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Conformational Changes in Polymers with Interactive Side Chains

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Conformational Changes in Polymers with Interactive Side Chains

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It is privilege and a pleasure for me to present a lecture in this symposium honoring the awarding of an Honorary Doctor of Science Degree to Professor Carl S. Marvel of the University of Arizona, by the Polytechnic Institute of New York. It was my privilege to work under the direction of Professor Marvel for my PhD degree, and then for two additional years as a research associate or postdoctoral fellow.

He was the prime influence on my scientific life, and indeed those early impressions that I received at the University of Illinois as a graduate student under his guidance were the building blocks of my own habit patterns for scientific endeavor. The atmosphere of his laboratory was a stimulating experience. He always impressed on me the fact that an idea was a good thing, but unless you tried the idea and made a major effort, your chances of finding something interesting were minimal. He was an individual very open to suggestion and I am sure there were times when he said to me, "Well, why don't you try it," when he really thought, this isn't a very good idea but if it doesn't work, Charlie has learned a lesson, that everything that looks good doesn't work. He was a wonderful sounding board and he was never too busy to talk to me.

He fought many battles for his students, both in the administrative structure of the University of Illinois and advice on personal matters.

I think one of the greatest lessons that I received during that formative period was the example he demonstrated to all of his students re-

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lated to his complete interest in their futures. This attitude on his part prevailed long after I left the University of Illinois. These kinds of impressions, the formative stages of my career, were perhaps the most important part of growing up scientifically, perhaps even more so than the scientific material itself.

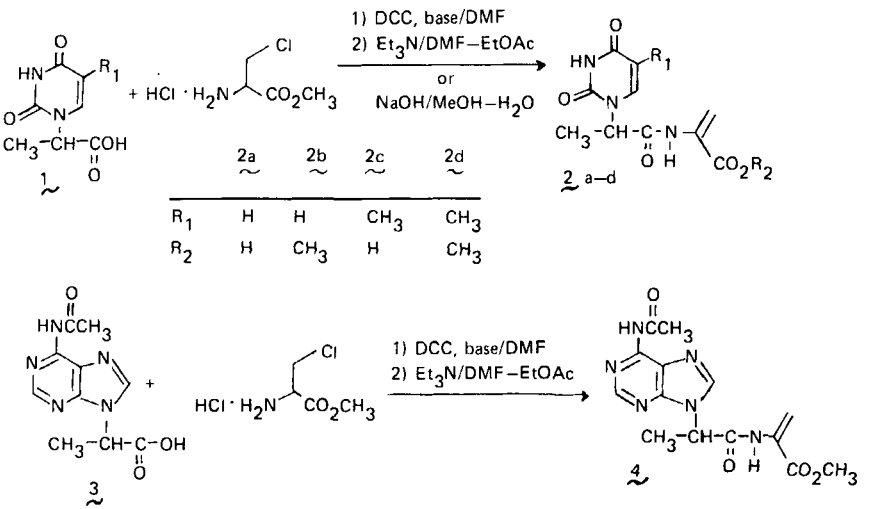
I want today to describe some of our recent research in the field of synthetic polynucleotide analogs.

* * *

Shortly after the discovery of the DNA double-helix, chemists began to make synthetic analogs of the polynucleotides. The motivation for this work is twofold. By making structurally simpler models of these complex polymers, some understanding of structure-behavior relationships can be gained. In addition, both similar and remote analogs have exhibited promising biological activity: single-stranded homopolynucleotides have shown antiviral and antitumor activity, while synthetic double-stranded complexes [most notably poly(I)·poly(C)] can induce interferon production [1]. For these reasons, many analogs varied with respect to both polymer backbone and nitrogenous base have been described [2].

Nucleic acids contain several characteristic structural features: a chiral center adjacent to the base; a hydrophilic, stereoregular poly(phosphate-ribose) backbone which is negatively charged at neutral pH; and most importantly, an ordered secondary structure which is a consequence of both intramolecular base-stacking and interchain hydrogen bonding that stabilizes the double-helix. Few high-molecular weight polynucleotide analogs contain this chirality, charge, and order. We have previously explored the synthesis and solution behavior of analogs having linear poly(ethylenimine) (PEI) [3, 4] and poly(vinylamine) (PVAm) [5] backbones with chiral nucleic acid base pendants attached through amide bonds. These polymers showed base stacking comparable to polynucleotides. Placing a chiral center adjacent to the chromophore allows study by circular dichroism (CD) as well as analysis of stacking interactions by UV. Both techniques are important because the former is sensitive to the angle between adjacent transition dipoles whereas the latter is dependent on the distance between bases. In these models the amide bond between the backbone and base moiety increases structural order through its partial double bond character, resulting in restricted rotation.

Although our model systems mimic the behavior of single- and double-stranded polynucleotides, higher molecular weight polymers had low water solubility. A more hydrophilic modification of these systems is the subject of this paper. Dehydroalanine derivatives have been polymerized to high molecular weight, linear products. We have extended our previously described synthesis of thyminyl dehydroalanine monomers [6] to an adenine and uracil series [7]:



The yields of 2 and 4 are from 40-60% from 1 and 3. The corresponding monomer models were made by reacting 1 and 3 with α-aminoisobutyric acid methyl ester hydrochloride.

Monomers 2 and 4 were polymerized by free radical catalysis in DMF or DMSO to give the expected structures (Table 1). The polymer from monomer 4 undergoes ester hydrolysis and deacetylation upon treatment with dilute NaOH, providing a complementary polymer for interaction with polymers from 2. The polymers containing free acid groups are highly water soluble at neutral or basic pH and show polyanionic viscosity behavior. Significant base-stacking is indicated by the hypochromicity values. High temperature 360 MHz NMR veri-

TABLE 1. Polymerizations of 2 and 4 (AIBN, 60°C, 19 h)

Monomer	R_2	Solvent	Conversion (%)	$n_{inh}^{26°}$ [a]	%h (solvent)[b]
2d	CH_3	DMF	80	0.50	28 (H_2O)
2c	H	DMF	65	0.86[c]	14 (H_2O)
4	-	DMSO	50	0.53	13 (DMSO)

[a] At 0.5 g/dL, DMF.
[b] Percent hypochromicity versus monomer model, 20°C, at λ_{max}.
[c] $\bar{M}_w$ = 170,000 by light scattering in 0.05 M NaCl.

fies the poly(dehydroalanine) structure and also suggests conformational order. The potentiometric and viscometric titration curves of the polyacids indicate considerable conformational rigidity. We are investigating the tacticity of the polymers, as this should have a strong effect on the conformational mobility of the backbone.

By using optically active 1, an optically active monomer is obtained if racemization-suppressing additives such as 1-hydroxybenzotriazole are used in the coupling reaction. Polymerization gives a product with a CD spectrum similar to the PEI and PVAm models mentioned above.

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