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Marta Oleszczuk^a; Sylwia Rodziewicz-Motowidło^b; Bogdan Falkiewicz^b

^a Polish Academy of Science, Institute of Biochemistry and Biophysics, Warszawa, Poland ^b Faculty of Chemistry, University of Gdańsk, Gdańsk, Poland

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RESTRICTED ROTATION IN CHIRAL PEPTIDE NUCLEIC ACID (PNA) MONOMERS - INFLUENCE OF SUBSTITUENTS STUDIED BY MEANS OF ^1H NMR

Marta Oleszczuk,¹ Sylwia Rodziewicz-Motowidło,²
and Bogdan Falkiewicz^{2,3,*}

¹Institute of Biochemistry and Biophysics, Polish Academy of
Science, Warszawa, Poland

²Faculty of Chemistry, University of Gdańsk, Gdańsk, Poland

³Faculty of Biotechnology, University and Medical University of
Gdańsk, Kładki 24, 80-822 Gdańsk, Poland

ABSTRACT

The influence of amino acid side chains [derived from: Ala, Val, Leu, Ile, Phe, Tyr(Bzl), Ser(Bzl), Thr(Bzl), Pro, Trp], incorporated into “aminoalkyl” part of PNA monomers, on the temperature-dependent distributions of rotamers about the tertiary amide bond was studied by means of ^1H NMR at 0, 25 and 40°C in CDCl_3 . The ΔG^0 values of the energy differences between individual rotamers were calculated. The results may be helpful in the designing of monomers with desirable properties.

PNAs represent a relatively novel group of nucleic acid analogues, in which the phosphodiester backbone of DNA or RNA is replaced by a chiral or achiral peptide-like polyamide, to which natural nucleobases are attached by appropriate linkers (Fig. 1) (1). Depending on the basic manner of the attachment of the nucleobase to backbone, two groups of PNAs may be singled out (2):

*Corresponding author. Fax: +48-58-3012807; E-mail: bogdanf@chemik.chem.univ.gda.pl

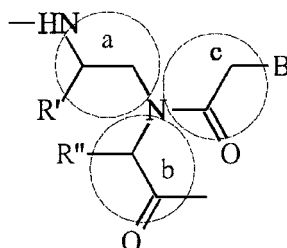


Figure 1. (left) Type I chiral PNA monomer. Conventional parts: aminoalkyl (a), amino acid (b), linker (c), and nucleobase (B) (d). R' or R'' (or both) are different from H.

- Type **I**: containing a backbone consisting of *N*-(aminoalkyl)aminoacid units, to which secondary amine nucleobases are attached by an alkylcarbonyl linker (Fig. 1).

- Type **II**: containing a backbone consisting of amino acid residues carrying the nucleobases in their side chains; frequently referred to as “chiral PNA”.

The most widely known PNAs are based on the *N*-(2-aminoethyl)glycine type **I** backbone (1). They seem to have the most interesting properties and prove to be better ligands of DNA and RNA than native nucleic acids [for recent reviews see (3)]. PNA oligomers have been applied as tools in molecular biology and diagnostics, and as potential therapeutic agents in antisense and antigene strategies (3), may also be expected to find interesting applications in chemistry and technology (4).

In the standard type **I** PNAs nucleobases are attached to the backbone by alkylcarbonyl linkers (1), what results in the introduction of amide with rotational barrier. PNA hybridization characteristics may also be strongly modified by the employment of non-standard monomers incorporated into oligomeric structures (2). The studies on monomer structure/oligomer hybridisation tendency relationships show that if oligomers are to retain a strong hybridisation potential, the possibility of forming of both intra- and inter-residue hydrogen bonds in oligomers is necessary (Fig. 2) (2). This is not sufficient for the formation of stabile hybrids alone; other structural properties (probably more subtle requirements, e.g. related to dipole-dipole interactions or oligomers' hydration) have to be present as well. Modification

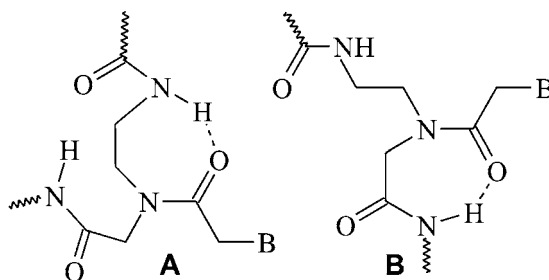


Figure 2. (right) Scheme of intra- (A) and inter-residue (B) hydrogen bonds in standard (achiral) type **I** PNA oligomers (2).



RESTRICTED ROTATION IN CHIRAL PNA MONOMERS

1401

Table 1. Temperature-Dependent Distribution of Individual Rotamers (% of the Major Rotamer) and the ΔG^0 Values of Energy Differences Between Rotamers Among Tertiary Amide Bond (kcal/mol) in the Protected Chiral PNA Monomers

Protected monomer	0°C		25°C		40°C	
	%	ΔG^0	%	ΔG^0	%	ΔG^0
Boc-PNA[Gly]-OMe	70	0.458	64	0.311	59	0.196
Boc-PNA[Ala]-OMe	51	0.022	56	0.130	59	0.196
Boc-PNA[Leu]-OMe	73	0.538	62	0.265	57	0.175
Boc-PNA[Ile]-OMe	52	0.043	52	0.043	57	0.175
Boc-PNA[Phe]-OMe	62	0.265	81	0.784	81	0.784
Boc-PNA[Tyr(Bzl)]-OMe	61	0.242	67	0.578	84	0.896
Boc-PNA[Ser(Bzl)]-OMe	80	0.749	75	0.594	72	0.511
Boc-PNA[Thr(Bzl)]-OMe	67	0.383	56	0.130	53	0.065
Boc-PNA[Pro]-OMe	—	—	60	0.219	55	0.108
Boc-PNA[Trp]-OMe	55	0.108	55	0.108	54	0.087

of the monomers may influence the possibility of the bond formation. Altered, e.g. chiral (5) monomers incorporated into PNA oligomers have modified properties as compared to standard *N*-(2-aminoethyl)glycine based units when incorporated into PNA oligomers (2). In general, oligomers with partially chiral backbone retain strong hybridisation properties, some observable changes are dependent on the configuration of the chiral unit, dimension and chemical properties of the substituent (2).

The aim of this work was to study the influence of diverse amino acid side chains [derived from: Gly, Ala, Val, Leu, Ile, Phe, Tyr(Bzl), Ser(Bzl), Thr(Bzl), Pro, Trp], incorporated into PNA “aminoalkyl” part of methyl esters of *N*-*t*-butoxycarbonyl (Boc) protected chiral PNA monomers, on the percentage distribution of rotamers (about the amide bond) in various temperatures. The energy differences between individual rotamers were calculated from the temperature-dependent changes in percentage distribution of rotamers, studied by means of ^1H NMR spectroscopy. 22k points were collected, 6 kHz spectral width was used. Temperature dependencies of major rotamer populations were obtained from the signals of Boc and ester methyl protons from spectra obtained at 0°C, 25°C and 40°C in CDCl_3 . All experiments were performed on a Varian Unity 500+ spectrometer operating in 500 MHz resonance frequency. The signals were integrated using VNMR 6.1B software. The ΔG^0 values of the energy differences between individual rotamers were calculated from the rotamer concentrations using van't Hoff equation.

RESULTS AND DISCUSSION

All NMR spectra showed two (four in a case of Pro-derived monomer) well-separated signals, independently of temperature; it suggest that the lifetime of



individual rotamers was rather long and barrier to rotation about the amide bond rather high. Differences among the ΔG^0 values obtained for various monomers are relatively small, but the results may be helpful in the designing of monomers and oligomers with desirable properties.

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