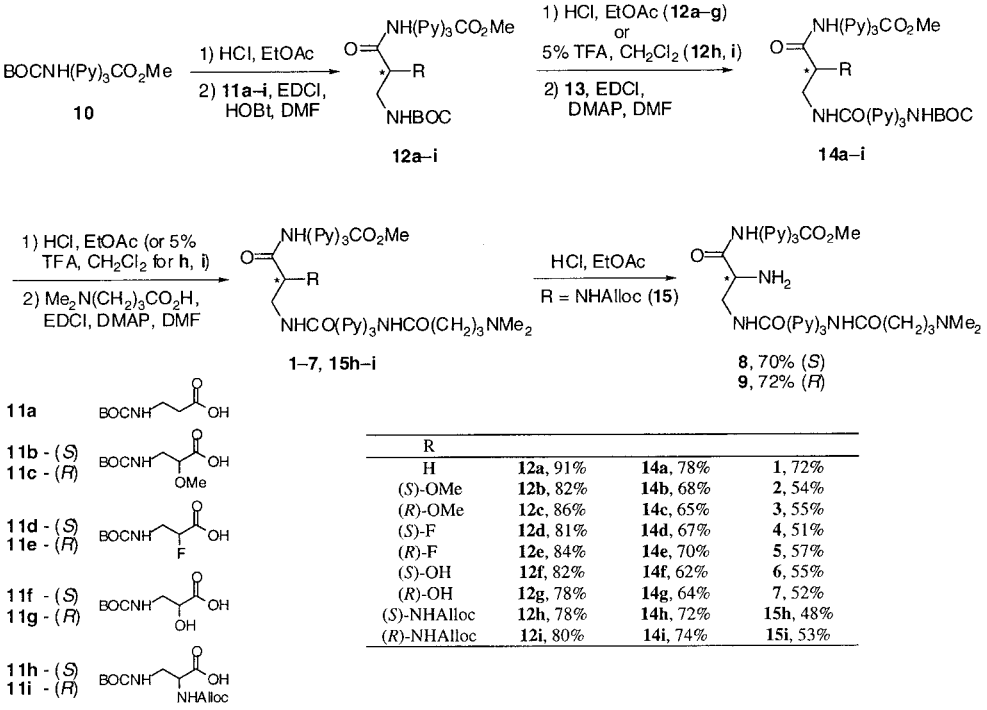


Figure 1. β-Alanine linked polyamides **1**−**9**. A/T-rich hairpin deoxyoligonucleotides containing 5−12 bp binding sites.

Scheme 1



R			
H	**12a**, 91%	**14a**, 78%	**1**, 72%
(*S*)-OMe	**12b**, 82%	**14b**, 68%	**2**, 54%
(*R*)-OMe	**12c**, 86%	**14c**, 65%	**3**, 55%
(*S*)-F	**12d**, 81%	**14d**, 67%	**4**, 51%
(*R*)-F	**12e**, 84%	**14e**, 70%	**5**, 57%
(*S*)-OH	**12f**, 82%	**14f**, 62%	**6**, 55%
(*R*)-OH	**12g**, 78%	**14g**, 64%	**7**, 52%
(*S*)-NHAlloc	**12h**, 78%	**14h**, 72%	**15h**, 48%
(*R*)-NHAlloc	**12i**, 80%	**14i**, 74%	**15i**, 53%

of the linked Fe-EDTA affinity cleavage derivatives, and do not as easily distinguish between such alternative binding modes.

While our studies were underway, the effects of a β-alanine α-substituent on the side-by-side β/β pairing within a long γ-hairpin were disclosed in efforts to alter the β/β degenerate T−A and A−T selectivity using a smaller set of derivatives.[22] Although conducted in a different system with different objectives, Dervan et al. observed analogous substituent-induced reductions in T−A and A−T binding affinity for (*R*)-OH, (*S*)-NH_2, (*S*)-F α-substituted β-alanines, and a minor T−A, but large A−T reduction with the corresponding (*S*)-OH derivative.

Results

Synthesis. The parallel solution-phase synthesis of the polyamides was performed using a series of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDCI)-mediated coupling reactions as described previously[11] (Scheme 1). N-Boc deprotection (HCl−EtOAc) of BocNH-PyPyPy-CO_2CH_3[23] (**10**), followed by coupling with the parent and α-substituted N-Boc-β-alanines **11a**−**i** (EDCI, HOBt, DMF, 25 °C, 78−91%) provided **12a**−**i**. Subsequent N-Boc deprotection (HCl−EtOAc) followed by coupling with BocNH-PyPyPy-CO_2H (**13**,[23] EDCI, HOBt, DMF, 25 °C, 78−91%) provided **14a**−**g** in good yields (62−78%), but **14h** and **14i** in poor yields (2−5%) due to an unanticipated, competitive N-Alloc deprotection. This competitive N-Alloc deprotection was avoided through the use of 5% TFA−CH_2Cl_2 for selective N-Boc deprotection (Scheme 2), providing **14h** and **14i** in superb conversions (72−74%). Similarly, the N-terminus Boc of **14a**−**g** was removed by treatment with HCl−EtOAc and that of **14h**−**i** was removed

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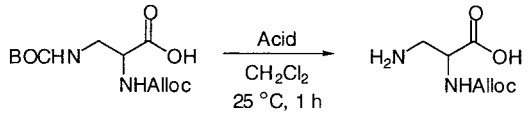
Scheme 2



	Deprotection	
Acid	Alloc	BOC
50% TFA	100%	100%
10% TFA	75%	100%
5% TFA	0%	99%
1% TFA	0%	55%
100% HCO_2H	100%	100%
50% HCO_2H	0%	40%

Table 1. Binding to Poly[dA]·[dT]

cmpd	R	C_{50} (μM)[a]
1	H	0.08
2	(*S*)-OMe	0.44
3	(*R*)-OMe	0.12
4	(*S*)-F	0.25
5	(*R*)-F	0.46
6	(*S*)-OH	0.28
7	(*R*)-OH	0.40
8	(*S*)-NH_2	0.33
9	(*R*)-NH_2	0.38

[a] Concentration (±10%) required to displace 50% of the prebound ethidium bromide, poly[dA]·[dT] at 8.8 μM bp, EtBr at 4.4 μM.

by exposure to 5% TFA−CH_2Cl_2, and the resulting free amines were coupled with 4-dimethylaminobutyric acid (Dba) (EDCI, HOBt, DMF, 25 °C, 48−60%) to provide **1**−**7** and **15h**−**i**. The latter were converted to **8** and **9** upon N-Alloc deprotection through treatment with HCl−EtOAc (70−72%).

Initial Assessment of Substituent Effects on DNA Binding. The compounds **1**−**9** were initially screened for DNA binding using poly[dA]·[dT] in a FID assay. Thus, the relative binding affinities were established by monitoring the loss of fluorescence derived from titration displacement of prebound ethidium bromide from poly[dA]·[dT]. A comparison of the compound concentration required for 50% displacement of the ethidium bromide (C_{50}) revealed that only **3** approached the binding affinity of the parent β-alanine **1**, Table 1. The differences between **1** and **2**, **4**−**9** are more significant than the simple C_{50} comparisons might suggest and translate into affinity constants that differ by more than 1 order of magnitude.[24] Thus, analogous to the observations of Dervan,[22] α-substitution of the β-alanine typically reduced binding affinity. More interestingly, the *S*-enantiomer was typically more effective than the corresponding *R*-enantiomer, the exception being the α-methoxy derivatives **2** versus **3**. Moreover, the binding affinity trends reverse in the two series ((*S*), F > OH > NH_2 > OMe versus (*R*), OMe > NH_2 > OH > F). Thus, not only was the (*R*)-OMe derivative **3** the best in the series approaching the binding affinity of the parent β-alanine **1**, but the distinction between the two enantiomers (**2** versus **3**) was also greatest with this pair. Consequently, this pair of derivatives was more carefully examined alongside **1**.

Binding to Hairpin Deoxyoligonucleotides Containing Variable Length A/T-Rich Binding Sites. The comparisons of **1**−**3** were made using a FID titration assay with a series of DNA hairpins, where the A/T-rich binding site was varied from 5 to 12 bp, Figure 2 and Table 2. With the shortest hairpin

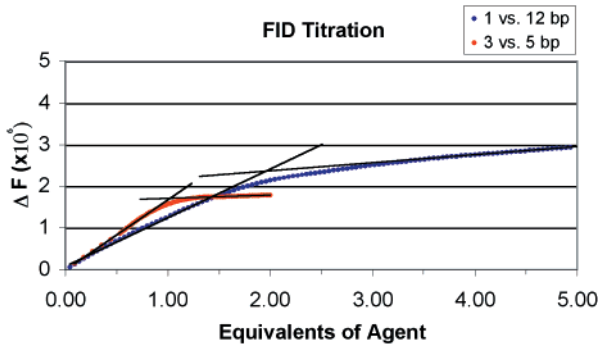


Figure 2. Fluorescent intercalator displacement (FID) titration of **1** (blue) and **3** (red) versus the 12 and 5 bp A/T-rich hairpin deoxyoligonucleotides, respectively.

Table 2. Binding of **1**−**3** to Hairpin Deoxyoligonucleotides Containing 5−12 bp A/T-Rich Sites[a]

A/T-rich	1		2		3			
site length (bp)	stoich	K ($\times 10^7$ M^{-1})	stoich	K (M^{-1})	stoich	K ($\times 10^7$ M^{-1})	stoich	K ($\times 10^7$ M^{-1})
5	~1.5	1.4	<1	$<10^6$	0.98	8.4		
6	~1.5	2.8	<1	$<10^6$	0.95	9.1		
7	~1.5	1.9	<1	$<10^6$	0.93	8.6		
8	1.9	120	<1	$<10^6$	0.96	6.4		
9	1.9	130	<1	$<10^6$	0.97	8.2		
10	1.9	130	<1	$<10^6$	0.95	8.0		
11	2.0	200	<1	$<10^6$	0.96	9.5	2.02	0.74
12	2.0	190	<1	$<10^6$	1.02	7.1	1.98	0.90

[a] Average of triplicate determination, stoichiometry and K (<±5%).

containing a five bp A/T-rich site, the (*R*)-enantiomer **3** (K = 8.4 × 10^7 M^{-1}) bound much more effectively than the (*S*)-enantiomer **2** (K < 10^6 M^{-1}), whereas the parent β-alanine **1** (K = 1.4 × 10^7 M^{-1}) bound with an intermediate affinity. Throughout the series of DNA hairpins, polyamide **2** consistently showed poor ability to bind in the minor groove. Very little change in the behaviors of **1** and **3** is seen until the length of the binding site reaches eight bp where the behavior of **1** dramatically changes. The binding constant increases from 10^7 to 10^9 M^{-1} with the stoichiometry of binding increasing from roughly 1.5 to 2. This corresponds to the expected behavior of extended binding over a 8−9 bp site as an antiparallel 2:1 side-by-side dimer.[25−27] In contrast, the binding stoichiometry of **3** remains constant at 1:1 displaying binding of ~8 × 10^7 M^{-1} throughout the binding site range of 5−10 bp until a binding site length of 11 bp is reached where a second binding event is seen. With these longer sequences, the binding constant of the first binding event remains similar to that observed with the shorter sequences (7.1−9.5 × 10^7 M^{-1} for 11 and 12 bp vs 6.4−9.1 × 10^7 M^{-1} for 5−10 bp), and the second binding event is an order of magnitude less effective (0.74−0.90 × 10^7 M^{-1} for 11 and 12 bp). We have interpreted this behavior as two sequential binding events of **3** adopting a hairpin conformation, each requiring nonoverlapping five bp A/T-rich sites.

Bound Conformation. Comparison of the agent binding stoichiometry with the number of ethidium bromide molecules displaced upon binding provided additional information on the binding site size and bound conformation of the flexible molecules. The number of ethidium bromide molecules dis-

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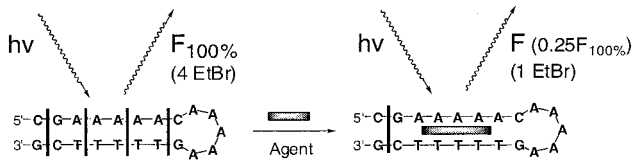


Figure 3. Reduction in ethidium bromide fluorescence from saturated ($F_{100\%}$) occurs upon binding by agent, yielding a final state (F) where three of four intercalated ethidium bromide molecules, shown as (|), have been displaced from the five bp A/T-rich hairpin deoxynucleotide ($F = 0.25F_{100\%}$).

Table 3. Number of Ethidium Bromide Molecules Displaced upon Binding of **1**−**3** to Hairpin Deoxyoligonucleotides Containing 5−12 bp A/T-Rich Sites

		1		**3**			
A/T-rich sequence length (bp)	number of EtBr bound	$F/F_{100\%}$[a]	EtBr displaced ($F_t/F_{100\%}$)[b]	$F/F_{100\%}$[a]	EtBr displaced ($F_t/F_{100\%}$)[b]	$F/F_{100\%}$[a]	EtBr displaced ($F_t/F_{100\%}$)[b]
5	4	0.41	2 (0.50)	0.27	3 (0.25)		
6	4	0.29	3 (0.25)	0.34	3 (0.25)		
7	5	0.27	4 (0.20)	0.40	3 (0.40)		
8	5	0.30	4 (0.20)	0.44	3 (0.40)		
9	6	0.38	4 (0.33)	0.45	3 (0.50)		
10	6	0.40	4 (0.33)	0.45	3 (0.50)		
11	7	0.44	4 (0.43)	0.48	3 (0.57)	0.20	6 (0.14)
12	7	0.46	4 (0.43)	0.49	3 (0.57)	0.17	6 (0.14)

[a] $F/F_{100\%}$ is the experimentally derived ratio of remaining fluorescence. [b] $F_t/F_{100\%}$ is the theoretical ratio of remaining fluorescence after the indicated number of ethidium bromide (EtBr) molecules have been displaced.

placed can be approximated by examining the fluorescence value for DNA saturated with ethidium bromide ($F_{100\%}$) versus the final fluorescence value after the titration is complete and the DNA is saturated with agent (F). Assuming ethidium bromide intercalates at a ratio of one molecule per two bp of DNA, the ratio of $F/F_{100\%}$ can be compared to the theoretical fluorescence decrease (F_t) expected for any stoichiometry of ethidium bromide displacement (Figure 3).

The number of ethidium bromides displaced by **1** most closely approximates the constant value of 4 throughout elongation of the A/T binding site from 7 to 12 bp consistent with antiparallel 2:1 side-by-side binding across an eight bp site (Table 3). Although side-by-side antiparallel binding could allow slippage of **1** along the minor groove leading to partial and nonoverlapping regions with the longest A/T-rich sites,[5] the estimated number of ethidium bromide molecules displaced does not increase as the binding region is lengthened, suggesting that direct overlap is maintained. For **3**, the first binding event displaces three ethidium bromides and is observed without change throughout the 5−10 bp binding site size range. The second binding event displaces an additional three ethidium bromides and is only observed with the longer sequences (11 and 12 bp). Since the stoichiometry of binding for the first event is one and the latter is two, this implies two consecutive binding events of **3** adopting a hairpin conformation, each requiring nonoverlapping 5−6 bp A/T-rich sites.

Models of Bound 1 and 3. The destabilizing effects of the β-alanine α-substituents on the extended binding of **1** can be rationalized by examining models[28] of a 2:1 side-by-side antiparallel complex adopting the expected N to C/5′ to 3′ binding directionality, Figure 4. In addition to substituent conformational effects which may disfavor adoption of the extended conformation, substituents replacing either the β-alanine pro-*R* or the pro-*S* α-hydrogen are oriented into the minor groove with the pro-*S* hydrogen directed at the minor groove

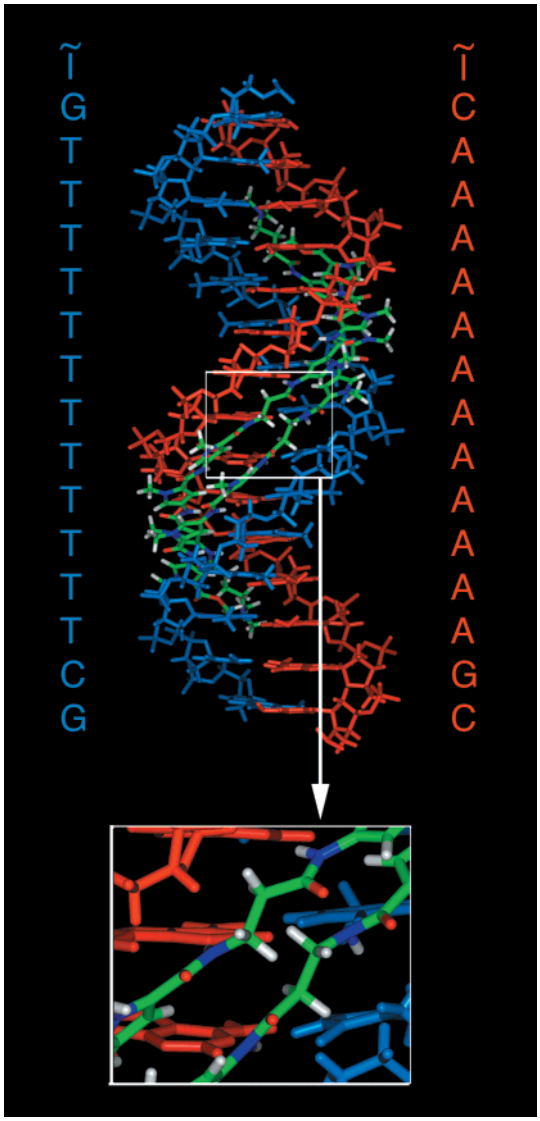


Figure 4. Model of the side-by-side antiparallel 2:1 binding of **1** to the 12A region of the longest A/T-rich hairpin with an expanded view of the β-alanine region highlighting the disposition of the pro-*R* and pro-*S* α-hydrogens.

floor and the pro-*R* hydrogen directed at the deoxyribose walls. Presumably the destabilizing interactions differ within these two environments resulting in the reversed trends in the *S* versus *R* binding. It would not be unreasonable to expect the *S*-enantiomers to be especially sensitive to the size of the substituent producing trends in the binding affinity following those observed with poly[dA]·[dT] (F > OH > NH_2 > OMe), whereas the trends of the *R*-enantiomers may reflect additional characteristics (H-bond donor/acceptor) or be diagnostic of trends expected of a bound hairpin conformation.

Comparisons of models[28] of several potential bound hairpin conformations of **3** revealed one that provides an intrinsically

(28) Molecular modeling was carried out using the Biosym molecular modeling package Insight II (Biosym, San Diego) running on a Silicon Graphics Ozone workstation. The DNA model was constructed using the Biopolymer module of Insight II from standard B-form DNA and polyamide using the Builder module. Energy minimizations were performed using Discover 3 (with the AMBER force field) and were combined with molecular dynamics to relax linker conformation and ligand arrangement. For representative methods regarding molecular modeling of polyamide−DNA systems, see ref 30.

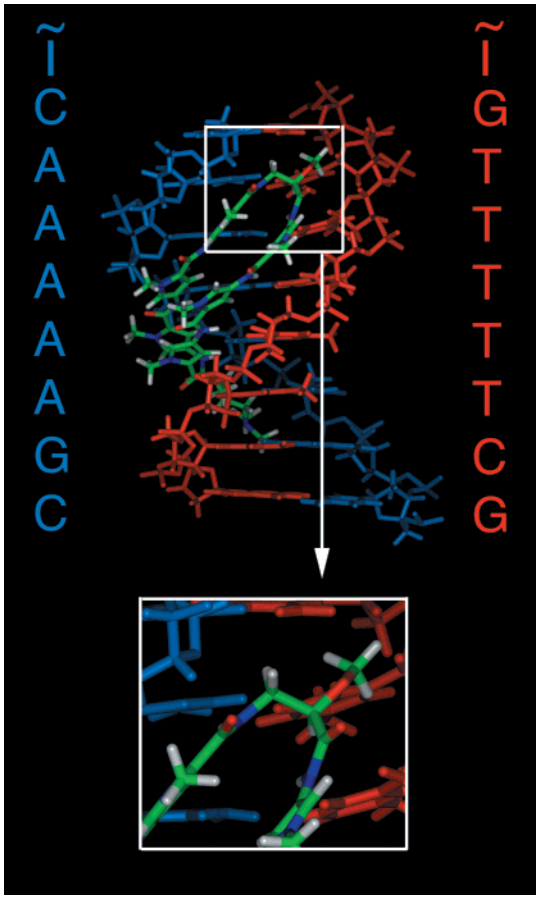
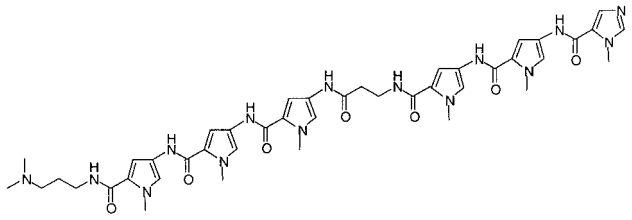


Figure 5. Model of the bound hairpin conformation of **3** within the 5A region of the shortest A/T-rich hairpin (N to C/5′ to 3′ binding directionality) with an expanded view of the β-alanine region highlighting the favorable disposition of the (*R*)-OMe group in the minor groove.

satisfying explanation for the observed behavior. This hairpin conformation is represented in Figure 5 and constitutes antiparallel side-by-side binding in the preferred N to C/5′ to 3′ binding directionality. This hairpin conformation places the pro-*S* hydrogen directed at the floor of the minor groove with the pro-*R* hydrogen lying comfortably in the minor groove roughly coplanar with the Py subunits. Replacement of the pro-*S* hydrogen with a substituent would suffer destabilizing steric interactions, whereas replacement of the pro-*R* hydrogen would not. Among the substituents examined, only placement of the hydrophobic (*R*)-OMe substituent in the minor groove would be expected to contribute significant stabilization to such a bound hairpin conformation. Implicit in this bound hairpin conformation is the reinforcement of the preferred N to C/5′ to 3′ binding directionality.

Discussion

β-Alanine α-substitution has a pronounced effect on the ability of polyamides to bind the DNA minor groove. For compounds **2** and **4**−**9**, the α-substitution effectively disrupts the binding ability relative to the unsubstituted β-alanine polyamide **1**. In an unrelated system **16**, Dervan[22] observed a similar decreased binding ability of α-substituted β-alanine linkers. In sharp contrast to **2** and **4**−**9**, **3** maintains a high DNA binding affinity. More significantly, **3** preferentially adopts a hairpin bound conformation rather than the extended binding of **1**, providing an alternative hairpin linker to γ-aminobutyric acid.



16

In prior studies, the optimal length of a hairpin linker was established to be five atoms (γ, 5 > 6 > 4) providing the optimal degree of flexibility and orientation to accommodate a bound hairpin conformation with such bis-distamycin analogues.[6] With shorter linkers, the hairpin conformation is less accessible, and a 2:1 side-by-side antiparallel binding arrangement of agents in an extended conformation is observed.[6,29−32] This behavior is observed with **1** and most likely with **2** and **4**−**9** whose antiparallel side-by-side binding is destabilized by the β-alanine α-substitution. However, **3** exhibits hairpin binding within the minor groove attributable to the presence of the (*R*)-OMe substituent. Hairpin complexes of Py polyamides containing an unsubstituted β-alanine linker have been observed with DNA binding sites incapable of accommodating the length of an antiparallel side-by-side dimer[30] and as initial intermediate complexes with longer binding sites.[29] In addition to conformational effects of the substituent which may facilitate adoption of the hairpin conformation, the hydrophobic nature of the methoxy group is likely key to the unique behavior of **3**. Models of one such complex indicate the methoxy group may reside in the minor groove providing further stabilization to the bound hairpin conformation. Such an orientation of the methoxy group suggests additional modifications that may further facilitate this mode of binding or provide a site permitting linkage to additional DNA recognition or effector domains.

More fundamentally, the studies illustrate that a generalized variant of a FID assay conducted on a series of systematically varied hairpin deoxyoligonucleotides may be utilized to distinguish hairpin versus extended DNA binding, complementing its use to establish binding stoichiometry, affinity (*K*), and selectivity.

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Supporting Information Available: Characterization and experimental details for the preparation of **1**−**9** (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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