Contents

List of Contributors xv
Preface xix

Part I (Non-) Covalently Modified DNA with Novel Functions 1

1.1 DNA-Based Construction of Molecular Photonic Devices 3
1.1.1 Introduction 3
1.1.2 Using DNA as a template to construct discrete optoelectronic nanostructures 5
1.1.3 Assembly of photonic arrays based on the molecular recognition of single-stranded DNA templates 7
1.1.4 Assembly of photonic arrays based on the molecular recognition of double-stranded DNA templates 10
   1.1.4.1 Intercalation 10
   1.1.4.2 Minor-groove binding 12
1.1.5 Towards the construction of photonic devices 13
1.1.6 Outlook 13
   1.1.6.1 Optoelectronic circuits 13
   1.1.6.2 Diagnostic platforms 14
References 15

1.2 π-Conjugated DNA Binders: Optoelectronics, Molecular Diagnostics and Therapeutics 22
1.2.1 π-Conjugated compounds 22
1.2.2 DNA binders for different applications 23
   1.2.2.1 Molecular diagnostics 23
   1.2.2.2 Therapeutics 26
   1.2.2.3 Optoelectronics 26
1.2.3 Targeting duplex DNA 27
   1.2.3.1 Examples of π-conjugated compounds interacting with double-stranded DNA – minor groove binders 29
   1.2.3.2 Examples of π-conjugated DNA binders interacting with double-stranded DNA – intercalators 32
1.2.4 Examples of π-conjugated compounds interacting with hybrid duplexes and higher order nucleic acid structures 32
   1.2.4.1 Examples of π-conjugated compounds interacting with DNA•RNA and DNA•PNA hybrid duplexes 33
   1.2.4.2 Examples of π-conjugated compounds interacting with higher order nucleic acid structures 33

1.2.5 Conclusions 33

References 34

1.3 Metal Ion- and Perylene Diimide-Mediated DNA Architectures 38
   1.3.1 Introduction 38
   1.3.2 Metal ion complexes as DNA modifications: hydroquinoline and terpyridine 39
   1.3.3 Perylene diimide-based DNA architectures 42
   1.3.4 Conclusions 49

References 49

1.4 DNA with Metal-Mediated Base Pairs 52
   1.4.1 Introduction 52
   1.4.2 Metal-mediated base pairs with natural nucleobases 53
      1.4.2.1 Pyrimidines 53
      1.4.2.2 Purines 54
   1.4.3 Metal-mediated base pairs with artificial nucleobases 54
      1.4.3.1 Individual metal-mediated base pairs 54
      1.4.3.2 Stacks of metal-mediated base pairs 58
      1.4.3.3 Doubly metalated base pairs 59
   1.4.4 Outlook 61

References 61

1.5 Metal-Aided Construction of Unusual DNA Structural Motifs 65
   1.5.1 Introduction 65
   1.5.2 DNA duplexes containing metal-mediated base pairs 66
   1.5.3 Metal-aided formation of triple-stranded structures 69
   1.5.4 Metal-aided formation of four-stranded structures 71
   1.5.5 Metal-aided formation of DNA junction structures 73
   1.5.6 Summary and outlook 75

References 75

Part II DNA Wires and Electron Transport Through DNA 79

2.1 Gating Electrical Transport Through DNA 81
   2.1.1 Introduction 81
   2.1.2 DNA structure 82
   2.1.3 Direct electrical measurements of DNA 82
   2.1.4 Gate modulation of current flow in DNA 84
   2.1.5 DNA transistors 86
   2.1.6 Summary and outlook 92

References 92
3.1.5 Genosensors incorporating DNA probes modified with redox active molecules – ‘signal-off’ and ‘signal-on’ working modes 145
3.1.6 Genosensors for simultaneous detection of two different DNA targets 151
3.1.7 Conclusions 154
Acknowledgements 154
References 154

3.2 Oligonucleotide Based Artificial Ribonucleases (OBANs) 158
3.2.1 Introduction 158
3.2.2 Early development of OBANs 159
3.2.3 Metal ion based artificial nucleases 159
3.2.4 Non-metal ion based systems 161
3.2.5 Creating bulges in the RNA substrate 162
3.2.6 PNAzymes and creation of artificial RNA restriction enzymes 164
3.2.7 Conclusions 167
References 168

3.3 Exploring Nucleic Acid Conformations by Employment of Porphyrin Non-covalent and Covalent Probes and Chiroptical Analysis 172
3.3.1 Introduction 172
3.3.2 Non-covalent interaction of porphyrin–DNA complexes 174
3.3.2.1 Interaction with single-stranded DNA 174
3.3.2.2 Double helix conformations B- and Z-DNA 176
3.3.2.3 G-quadruplex 181
3.3.3 Porphyrins covalently linked to DNA 187
3.3.3.1 Porphyrins attached to 5’- and 3’-termini of DNA with phosphates and amides 187
3.3.3.1.1 5’-Phosphate linkage 187
3.3.3.1.2 Detection of the B- to Z-transition 189
3.3.3.1.3 3’-Amide linkage 191
3.3.3.1.4 5’-Amide linkage 192
3.3.3.2 Capping effect 193
3.3.3.3 Porphyrin C-nucleoside replacement of natural nucleobases 197
3.3.3.4 Porphyrins embedded in the backbone of DNA 197
3.3.3.5 Diastereochemically pure anionic porphyrin–DNA dimers 198
3.3.3.6 Incorporation of rigid and flexible linked porphyrins to DNA nucleobases 200
3.3.4 Conclusions 203
References 203

3.4 Chemical Reactions Controlled by Nucleic Acids and their Applications for Detection of Nucleic Acids in Live Cells 209
3.4.1 Introduction 209
3.4.2 Intracellular nucleic acid targets 211
3.4.3 Methods for monitoring ribonucleic acids in live cells 211
3.4.3.1 Genetically encoded reporters 212
3.4.3.2 Hybridization-responsive oligonucleotide probes 213
3.4.3.3 Fluorogenic templated reactions
  3.4.3.3.1 Nucleophilic substitution reactions 214
  3.4.3.3.2 Staudinger reduction 216
3.4.3.4 Photochemical reactions 221
3.4.4 Perspectives 225
References 226

3.5 The Biotechnological Applications of G-Quartets 229
3.5.1 Introduction 229
3.5.2 Nucleobases and H-bonds 229
3.5.3 Duplex-DNA mimics 231
3.5.4 Guanine and G-quartets 232
3.5.5 G-Quartets and G-quadruplexes 232
  3.5.5.1 Colorimetric detection 234
  3.5.5.2 Luminescence–fluorescence detection 234
  3.5.5.3 Electrochemical detection 235
3.5.6 Quadruplex-DNA mimics 236
  3.5.6.1 Intermolecular SQ: G-monomers 236
  3.5.6.2 Intermolecular interconnected SQ: G-dimers 239
  3.5.6.3 Intramolecular SQ (or iSQ): G-tetramers 240
3.5.7 Conclusions 244
References 244

Part IV Conjugation of DNA with Biomolecules and Nanoparticles 247

4.1 Nucleic Acid Controlled Reactions on Large Nucleic Acid Templates 249
4.1.1 Introduction 249
4.1.2 Nucleic acid controlled chemical reactions 250
4.1.3 Applications
  4.1.3.1 Reactions on intracellular RNA 257
  4.1.3.2 Reactions on large biogenic DNA and RNA templates in vitro 259
  4.1.3.3 Drug screening 262
  4.1.3.4 Materials science 266
4.1.4 Conclusions 268
References 270

4.2 Lipid Oligonucleotide Bioconjugates: Applications in Medicinal Chemistry 276
4.2.1 Introduction 276
4.2.2 Chemical approach to the synthesis of lipid–oligonucleotide conjugates
  4.2.2.1 Solid-phase (or pre-synthetic) approach 277
    4.2.2.1.1 Lipid conjugation at the 3’-terminal 277
    4.2.2.1.2 Lipid conjugation at 5’-terminal 280
    4.2.2.1.3 Lipid conjugation at internal position (intra-chain) 282
  4.2.2.2 Solution-phase (or post-synthetic) approach 284
4.2.3 Biomedical applications
  4.2.3.1 LONs as efficient delivery vehicles in gene therapy 286
  4.2.3.2 Other biomedical applications of LONs 288
4.2.4 Conclusions 288
Acknowledgements 289
References 289

4.3 Amphiphilic Peptidyl–RNA 294
  4.3.1 Introduction 294
  4.3.2 Three souls alas! are dwelling in my breast [2] 295
  4.3.3 Why RNA? Why peptides? 296
  4.3.4 Hydrolysis-resistant amphiphilic 3′-peptidyl–RNA 297
  4.3.5 Synthetic strategy 299
  4.3.6 Pros’n cons 300
  4.3.7 Alternative methods and strategies 302
  4.3.8 Molecular properties 302
  4.3.9 Supramolecular properties 302
  4.3.10 Conclusions and perspectives 304
Acknowledgements 306
References 306

4.4 Oligonucleotide-Stabilized Silver Nanoclusters 308
  4.4.1 Introduction 308
  4.4.2 Sensors 311
    4.4.2.1 Metallic sensors 311
    4.4.2.2 Small molecule sensors 312
    4.4.2.3 Protein sensors 313
    4.4.2.4 Nucleic acid sensors
      4.4.2.4.1 DNA sensors 317
      4.4.2.4.2 MiRNAs sensors 319
    4.4.2.5 Cells 320
  4.4.3 DNA computing (logic gates) 321
  4.4.4 Assorted examples 322
  4.4.5 Conclusions 323
References 323

Part V Alternative DNA Structures, Switches and Nanomachines 329

5.1 Structure and Stabilization of CGC+ Triplex DNA 331
  5.1.1 Introduction 331
  5.1.2 Classification of DNA triplets 332
  5.1.3 Structure of triplexes 332
  5.1.4 Triplex stabilizing factors
    5.1.4.1 Effect of pH on the triplex 335
    5.1.4.2 Effect of cations on the triplex 335
    5.1.4.3 Effect of length and composition of the three strands on the triplex 336
    5.1.4.4 Molecular crowding 337
5.1.5 Formation of stable CGC+ triplex DNA
   5.1.5.1 Analogues mimicking protonated cytosine
   5.1.5.2 Analogues with increased $pK_a$
   5.1.5.3 Backbone modification
   5.1.5.4 Triplex binding ligands
   5.1.5.5 Other stabilizing effects
      5.1.5.5.1 Polyamines
      5.1.5.5.2 Basic oligopeptides
      5.1.5.5.3 Silver ions and silver nanoclusters
      5.1.5.5.4 Single-walled carbon nanotubes

5.1.6 Summary

References 346

5.2 Synthetic Molecules as Guides for DNA Nanostructure Formation 353
   5.2.1 Introduction
   5.2.2 Covalent insertion of synthetic molecules into DNA
      5.2.2.1 Incorporating organic molecules into DNA
      5.2.2.2 Adjusting flexibility
         5.2.2.2.1 Mediating DNA self-assembly
      5.2.2.3 Direct effect of synthetic organic linkers on DNA stability and assembly
         5.2.2.3.1 Supramolecular assembly guided through synthetic additions to DNA
         5.2.2.3.2 Backbone insertion of metal binding organic molecules
   5.2.3 Non-covalently guided DNA assembly
      5.2.3.1 DNA intercalators
      5.2.3.2 Groove binding

5.2.4 Conclusions

References 369

5.3 DNA-Based Nanostructuring with Branched Oligonucleotide Hybrids 375
   5.3.1 Introduction
   5.3.2 Branched oligonucleotides
   5.3.3 Hybrids with rigid cores
   5.3.4 Second-generation hybrids with a rigid core
   5.3.5 Solution-phase syntheses: Synthetic challenges
   5.3.6 Hybrid materials
   5.3.7 Outlook
   5.3.8 Conclusions

Acknowledgements

References 394

5.4 DNA-Controlled Assembly of Soft Nanoparticles 397
   5.4.1 Introduction
   5.4.2 Sequence design
      5.4.2.1 Double membrane anchor ssDNA design
      5.4.2.2 Single membrane anchor multiple ssDNA design
      5.4.2.3 Single membrane anchor multiple ssDNA design for irreversible assembly (fusion/hemifusion)
Contents

5.4.3 Lipid membrane anchors 400
5.4.4 DNA-controlled assembly studied by UV spectroscopy 402
   5.4.4.1 Thermal stability of lipid-modified DNA conjugates 404
   5.4.4.2 DNA mismatch discrimination studies 405
5.4.5 Assembly on solid support 406
5.4.6 Assembly of giant unilamellar liposomes (GUVs) 408
5.4.7 Conclusions 409
Acknowledgements 409
References 409

5.5 Metal Ions in Ribozymes and Riboswitches 412
5.5.1 Introduction 412
5.5.2 Coordination chemistry of RNA 413
5.5.3 Ribozymes 415
   5.5.3.1 Overview of the ribozyme world 415
   5.5.3.2 Small ribozymes 415
   5.5.3.3 Large ribozymes 417
5.5.4 Riboswitches 420
   5.5.4.1 Overview of the riboswitch world 420
   5.5.4.2 Metal ions assisting riboswitch folding and ligand recognition 422
   5.5.4.3 Riboswitch ligands containing a metal 423
      5.5.4.3.1 Mg\(^{2+}\)-sensing riboswitches 423
      5.5.4.3.2 B\(_{12}\)-riboswitches 424
      5.5.4.3.3 MoCo/TuCo-riboswitches 425
5.5.5 Summary 425
Acknowledgement 426
References 426

5.6 DNA Switches and Machines 434
5.6.1 Introduction 434
5.6.2 Ion-stimulated and photonic/electrical-triggered DNA switches 438
   5.6.2.1 Ion-stimulated DNA switches 438
   5.6.2.2 Photonic and electrical triggering of DNA switches 443
5.6.3 Switchable DNA machines 447
   5.6.3.1 Two-state switchable DNA machines 448
   5.6.3.2 Multi-state DNA machines 455
5.6.4 Applications of DNA switches and machines 459
5.6.5 Conclusions and perspectives 466
References 467

5.7 DNA-Based Asymmetric Catalysis 474
5.7.1 Introduction 474
5.7.2 Concept of DNA-based asymmetric catalysis 474
5.7.3 Design approaches in DNA-based asymmetric catalysis 475
5.7.4 Covalent anchoring 476
5.7.5 Supramolecular anchoring
   5.7.5.1 First generation DNA-based catalysts 478
   5.7.5.2 Improvement of the catalytic system – second generation catalysts 478
   5.7.5.3 Catalytic scope of DNA-based catalysts 479
      5.7.5.3.1 Conjugated addition reactions 480
      5.7.5.3.2 Miscellaneous reactions 483
   5.7.5.4 Mechanistic studies and role of DNA in catalysis 484
      5.7.5.4.1 Diels–Alder cycloaddition 485
      5.7.5.4.2 Friedel–Crafts reaction 486
      5.7.5.4.3 Michael addition 486
      5.7.5.4.4 Hydration of enones 487
      5.7.5.4.5 Stereochemistry in DNA-based catalytic asymmetric reactions 487

5.7.6 Conclusions and perspectives 488
References 489

Index 491