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Book Review

Protocols for Oligonucleotides and Analogs. Synthesis and Properties
(Methods in Molecular Biology/20)
Edited by Sudhir Agrawal
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Whereas much of the current wisdom in the biological application of antisense oligonucleotides and oligonucleotide analogues rests upon the extremely shaky foundations of circumstantial evidence and ill-controlled experiments, the same criticism cannot, for the most part, be levelled at the chemistry that went into their development. At the same time, increasing interest in the potential fulfilment of the dream of oligonucleotides as tools of genetic research and as future therapeutic agents has created the need for laboratory handbooks which describe the chemical properties of these molecules and experimental procedures by which they may be synthesized. "Protocols for Oligonucleotides and Analogs. Synthesis and Properties" goes a long way towards fulfilling this need.

The editor has succeeded in securing contributions from most of the international gurus of oligonucleotide chemistry to produce a volume which is both comprehensive and authoritative. The book, with 19 chapters, spans a wide range of complexity. Some of the chapters, or parts thereof (such as: "Oligodeoxyribonucleotide synthesis: phosphoramidite approach", "Oligodeoxynucleotide synthesis: H-phosphonate approach", "Oligoribonucleotide synthesis: the silyl-phosphoramidite method", "Synthesis of 2′-*O*-alkyloligoribonucleotides", "An improved method for the synthesis and deprotection of methylphosphonate oligonucleotides", "Oligonucleoside phosphorothioates", "Synthesis and purification of phosphorodithionate DNA", "Oligodeoxyribonucleotide phosphotriesters", "α-Oligodeoxynucleotides", and "Solid-phase supports for oligonucleotide synthesis") present synthetic procedures which are sufficiently straightforward and clearly described as to tempt the biochemist or pharmacologist with a small chemistry set into the fume hood. Other parts of the book rquire recourse to the cited original literature for full experimental details, but provide useful entry points to the particular aspects of the subject. Elsewhere, the chemistry gets quite heavy going (as in: "Oligonucleoside boranophosphate (borane phosphonate)", "Oligonucleotide phosphorofluoridates and fluoridites", "Oligonucleotide analogs with dimethylenesulfide, -sulfoxide and -sulfone groups replacing phosphodiester linkages", and "Oligonucleotide analogs containing dephospho-internucleoside linkages"), and these particular chapters are more likely to appeal to the dedicated synthetic organic chemist.

The old phosphotriester approach to oligonucleotide synthesis is resurrected by Brown, for historical reasons, and also by Christodoulou, on the grounds that, in solution phase, it might provide a more convenient means to bulk synthesis, as required for therapeutic trials. The related strategies of solution-phase scale-up are described in a separate chapter by Seliger, and, on the subject of increasing yields, the Millipore Corporation gain some free publicity for their 8800 DNA synthesizer in a chapter by Sinha, describing the scale-up of solid-phase synthesis, which is marred only by several typesetting errors.

Overall, the book is of a very high standard. Particular highlights are the excellent chapters by Pon on solid-phase supports, including those for 3′-introduction of ligands and receptor groups such as fluorescein, and that by Zon on oligonucleoside phosphorothioates. The latter draws attention to a new strong anion exchange HPLC technique to determine the level of P-O contamination in these molecules. This is particularly important since commercial preparations of phosphorothioate oligodeoxynucleotides may contain quite considerable proportions of contaminant oligomers, with at least one normal phosphodiester linkage present, which are not resolved by the popular reverse phase HPLC analytical technique, and which could conceivably affect the biological properties of these preparations. Also noteworthy is the very interesting chapter by Stec & Lesnikowski on stereocontrolled synthesis of methylphosphonates and phosphorothioates, where current routine methods of synthesis produce mixtures of 2^n diastereoisomers, n being the number of internucleoside linkages, and where only one diastereoisomer homogeneous in configuration at each phosphorous might be the most effective species biologically.

On the other hand, it is apparent that some of the structures described in this book are of purely chemical rather than biological interest. For example, carboxymethyl-bridged oligonucleotide analogues are unstable at pH 7·5, exhibiting a half-life of 7 h, while acetamidate-bridged oligomers do not show any tendency to hybridize with their complementary natural polynucleotides. Also, the phosphorofluoridate internucleoside linkage is susceptible to cleavage by exonucleases, and consequently, would not be expected to impart any particular advantage biologically over the normal phosphodiester group. Borane phosphate chemistry has not as yet been perfected for the synthesis of oligonucleotides larger than trimers, and while the present state of development is clearly and convincingly presented, speculation about future applications of longer molecules in combined antisense-boron neutron capture therapy is pure fantasy.

Notwithstanding those approaches which appear to be of limited potential from a biological or therapeutic perspective, "Protocols for Oligonucleotides and Analogs" is definitely required reading for the would-be oligonucleotide chemist and for those involved in biological applications of oligonucleotides who would like to become more involved themselves in at least some aspects of the chemistry of these molecules.

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