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Preview

Self-Assembling, Dynamic αPNAs

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In the recent report published in *Science*, Ghadiri and coworkers describe dynamic tPNAs, αPNA derivatives with a nucleobase attached via a thioester bond that are a step forward toward self-repairing and replicating molecules.

"Chimeric" peptide nucleic acid (PNA) molecules exemplified by the original *aminoethylglycyl*PNAs (aegPNAs) (Nielsen et al., 1991; Figure 1) have attracted much attention during the past two decades, due to their unique properties and ability to structurally mimic the natural nucleic acids DNA and RNA, thereby providing molecular biology and genetic diagnostic tools as well as possible lead compounds for gene therapeutic drug discovery (Lundin et al., 2006). Furthermore, they have been brought into the discussion of possible preRNA world origin of life scenarios (Böhler et al., 1995; Nelson et al., 2000; Nielsen, 1993) because of the peptide-nucleic acid double identity—in essence, being pseudo-peptides with nucleic acid-like properties—and because of their chemical robustness and compatibility with prebiotic synthesis (Nelson et al., 2000).

Although most of the focus has been on the aegPNAs because of their excellent DNA/RNA structural mimicry, αPNAs (Howarth and Wakelin, 1997; Figure 1) are the closest relatives of α-amino acid peptides, as the unit building block is a dipeptide in which one amino acid bears a nucleobase (on an ethyl linker) on the α carbon. However, due to their poor hybridization properties to DNA or RNA, hardly any attention has been given to these PNAs.

Now, in a slightly different context, Ura et al. (2009) have created an exciting twist to these αPNAs by making a chemically dynamic oligomer in which the nucleobase is attached via a thioester bond (tPNA) (Figure 1). As a consequence of the thioester bond, tPNA oligomers may "exchange" (equilibrate) their nucleobases with nucleobase thioester synthons in the medium, analogous to the concept of a dynamic library (de Miguel and Sanders, 1998; Huc and Lehn, 1997). Furthermore, the authors show that such decameric, tPNAs form duplexes with sequence complementary DNA oligonucleotides. However, the most exciting characteristic of the tPNA-DNA system is its ability to adapt to the DNA complement in terms of the nucleobase sequence. Although the authors have not rigorously demonstrated this by subsequent sequencing of the tPNA, they provide convincing evidence that starting from the tPNA backbone and a mixture of nucleobase thioester synthons, the DNA will function as a template for sequence-directed synthesis of a complementary tPNA oligomer. Even more interesting, upon the addition of a new DNA template (and concomitant removal of the old), the tPNA will adapt to this by changing sequence.

Apart from demonstrating a very elegant approach to an information-bearing dynamic chemical library, these results may have implications on the future development of novel self-sustaining and/or repairing materials. The authors also argue that this concept could be of interest for future discovery of catalytic tPNAs or tPNA aptamers as well as in the discussion of the prebiotic origin of our genetic material.

Clearly, a functionalized backbone should be advantageous for the selection of PNA aptamers and especially for the discovery of catalytic PNAs, and αPNAs may be useful for this. However, as their nucleobase recognition hybridization

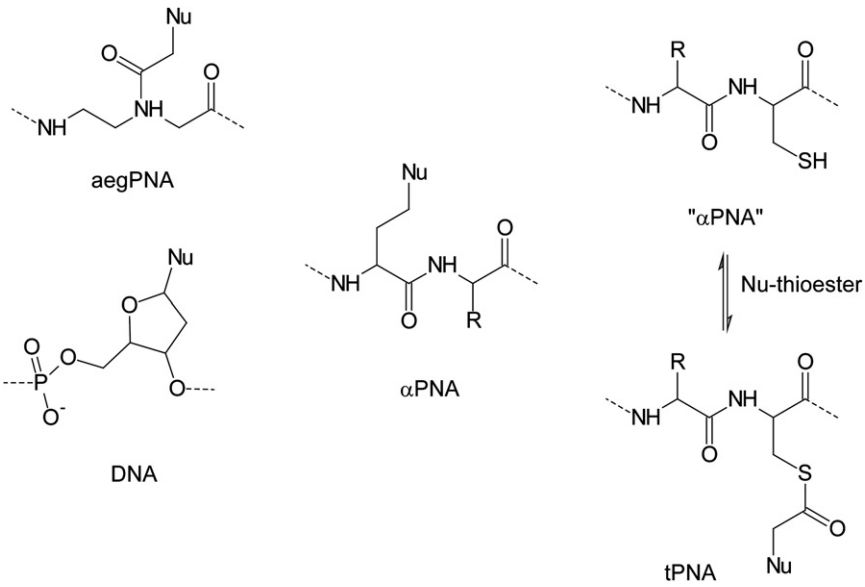

Figure 1. Chemical Structures of αPNA and tPNA
Chemical structures of aeg(aminoethylglycine)PNA, αPNA and DNA "units," as well as the cystein αPNA backbone ("αPNA ") used by Ghadiri and co-workers (Ura et al., 2009) and the equilibrium between this and tPNA by reaction with nucleobase thioesters (Howarth and Wakelin, 1997).

properties are inferior to aegPNA (for which functionalization is also fairly readily available via a simple exchange of the glycine moiety with other α-amino acids), it is not obvious why αPNA would show particular advantages in this respect. Nevertheless, the biggest obstacle in such approaches is the actual selection and identification of active PNA oligomers, as these cannot be selected through an amplification process, such as PCR that is used for DNA and RNA library approaches, but must be selected and identified directly form the original library.

In relation to the origin of life discussion, the present results add a new facet to the puzzle; a facile assembly onto a preformed peptide backbone of a nucleobase sequence guided by a template. Using a chemically stable template such as DNA, this is apparently an efficient reaction with reasonable information transfer fidelity. However, if one imagines a tPNA-tPNA system, one of the concerns could be that the sequence information might be scrambled rapidly, since both strands are dynamic and will template each other during the "replication" process. Thus, it does not seem likely that a dynamic system of this kind would be able to posses the informational robustness necessary for replication; it would chemically mutate much too fast.

Self-replicating and self-repairing molecules are one of the goals for material science. Although specific applications may not appear obvious at this time, the present results could inspire progress in this direction, as the properties of the tPNAs do indeed exemplify both guided chemical repair as well as adaptability to environmental changes. Future developments will show how and if such a strategy can be exploited for the discovery of novel dynamic materials.

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