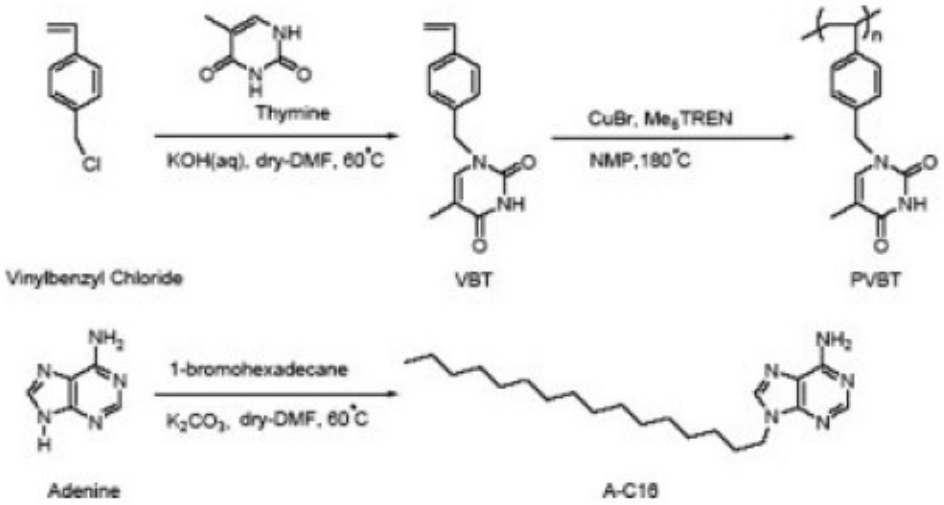
Nucleic Acid Derivatised Pyrrolidone
By: Robert B. Login

Templated polymer synthesis is a growing technology with many recent references illustrating for example how employing Nucleic acid bases attached to oligomers or polymers can be used. The idea is that monomers with nucleic acid bases attached by the same ring nitrogen employed in RNA and DNA bases but now attached to amino acids or vinyl monomers, can be used to mimic biological functions. For example:



Scheme 1. Synthetic procedures used to obtain PVBT and A-C16.

chains of the complexed A-C16 units. Therefore these complexes comprising a nucleobase polymer and amphiphilic moieties, could be applied widely as a means of manipulating the morphologies of biomaterials, because hydrogen bonding might provide them with biocompatibility. We are con-

DOI: 10.1002/pola.22949

These workers show the idea that derivatives of nucleobases would find their counterpart base in an actual biological system. A well designed derivative could hinder or enhance activity of the target. The most successful are now called antisence nucleic

acid oligomers and are in clinical trials or already approved for use. The goal is to find a sequence in the target DNA or RNA to block with the antisence “monkey wrench”; therefore, preventing the virus from replicating or a dangerous protein from being formed.

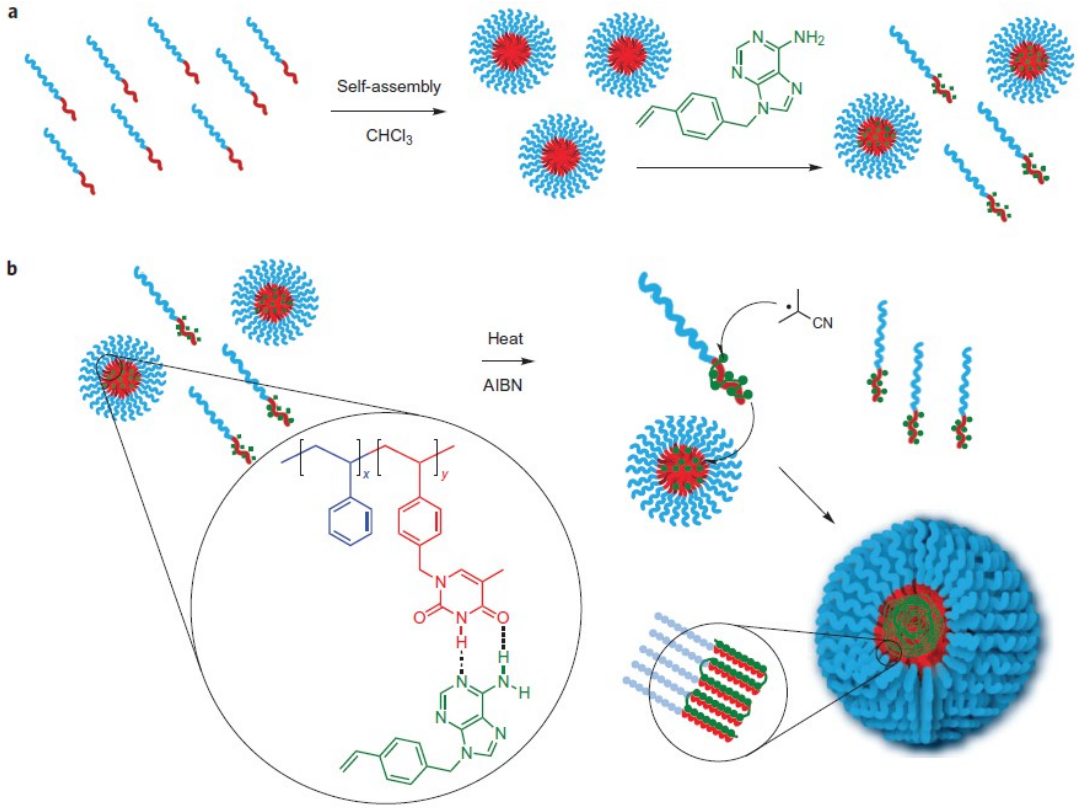


Figure 1 | Dynamic exchange and cooperative assembly of templates. a, Self-assembly of template block copolymer PSt-*b*-PVBT in $CHCl_3$ yields a stable monodisperse micellar system with PVBT cores. The addition of a complementary adenine monomer (VBA) induces dynamic exchange of VBA-loaded template unimers. **b**, On the addition of AIBN and heating, it is proposed that VBA initiation occurs on an exchanging unimer before returning to a micelle for continued propagation. Further dynamic VBA-loaded unimers add to the initiated micelle, from a reservoir of non-initiated micelles, to yield a stable, non-dynamic larger micelle that contains the high MW, low PDI PVBA daughter polymer.

NATURE CHEMISTRY | VOL 4 | JUNE 2012 | www.nature.com/naturechemistry

R. Mchale et. al. show, in micelle like structures, the complimentary monomer can polymerize and link together in larger chains than expected.

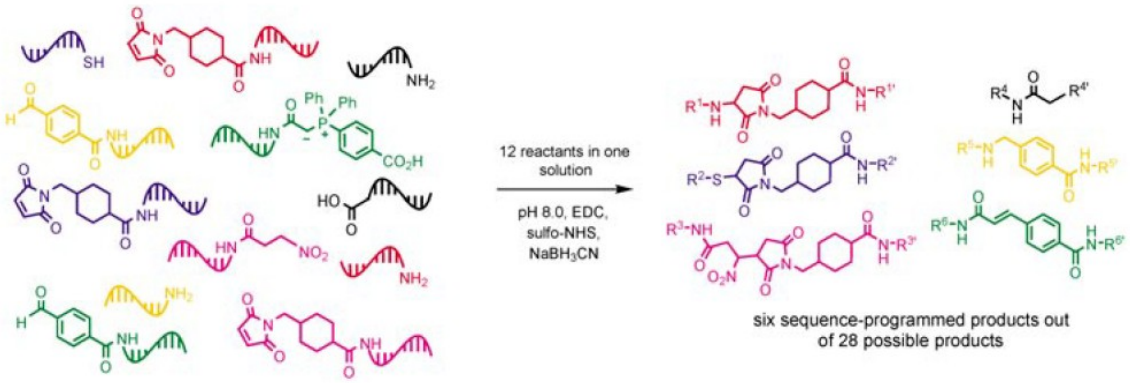
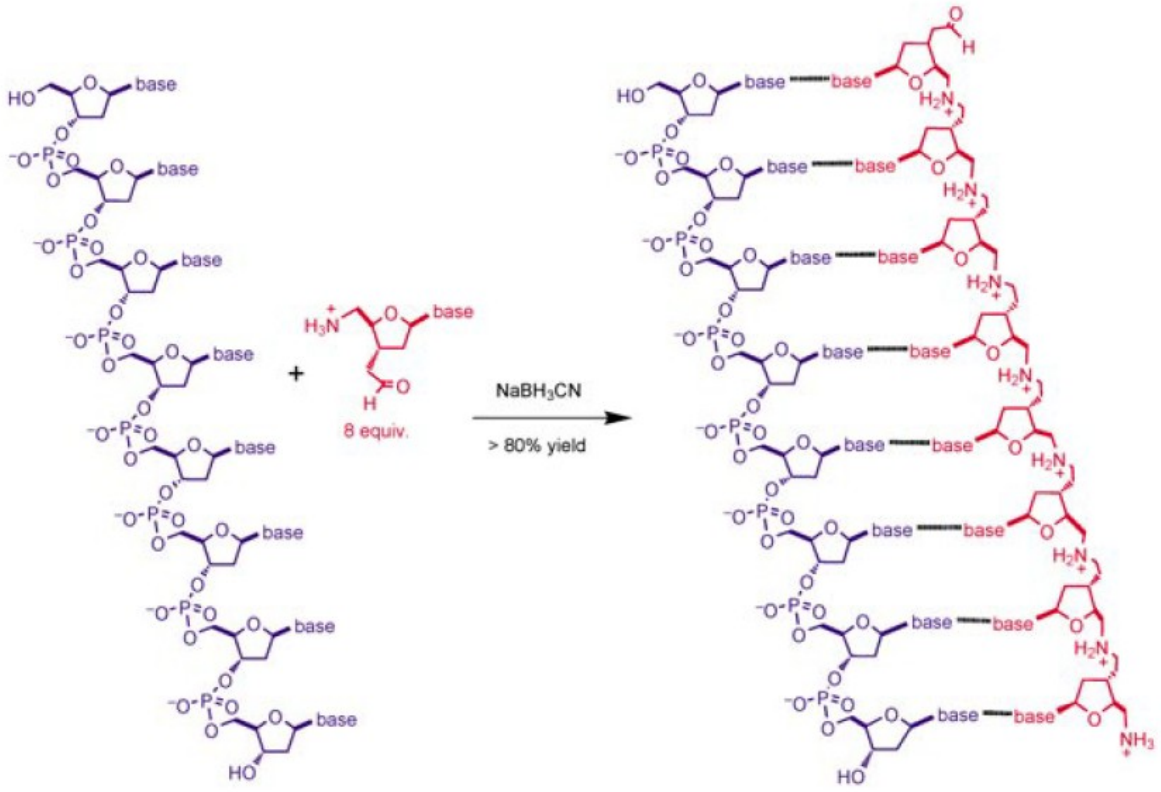


Figure 15. DTS can control multiple, otherwise incompatible reactions in a single solution. R″, R‴: linker or DNA oligonucleotide.[126]

In this case, compounds are attached to DNA complimentary chains that bring the reactants together where they react. This is much like how biological reactions work. Therefor dilute reactants at very low levels are brought together by templating. Cells accomplish these reactions with unique proteins enzymes but many scientists believe RNA molecules originally on the early earth did the similar reactions without enzymes much like the above templating synthetic approach.



DNA-templated polymerization of 5′-amino-3′-formyl-modified dT monomers.[34]

Angew. Chem. Int. Ed. **2004**, *43*, 4848 – 4870

Li and Liu,

But as an aside, considering the unbelievable complexity of even the simplest cells, one wonders how it all came about. Even the simplest prokaryots are beyond our comprehension. Although Dr. Venter has done remarkable things with simple bacteria cells, he and others cannot create life from scratch. The life force alludes them. The only thing the life force is concerned with besides metabolism is reproducing a copy of itself before entropy ends it. Think about it, the original life force never died out but created essentially perfect copies on and on for billions of years.

"Controlling monomer-sequence using supramolecular templates"

By Niels ten Brummelhuis
http://edoc.hu-berlin.de/oa/articles/reADzSD6V2Kk/PDF/23y5sJSih53qM.pdf

"The transcription and translation of information contained in nucleic acids that has been perfected by nature serves as inspiration for chemists to devise strategies for the creation of polymers with well defined monomer sequences. In this review the various approaches in which templates (either biopolymers or synthetic ones) are used to influence the monomer-sequence are discussed."

Interesting reviews:
http://nar.oxfordjournals.org/content/early/2015/12/15/nar.gkv1472.full.pdf+html

http://www.clicknainc.com/wp-content/uploads/2015/08/B-Sharma-Antisense-oligonucleotides-modifications-and-clinical-trials.pdf

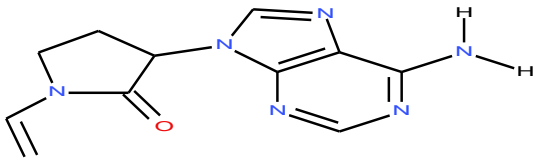
http://online.liebertpub.com/doi/full/10.1089/hum.2015.070

The literature concerning this topic is very large with both journal articles and patents.

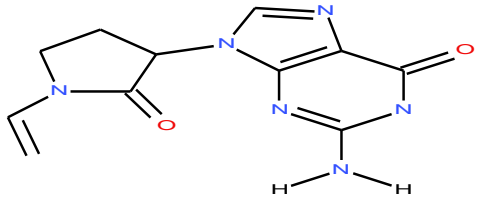
Pyrrolidone Nucleic Derivatives:

I suggest that a variety of derivatives can be visualized. I would start with NVP types.

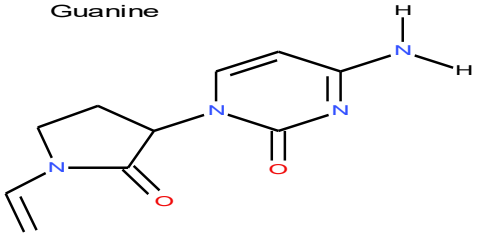
For example:



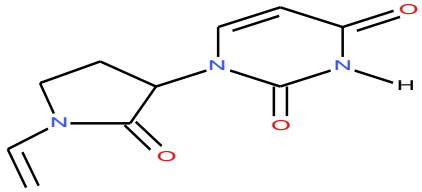
Adenine



Guanine



Thymine

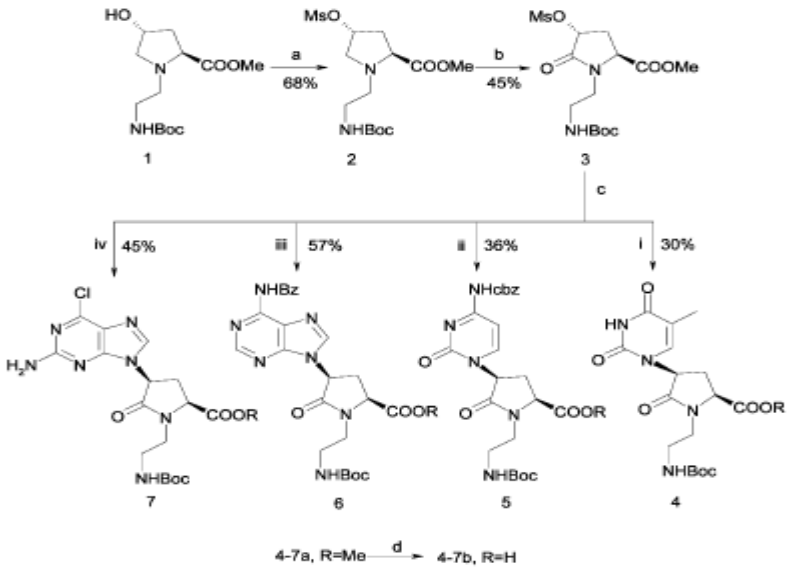


Uracil

The chemistry to do this addition of bases to pyrrolidone has been suggested in the references that follows.

With the advent of controlled radical polymerization such as ATRP, FR monomers can be added one by one to polymer chains. In this case one would want to synthesize oligomers with bases designed to bond with sequences in the target DNA to prevent translation thus preventing expression of problems associated with the prevented protein or for that matter preventing the DNA replicase from functioning thus killing cell reproduction. This approach is the basis of the most effective HIV medicinals.

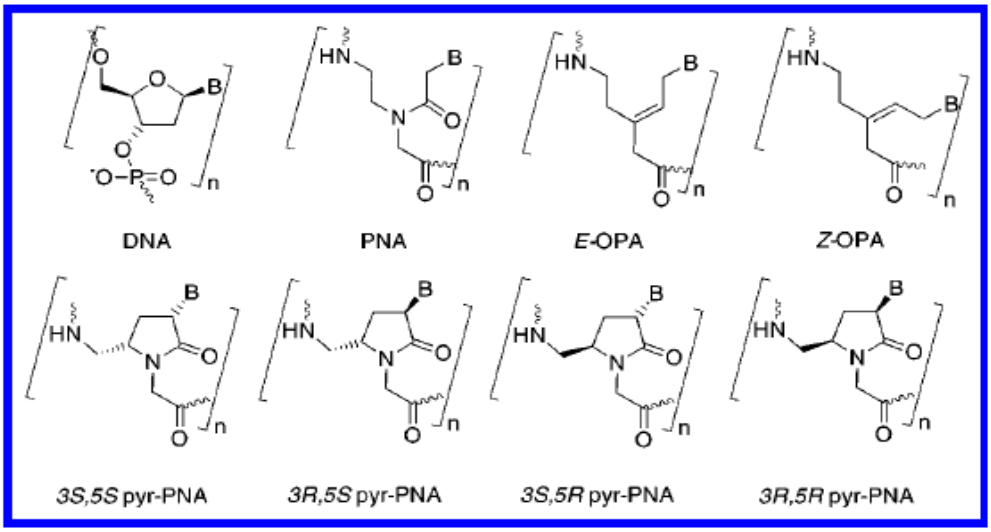
Alternatively, the following PNA has been investigated:



Scheme 1 Synthesis of aepone-PNA monomers. a) $MeSO_2Cl$, Et_3N in DCM at 0 °C; b) $NaIO_4$, $RuCl_3 \cdot xH_2O$, CH_3CN–CCl_4–H_2O (1 : 1 : 1.5), 20 min; c) K_2CO_3, 18-crown-6 ether, DMF, 70 °C; i) thymine; ii) N4-cbz-cytosine; iii) N^6-bz-adenine; iv) 2-amino-6-chloropurine.

CHEM. COMMUN., 2003, 2484–2485

J. Org. Chem., Vol. 66, No. 3, 2001



e 1. Structures of DNA, PNA, and PNA analogues.

.Puschl et al

"The (3*S*,5*R*) isomer was used to prepare a fully modified decamer which bound to rU10 with only a small decrease in *T*m (¢*T*m/mod) 1 °C). The slightly decreased *T*m compared to unmodified PNA indicates that the five membered ring may not be the optimal modification to restrict PNA . "

Although these pyrrolidone PNA's have been synthesized, they have not succeeded as antisense candidates. One of the major problems is aqueous solubility of the PNA's as the cytoplasm is aqueous. Those based on the pyrrolidine structure because of their basicity can be soluble as salts at acceptable pH's. Apparently the pyrrolidone PNA's are not as effective. Partial reduction to a mixture of pyrrolidine and pyrrolidone PNA's has not been tried, however.

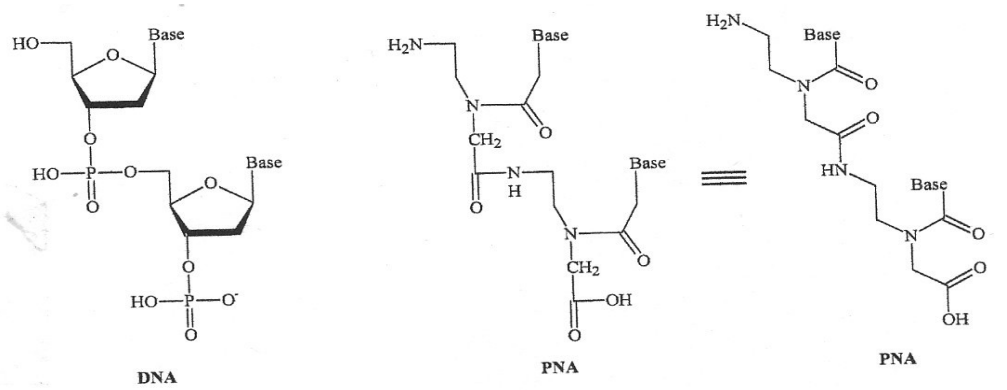


Figure 1.3. The chemical structure of PNA and its similarity to DNA.

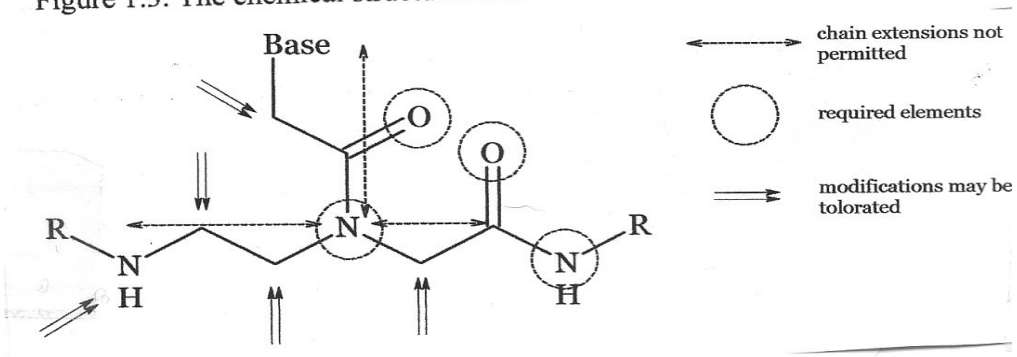
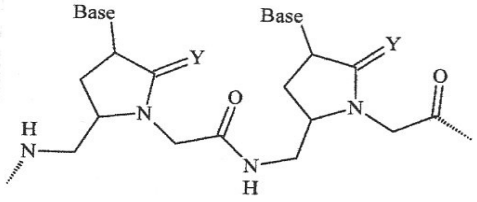
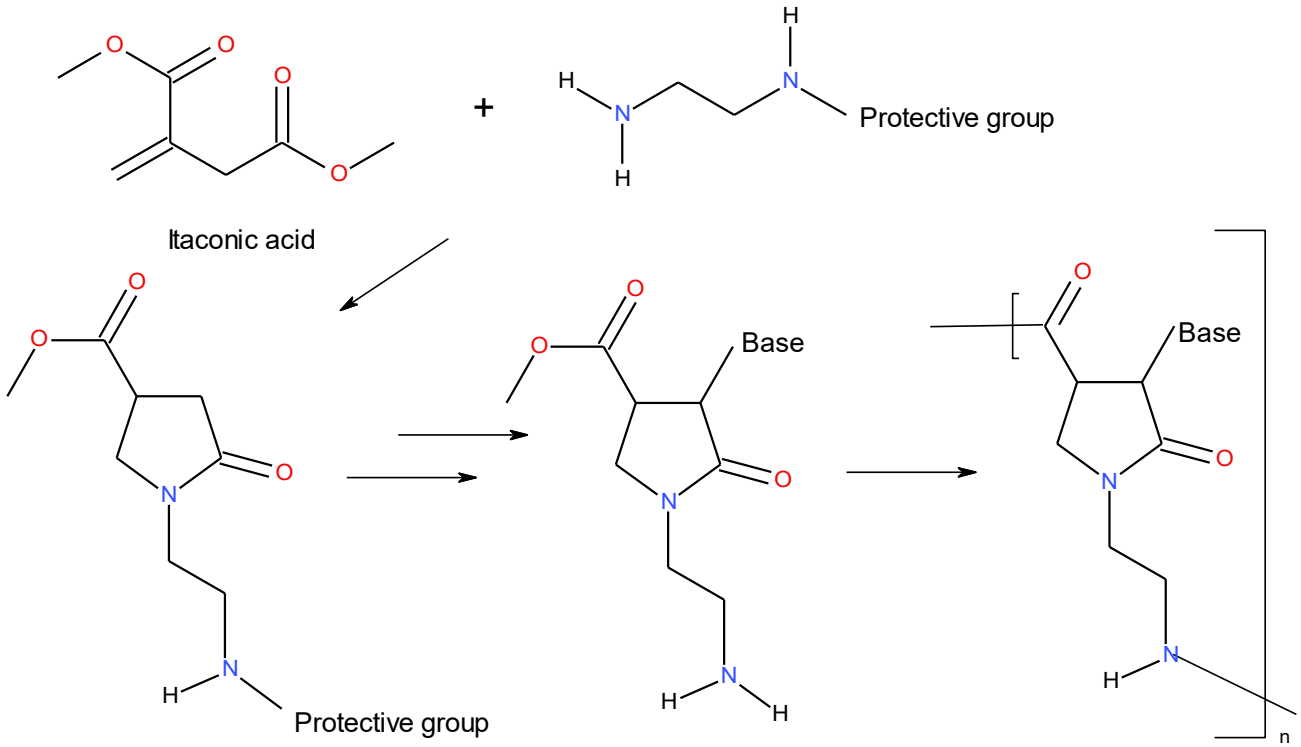


Figure 1.6. Towards the SAR of an acyclic backbone-based PNA.



The above figures are designed to show what would be required in new PNA analogs and how the pyrrolidone PNA shown fits the proposed model. My idea deviates by not having a carbonyl but its still a PNA type and further modifications can be visualized to comport more with the above PNA schematic. From: publications.ki.se/xmlui/bitstream/handle/10616/.../**thesis**.pdf?...1Karolinska Institutet by A Slaitas - 2004

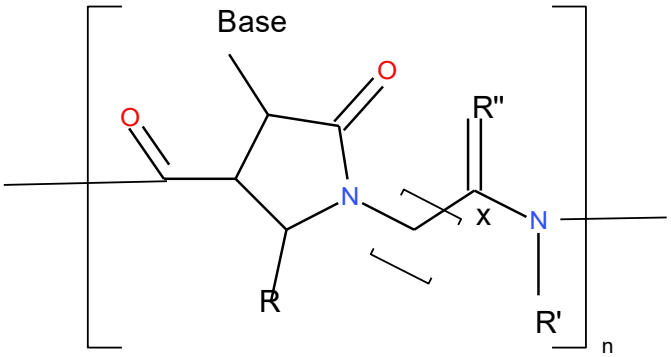
My approach is to reverse the above and move the carboxylate to the 4 position.



I have not found any references to adding bases to this chemistry. The polyamide is already known(USP 5,880,252). It is straight forward employing readily available RM's and itaconic acid which is available by fermentation. As with other PNA's this type can be synthesized with solid supports one base unit at a time affording any combination of base monomer sequences. The idea employs itaconic acid based polyamides which are relatively inexpensive and easily prepared.

Claims:

1. Nucleic acid derivatives of polyamides comprising the following structure,



Wherein n=2-100, and x=0-11, R is an alkyl group optionally substituted with aromatic groups and/or halgens or sulfur derivatives, R' is hydrogen or an alkyl group of 1-18 carbon atoms, R" is oxygen or a methylene or the original methylene and Base is the various nucleobases of DNA and RNA attached to the pyrrolidone by the same nitrogen as they are attached in DNA and RNA to their sugars.

2. Nucleic acid derivatives of N-vinyl pyrrolidone comprising said pyrrolidone substituted at the 3 position with the various nucleic acids that are found in DNA and RNA attached to said pyrrolidone by the same nitrogen as they are attached in DNA and RNA to their sugars.