Nucleotides and nucleic acids; oligo- and polynucleotides

David Loakes

DOI: 10.1039/b603852m

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1. Introduction

This review of oligonucleotides covers an 18-month period until the end of 2005. During this period over 1100 papers have been published using modified oligonucleotides, and the field expands every year. As in previous years, the largest portion of papers deal with base-modified nucleosides and their effects on oligonucleotides, but newer areas are beginning to develop. One of the main developments in this time is the field of nanotechnology, involving the control and manufacture of devices on the nanoscale. This covers a broad spectrum of devices from nanowires, molecular lithography and molecular self-assembly to the design of nanomachines. Oligonucleotides are playing a key part in this field, and are discussed in this review. Another area, linked with nanotechnology, is single-molecule detection, and once again many papers have been reported in this field. Interest in the analogues LNA and PNA continues, and advances have been made on their applications, as well as a number of new analogues of each having been reported. Finally, methods of exploring nucleic acid structures usually involve X-ray crystal and NMR structures, but a number of other methods are currently being explored, and these are included in this review.

1.1 Oligonucleotide synthesis

1.1.1 DNA synthesis. There have been very few reports on advances in DNA and RNA synthesis. The main developments in this area have concerned DNA microarrays (Section 1.1.2). There are now many genome sequences that have been sequenced, and following from this there is a need for the synthesis of large DNA fragments. The synthesis of a 32 kb gene cluster has been reported using synthetic 40-mer oligonucleotides which are assembled into 500–800 bp synthons by PCR.[1] Another significant use of oligonucleotides is in cell-based applications, such as antisense therapies. For this it is necessary to stabilise the oligonucleotides from nuclease digestion and one widely used method is the use of phosphorothioates. A method has been described in which sulfur and sodium sulphide in picoline is used to introduce phosphorothioate linkages with 99.8% sulfurisation efficiency.[2,3] Also, a thermolytic (*N*-formyl-*N*-methyl)aminoethyl thiophosphate protecting group has been used for the synthesis of phosphorothioate oligonucleotides.[4,5] Phosphorodithioate oligonucleotides have been prepared using bis(2,6-dimethylphenyl) phosphorochloridate as coupling agent using *H*-phosphonate oligonucleotide synthesis chemistry.[6] One problem associated with synthesis of phosphorothioate oligonucleotides is desulfurization during synthesis. This has been studied using ^{31}P-NMR and shown that 'old' solutions of trichloroacetic acid lead to desulfurization.[7] Phosphoroselenoate oligonucleotides have been prepared using the oxathiaphospholane analogue (**1**), coupling to a free 5′-hydroxyl group using DBU.[8] A method for synthesis of oligonucleotides in the 5′–3′ direction has been described using

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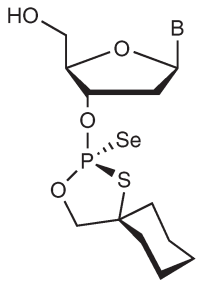
3′-*O*-allyl protection, which may be removed using palladium(II) and a water soluble triphenylphosphine.[9]



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A majority of reports concern the use of solid supports. Reusable solid supports have been described based on disulfide[10] and hydroxyallyl[11] between the controlled pore glass (CPG) and oligonucleotide, and a modified nucleoside has been used as a chemically cleavable linker for the synthesis of labelled oligonucleotides.[12] Large pore CPG gives improved synthesis of long oligonucleotides.[13] A method for more efficient loading of nucleosides onto CPG has been described using microwave-assisted functionalisation.[14] CPGs have been used to synthesise terminally-modified oligonucleotides; various 3′-conjugates have been reported using a diol-modified CPG,[15] and 3′-amino-modified oligonucleotides may be synthesised from an amino-modified CPG.[16,17] Reagents for the synthesis of 5′-phosphate- or 5′-thiophosphate-modified oligonucleotides have been described.[18] There are two reports describing the use of solid supports suitable for synthesis of oligonucleotides using *H*-phosphonate chemistry.[19,20]

A few new protecting groups have been described. Trimethylsilylethoxycarbonyl (Teoc) and trimethylsilylethanol (Tse) have been used to protect nucleobase amine groups,[21,22] and protecting groups are removed by treatment with zinc bromide, which stabilises purines from depurination. They may also be used in conjunction with *S*-acetyl-2-thioethyl (SATE) protecting group chemistry. *tert*-Butyl-1-pyrenyl-methylsilyl may be used as a protecting group for 5′-hydroxyl. It is removed under basic conditions, but its primary use is for its enhanced fluorescent properties, which makes it useful for purification of oligonucleotides.[23] A by-product of deprotection of 2-cyanoethyl phosphate groups is acrylonitrile, which can alkylate thymine residues. Nitromethane can be used as a scavenger of acrylonitrile to prevent alkylation reactions.[24] A photocleavable phosphate protecting group has been devised as a method for controlling the process of RNA interference. The process involves reaction of the siRNA with 4,5-dimethoxy-2-nitroacetophenone, which reacts with the phosphate backbone and prevents the siRNA from associating with the RISC complex until removed photochemically.[25]

Finally, a new method for the purification of oligonucleotides has been described. Using the fluorinated dimethoxytrityl derivative (**2**) oligonucleotides can be purified with the DMT-ON technique on a fluorinated adsorbent.[26,27] Oligonucleotides may be purified using this method directly from the ammonia solution with high recovery, and the method is suitable for long oligonucleotides.

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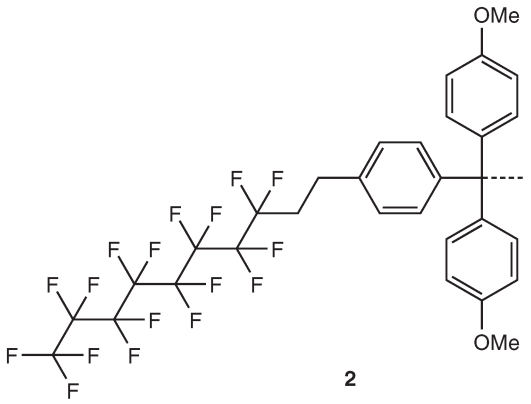

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1.1.2 DNA microarrays. Microarrays have become a standard tool used in molecular biology and genomics. There are many publications in which commercial microarrays have been used, and these are not described in this review. Only those reports which describe a new development in the field of microarrays are discussed, which include new synthetic methods and applications. A few new developments have been reported regarding the synthesis of oligonucleotide microarrays. An improved method for photolithographic synthesis makes use of new photosensitive phosphoramidite monomers, which are more sensitive to UV light and hence improves synthesis time.[28] An electrochemical deblocking step for array synthesis reduces reaction times and side reactions associated with acid treatment of oligonucleotides.[29] 'Click' chemistry[30] has also been used to couple 5′-modified nucleoside to solid supports for microarray synthesis.[31] Two reports describe microfluidic devices for the assembly of microarrays.[32,33]

One report presents the post-synthesis characterisation of microarrays, though the authors claim that there is no overall 'best method' for microarray synthesis,[34] and a protocol for probe design for microarrays is described.[35] A method for the replication of microarrays is reported in which complementary probes bearing biotin residues are annealed to a microarray, and the bound probes may then be attached to a second surface bearing streptavidin residues.[36] There are a few publications that detail modifications to array assembly. Oligonucleotides have been attached to poly(dimethylsiloxane),[37] poly(mercaptopropyl)methyl siloxane[38] on a dendron-modified surface[39,40] and have been fabricated on nickel microparticles.[41] PNA has also been used in microarrays.[42–44]

Methodologies for detection that have been described include the use of quantum dot or gold-nanoparticles[45] and fluorescence, in which the position of the fluorophore for maximum signal intensity has been examined.[46] Analysis of DNA by amplification using multiplex microarray-enhanced PCR has also been developed.[47] Microarrays have varied applications, and examples that have been reported include single nucleotide polymorphism (SNP) detection,[48,49] including an electrochemical method of detection,[50] for detection of RNA modifications,[51] and expression profiling.[52–54]

1.2 RNA synthesis

There have also been very few reports concerning RNA synthesis. New 2′-hydroxyl protecting groups have been described. The 2-cyanoethoxymethyl protecting group, analogous to the TOM protecting group, has been introduced, and is readily removed using TBAF. The protecting group allows for more efficient RNA synthesis than TBDMS chemistry.[55] 2-(Cyanoethoxy)ethyl has also been used, being removed by treatment with TBAF.[56] The 4,5-bis(ethoxycarbonyl)-[1,3]dioxolan-2-yl is a cyclic

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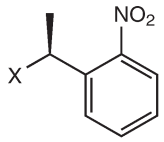
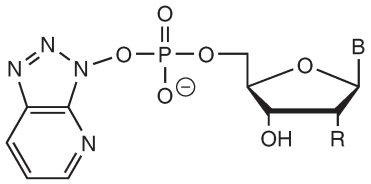
orthoester protecting group, which is removed under mildly acidic conditions.[57] It may also be used to introduce modifications; for example the reaction with amines leads to amide functionalities. 1-(4-Chlorophenyl)-4-ethoxypiperidin-4-yl (Cpep) has been reported as a 2′-hydroxyl protecting group particularly suited to large scale synthesis. It is also removed under mildly acidic conditions.[58] Novel caged RNA monomers (**3**) have been introduced to investigate RNA tertiary folding interactions.[59]



X = O-U or O-G
or = NH-C or NH-A

3

Finally, there are two reports on non-enzymatic template-directed synthesis of oligonucleotides. It has been well established that RNA oligonucleotides may be prepared by using activated monophosphate building blocks, though the rate of synthesis is slow, and there is a preference for the formation of 2′–5′ linkages. However, a novel activated monophosphate (**4**) has been shown to be more effective and sequence specific in the synthesis of either DNA[60] or RNA[61] oligonucleotides.



R = H or OH

4

1.3 The synthesis of modified oligodeoxyribonucleotides and modified oligoribonucleotides

1.3.1 Oligonucleotides containing modified phosphodiester linkages. Many new internucleotide linkages have been examined for their effects in oligonucleotide chemistry, and these include peptide nucleic acids (PNA) and their derivatives. One of the most common phosphodiester modifications is the phosphorothioate, first introduced by Eckstein,[62] but it is now so widely used that it is excluded from this review. A 5′-phosphorothiolate modified oligonucleotide has been used to examine the role of a critical cytosine residue in the hepatitis delta virus ribozyme, demonstrating that it is involved in acid catalysis.[63] Methyl phosphonates are another common modification, which give rise to a neutral backbone. They are rarely used now as they tend to be rather insoluble in aqueous media. Methylphosphonate residues have been substituted at the 3′-end of DNA in a DNA/RNA hybrid to examine the effect of internucleotide linkage on the complex with RNase H1.[64] The effect of substituting RNA nucleotides with *P*-chiral 2′-*O*-methylphosphonothioate linkages with either complementary DNA or RNA is a large increase in duplex stability.[65] An increase in duplex stability is also observed using hydroxymethylphosphonate substitutions.[66]

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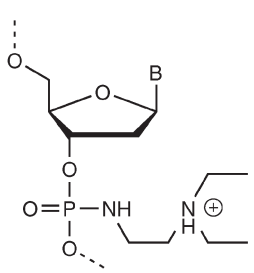
*N*3′-*P*5′-Phosphoramidates, introduced by Gryaznov,[67] are an internucleotide linkage in which either the 3′- or the 5′-oxygen is replaced by an amino group. They exhibit enhanced thermal stability in oligonucleotide duplexes and nuclease resistance. A single substitution of a phosphoramidate linkage at the scissile bond of a DNA duplex rendered the modified strand resistant to digestion by *Pvu*II endonucleases, though the unmodified strand was cleaved with usual kinetics.[68] Use of cationic phosphoramidate pyrimidine α-oligonucleotides as TFOs led to triplexes with higher Tms than the parent duplexes,[69] and phosphoramidate TFOs have been further stabilised by use of cationic copolymers.[70] Polypurine TFOs containing (**5**) modifications have been used to mediate site-specific genome modifications by induced recombination. Using (**5**), recombination levels were increased as a result of improved binding.[71] A DNA crosslinking method makes use of a phosphoramidate bearing a protected thiol (**6**).[72,73]



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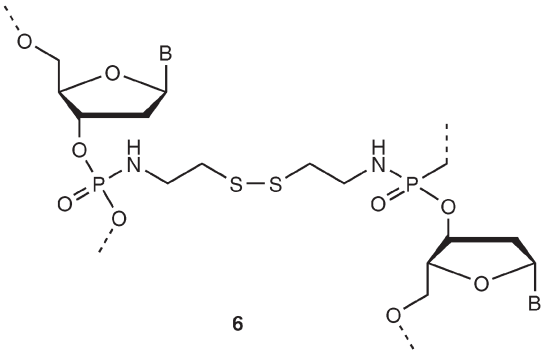

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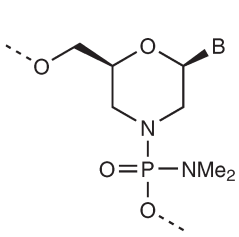
Substitution of the ribose sugar by morpholino (**7**) gives phosphoramidate morpholino nucleic acids, which are neutral and nuclease resistant, and have therefore been of particular interest in steric blocking antisense applications.[74,75] Pyrimidine-rich morpholino oligonucleotides also show enhanced triplex formation when used in the third strand.[76] Replacement of non-bridging oxygen by a borano group results in a boranophosphate linkage (**8**), which is isoelectronic and isosteric to the usual phosphodiester linkage, but has enhanced lipophilicity. The presence of the (**8**) group leads to a chiral centre, and in thermal melting studies of DNA duplexes with a single substitution of (**8**), *S*p-chirality is more stabilising than *R*p.[77] Boranophosphate-modified siRNA exhibits enhanced activity compared with phosphorothioate modifications.[78]



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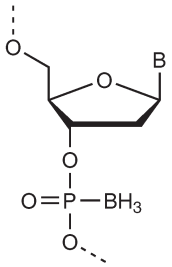

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2′–5′ linked oligoadenylates (2-5A) are naturally occurring oligoribonucleotides produced in interferon-treated cells, and their antiviral activity is brought about by inducing RNase L. The mechanism by which RNase L affects viral replication has been shown to be due to stimulation of transcription of genes which suppress viral replication.[79] 2-5A has also been used as an antisense agent to target respiratory syncytial virus, where it was found to be 50–100 times more efficient than ribavirin.[80]

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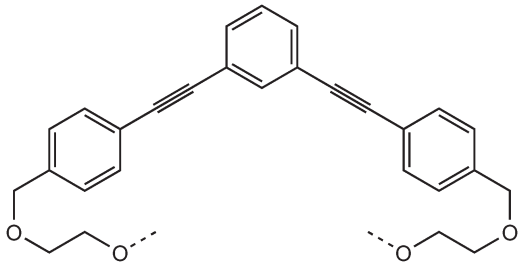
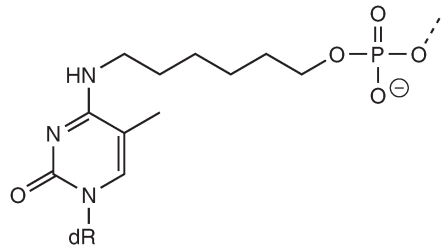
A morpholino antisense oligonucleotide, which does not induce RNase H activity, was found to induce RNase L when conjugated to 2-5A, endowing the morpholino oligomer with significant biological activity.[81] A comparison of DNA, RNA and 2′–5′-linked RNA hairpin structures as inhibitors of RNase H found that 3′–5′ linkages are more potent inhibitors than 2′–5′ linked hairpins.[82] 2′–5′-linkages in TFOs result in significant stabilisation of parallel-stranded triplexes.[83,84]

A new class of DNA quadruplexes has been described containing either a 3′–3′ or 5′–5′ inversion of polarity site. These contain TGG–GGT sequences in which the backbone polarity is inverted at the central G–G site.[85] 2′-*O*-methylribonucleotide sequences exhibit enhanced hybridisation properties with complementary RNA when the 3′-terminus is capped by a 3′–3′ linkage.[86] As a result of the 3′–3′ linkage, these oligonucleotides also have enhanced nuclease resistance. An alternate-strand Hoogsteen TFO has been designed having a 5′–5′ linkage, using the intercalator (**9**) to invert the backbone polarity.[87] The resultant oligonucleotide triplex shows enhanced thermal stability, and significant mismatch discrimination.



9

Cyclic oligonucleotides have been of use as they are used as templates in rolling circle DNA synthesis. Small circular DNA from the human C-rich $(CCCTAA)_n$[88] and G-rich $(GGGTTA)_n$[89] telomeric repeats have been prepared and examined as substrates for DNA polymerases. They are both substrates for Klenow fragment, synthesising telomeric DNA >1000 nucleotides in length. The mechanism by which large circular DNA is synthesised has shown that it is in agreement with the model for DNA bending, and that DNA bending and flexibility is a key criterion.[90] Ligation studies using human telomeric quadruplex sequences have established optimal pH and buffers for the formation of cyclic DNA sequences.[91,92] Cyclic DNA has been used as padlock probes for the detection of plant pathogens,[93] and as a novel method of single nucleotide polymorphism (SNP) detection.[94] In addition to cyclic DNA there are two routes describing the synthesis of branched DNA. One route involves coupling two solid-support oligonucleotides to a phosphorodiamidite, resulting in a phosphotriester branched oligonucleotide,[95] the other using a modified nucleobase (**10**) for synthesis of the third strand.[96] The first method requires that the two arms of the oligonucleotide have identical sequence, whilst the second method allows for differing sequences.



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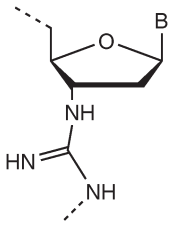
The remaining backbone modifications that have been described are completely altered from native sequences. Deoxynucleic guanidinium (DNG) (**11**) linked oligonucleotides are achiral and positively charged linkages. The binding of an octameric DNG-C_8 with DNG-G_8 showed a melting temperature of greater than 90 °C, and analysis of the thermodynamics indicated that this duplex is over 1000 times as stable as the corresponding DNA-C_8 with DNA-G_8.[97] Molecular modelling of DNG duplexes revealed that it has very shallow major grooves and very deep minor grooves, which are narrower than those in DNA.[98] When the corresponding RNA analogues (RNG) are paired with DNA they show exceptional thermal stability, and marked sequence specificity.[99]



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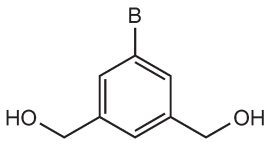
Replacement of the phosphate backbone by a benzene–phosphate backbone (**12**) shows enhanced duplex stability in homopurine–homopyrimidine sequences compared to DNA, but reduced stability with mixed sequences.[100] A backbone based on glycidol (**13**, *R* isomer shown) is one of the simplest acyclic backbone modifications, yet unlike many other acyclic nucleosides it exhibits remarkably high thermal stability when paired with itself, but it does not pair with DNA.[101] In contrast, the acyclic backbone (**14**, *R* isomer shown) based on an aminopropyl chain shows significant destabilisation when substituted into a DNA duplex, even when the modification is paired together.[102]



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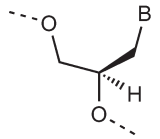

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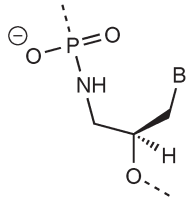

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Peptide nucleic acid (PNA) (see also Section 3.1 on oligonucleotide-peptide conjugates) was first introduced by Nielsen.[103] The nucleobases are attached to a backbone derived from 2-aminoethylglycine, and as a result PNA (**15**) is electrically neutral. It shows remarkable thermal stability when hybridised with complementary DNA or RNA, and of course is resistant to nucleases. This is a widely used oligonucleotide analogue, and as well as a number of applications of PNA there have been many attempts to prepare analogues of the PNA backbone that have improved properties. New methods of PNA synthesis include a fully-protected backbone approach (Fmoc and alloc),[104] the use of an Fmoc-orthogonal protecting group (Dde)[105] and the use of native chemical ligation for the synthesis of long PNA oligomers.[106] DNA template-directed ligation using native chemical ligation of PNA was found to be fast and sequence-selective, with matched sequences being 3000 times more discriminating than mismatched ones.[107,108]

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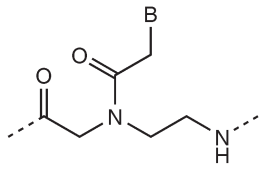

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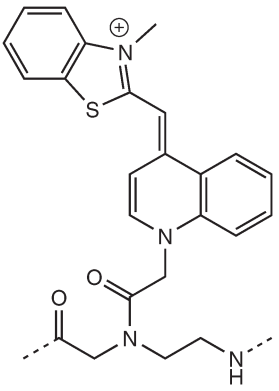
There are two classes of PNA analogue, base and backbone modifications, of which backbone modifications are the larger group. PNA containing orotic acid (uracil-6-carboxylic acid) binds preferentially to RNA though it will also bind to DNA.[109] Orotic acid residues are best tolerated at terminal positions, internally being as destabilising as a mismatch. The nucleobase of PNA has been replaced by the fluorophores thiazole orange[110,111] (**16**) and fluorene,[112] the latter being used as a molecular beacon probe for target DNA. 8-Hydroxyquinoline as a PNA nucleobase has been used as a metal ion probe for DNA mismatches.[113] 5-Thiomethyluracil, protected as a disulfide, has been synthesised for incorporation of either an imidazole or a coumarin ester in nucleic acid-triggered probe activation.[114] A chelating dendrimer based on diaminopropionate has been synthesised on the N-terminus of PNA to increase the number of paramagnetic ions for magnetic resonance imaging.[115] Acetylenic and stearoyl groups attached to either terminus of PNA have been studied to increase the lipophilicity of PNA.[116] A copper complex (**17**) formed by two proximal PNA strands has been prepared, which, if brought together with a matched DNA target, leads to cleavage of the picolinate ester.[117]



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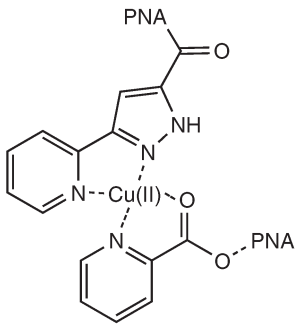

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There are two type of backbone modification, linear, analogous to PNA and cyclic, which reduces conformational flexibility of the PNA strand. Replacement of the 2-aminoethylglycine backbone by alanyl or norvalyl (**18**) results in considerable destabilisation of duplexes with DNA, partly as a result of greater flexibility which allows Hoogsteen and Watson-Crick base pairing.[118] Cationic cyanine dyes give rise to a visible colour change on binding to duplex DNA-PNA, for which it was believed that the dye aggregates in the minor groove. This has been confirmed by use of the isobutyl-modified PNA (**19**, D-isomer shown), in which the isobutyl group resides in the minor groove, preventing cyanine dye aggregation.[119] The isostructural PNA analogue (*Z*-F-OPA) (**20**) binds complementary DNA, but its hybridisation properties are sequence-dependent, and fully-modified sequences preferentially form parallel duplexes with DNA.[120] Use of D- and L-lysine to introduce a chiral centre into the backbone is also generally destabilising, though it also depends on the configuration of the stereogenic centres.[121] Substituting PNA backbone units with the more flexible reduced secondary amine results in almost unchanged binding

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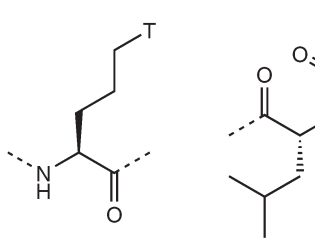
affinity towards target DNA.[122] Introduction of a disulfide bond into the PNA backbone leads to significant destabilisation.[123] PNA is electronically neutral. Introduction of a positive charge using guanidine-based PNA (**21**) gives an oligomer that binds to RNA, though is also destabilising compared to PNA.[124] However, (**21**) is readily taken up by somatic and embryonic stem cells. Introduction of negative charges (**22**) is also destabilising, though the range of applications of (**22**) oligomers include nucleic acid analysis and inhibition of gene expression.[125]



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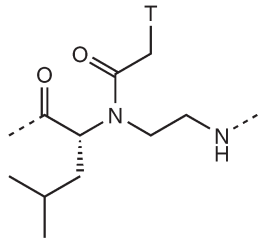

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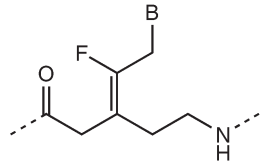

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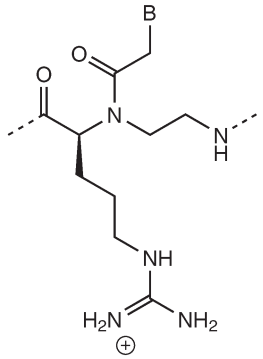

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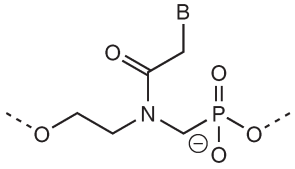

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A number of different cyclic structures have been introduced into the backbone of PNA for enhanced pre-organisation of the PNA for oligonucleotide binding. Introduction of a cyclopropane ring into the backbone of a homothymine oligomer results in reduced binding to both DNA and RNA; however, the cyclopropyl oligomer also forms a stable triplex structure with DNA, unlike corresponding PNA.[126] Introduction of *cis*- and *trans*-cyclopentane groups into PNA, however, both lead to enhanced stability in duplexes with DNA and RNA.[127–129] The use of cyclohexyl groups results in destabilisation with complementary DNA, but significantly enhanced stabilisation with RNA.[130] The use of a positively charged pyrrolidine backbone (**23**, 2*S*,4*S*-isomer shown) affords oligomers that exhibit enhanced stability and selectivity towards complementary RNA,[131,132] whilst with pipecolyl (**24**) selectivity is towards DNA duplexes and triplexes.[133–135]

PNA often infers enhanced thermal stability with complementary oligonucleotides compared to either DNA or RNA. There are therefore a number of reports describing the hybridisation properties of PNA, including new methods of detection such as electrochemical impedance spectroscopy[136] and temperature gradient focusing.[137] PNA is also well known to strand invade a DNA duplex, though more usually in homopolymeric sequences. However, PNA of mixed sequence can strand invade a duplex if the complementary sequence is at one of the termini of the duplex.[138] PNA-amphiphile conjugates form self-assemblies, which exhibit enhanced binding and specificity to DNA and to RNA.[139,140] PNA conjugated to gold nanoparticles is also reported to exhibit enhanced binding with increased discrimination to DNA.[141] As

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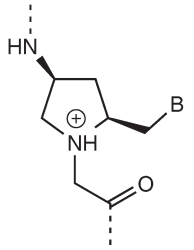
PNA exhibits both enhanced binding and discrimination towards DNA, it has been used in a variety of SNP applications.[142,143]



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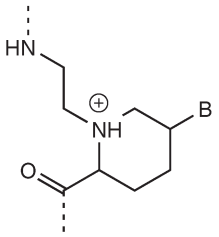

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Other applications include PNA-DNA chimeras, which have been used to study DNA unwinding by Dda helicase,[144] tagging of peptide libraries targeted towards cysteine protease inhibition,[145] chelator-peptide-PNA-peptide chimeras used for non-invasive imaging of cancer cells[146] and tagging of PCR products on a microarray.[147] PNA-conjugated with fluorophores have been used in energy transfer measurements,[148] conjugated to EDTA to affect site-specific strand cleavage of complementary DNA,[149] conjugated to minor-groove binders to extend target sequence selectivity[150] and conjugated to amino acid thioesters to study *in situ* chemical aminoacylation.[151]

There are reports of PNA involved in quadruplex formation, including self-templating PNA,[152] hybridisation with DNA,[153] and a PNA-DNA chimera.[154] A further report describes the use of PNA to strand invade a RNA quadruplex to form a hybrid quadruplex structure.[155] The sequences (C_5T) and (C_8T) form i-motif structures, with similar thermal stability to complementary DNA sequences, but over a narrower pH range.[156,157]

Uses of PNA are primarily for cellular uptake either as antisense or for delivery of other biomolecular cargoes. A cyclic PNA analogue was shown to be delivered into cells,[158] and three reports describe PNA used as antisense to inhibit transcription, targeted against various mRNA targets.[159–162] PNA has also been used as an antisense agent whilst conjugated to other biomolecules. A common cargo for delivery of DNA or PNA is the nuclear localisation signal (NLS) peptide, which has been used to inhibit transcription of oncogenic *KRAS*,[163–165] as has Tat-peptide[166] and transportan.[167] In addition, various other PNA-peptide conjugates are taken up into cells[168,169] in particular with polyarginine peptides.[170,171] PNA-peptides have also been used for cellular delivery conjugated to technetium (^{99}Tc) for imaging of breast cancer[172] to neamine to cleave TAR RNA[173] and to the DNA intercalator 9-aminoacridine.[174]

1.3.2 Oligonucleotides containing modified sugars. There have been many new sugar derivatives, with modifications at each of the ribose carbon atoms. Only one C1′-modified report has been described in this review period. 1′-Aminomethylthymidine and its acetyl-derivative have been synthesised and incorporated into DNA where it aids duplex stability.[175] The C2′-position is most commonly used to modify the nucleosides. 2′-*O*-Methyl modifications have been widely used in oligonucleotides as they increase thermal stability and resistance to nucleases, and as they are now so widely used they are excluded from this review.

2′-*O*-Modifications are the most common, and a number of new analogues have been reported. 2′-*O*-Tetrahydropyranyloligonucleotides have been shown to be more susceptible to modification by arylazide photomodification.[176] A number of different 2′-*O*-modifications have been assessed for their ability to stabilise

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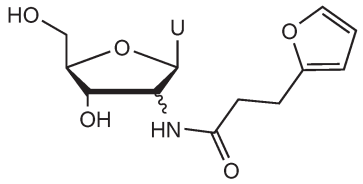
oligonucleotides to nuclease digestion. Positively charged analogues are more stable than phosphorothioate oligonucleotides, whilst larger substituents, like (benzyloxy)ethyl, are susceptible to nuclease digestion.[177] New 2′-*O*-carboxymethyl substituents have been used for conjugation to peptides *via* amide bond formation[178] or by oxime formation.[179] 2′-*O*-Carboxymethyl modifications have also been shown to have greater affinity for complementary RNA compared to their corresponding 2′-*O*-acyl derivatives.[180]

The 2′-*O*-(2-methoxy)ethyl (MOE) modification has been widely studied by the Isis group as a means of stabilising oligonucleotides (thermally and against nuclease digestion). The cytotoxicity of MOE-modified DNA has been studied,[181] and MOE-modified oligonucleotides has been applied with some success to siRNA.[182] Two groups have shown that 2′-*O*-ethylamine-modified uridine shows selectivity and enhanced affinity in TFOs,[183,184] but increasing the length of the amino-linker leads to instability in DNA duplexes.[185] A new synthesis of 2′-*O*-ethylamino- and 2′-*O*-ethylthiol-modified phosphoramidites for oligonucleotide synthesis has been described.[186] The 2′-*O*-cyanoethyl group has also been introduced and shown to enhance duplex and nuclease stability.[187]

The 2′-amino-modification has been primarily introduced for attachment of other functional groups. Two different spin labels have been incorporated onto 2′-amino groups to study conformational changes in the hammerhead ribozyme[188,189] and in TAR RNA in the presence of metal ions.[190] 2′-*N*-Methyl-2′-(anthraquinone carboxamido)uridine has been used for efficient attachment to glass, the presence of the anthraquinone group significantly increasing the capture of complementary DNA.[191] Attachment of pyrenylmethyl to the amino group also significantly increases duplex stability,[192] as did a range of aromatic aldehydes attached to the amino group post-synthetically.[193] The nucleoside (**25**) has been used to effect interstrand crosslinking upon oxidation of the furan,[194] whilst a variety of phenylazide crosslinking agents have been attached to the 2′-amino group of uridine to study the effects of magnesium ions on the hairpin ribozyme.[195]



25

The effects of various *C*-2′-alkyl modifications have been reported. *C*-2′-α-Hydroxymethyl modified thymidine is destabilising in 3′,5′- and 2′,5′-linked oligonucleotides,[196] and *C*-2′-α-(thymine-1-yl)ethyl-dU is also destabilising, but in a 3-way junction the stacking of the extra thymine base enhances stability.[197] *C*-2′-α-Difluoromethyluridine has also been incorporated into RNA by using T4 RNA and T4 DNA ligases.[198] Modification of the sugar hydroxyl groups by sulphur is a common change. 2′-Thioadenosine have been incorporated onto the terminus of an RNA sequence where it underwent spontaneous aminoacylation with amino acid thioesters.[199] Replacement of 2′-oxygen by selenium is less frequently used, but is very useful for heavy atom replacement in solving crystal structures. 2′-Selenouridine phosphoramidite has been prepared and incorporated into RNA,[200] and long RNA sequences containing 2′-methylseleno groups have been prepared using this methodology.[201]

Due to their enhanced nuclease resistance, 2′-fluoro-modified oligonucleotides have been used for cellular stability in siRNA oligonucleotides.[182,202,203] 2′-Fluoro-modified nucleosides have been incorporated into the P-site of tRNA where a 10^6-fold reduction in the rate of peptide bond formation was observed.[204]

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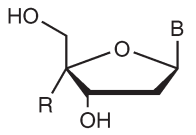
2′-Fluoro-modifications have also been used for characterisation of secondary structures by ^{19}F NMR spectroscopy.[205] The thermal stability of DNA duplexes containing the 2′-fluoro-modified 6-azapyrimidine and 7-deazapurine analogues has also been examined.[206]

A few C3′-modified oligonucleotides are reported, and the substituents used are varied. C3′-Phosphorothiolate linkages have been examined, and shown to give enhanced stability in DNA/RNA duplexes, as well as enhanced nuclease resistance.[207] A C3′-phosphorothiolate linkage has also been used to examine the mechanism of action of endonuclease (Vsr protein) activity, which was shown to proceed by inversion of stereochemistry at phosphorus.[208] A C3′-amino-modified thymidine analogue has been used to introduce a porphyrin residue into DNA, though little data is provided.[209] Photolytic ssDNA strand cleavage has been studied using a C3′-acetyl thymidine analogue, which generates a thymidinyl radical on photolysis.[210] 3′-*O*-Modified oligonucleotides have been used to synthesise consecutive tandem oligonucleotides *via* a range of linker phosphoramidites.[211]

The physicochemical properties of ribooligonucleotides incorporating the 4′-thionucleoside 4′-thiocytosine have been examined. The presence of the thiosugar has a slight destabilising effect (−1 °C per substitution), but there is little effect on the global structure as determined by X-ray crystallography.[212] The thiosugar adopts a C3′-*endo* conformation similar to native sugars. Substitution of the sugar oxygen by nitrogen results in an analogue that is positively charged at physiological pH. Introduction of pyrrolidino-sugars into TFOs aids stabilisation of the triplex strand due to the positive charge.[213]

A number of C4′ modified systems of general structure (**26**) are reported. The thymidine analogue (**26**), R = CH_2NH_2, has been introduced into DNA where the amino group may be further conjugated with pyrene. The resultant analogue has been used to detect SNPs as the analogue only exhibited enhanced fluorescence when opposed to adenosine.[214] The detection of mismatches has also been examined using the C4′-vinyl or the C4′-hydroxymethyl derivatives, which act as a steric probe of mismatches, with enhanced discrimination when the analogue is up to four nucleotides away from the mismatch site.[215,216] The bulky lesion (**26**), R = pivalolyl, has been used to study its effect in nucleoside excision repair, where repair was shown to occur by flipping the adducted nucleotide out of the duplex structure.[217] The 3′-deoxy analogue of (**26**), R = CH_2CH_2OH, has been incorporated into the loop of a hairpin structure, the C4′-side chain being used as the internucleotide linkage.[218] Such modified hairpins are more stable than unmodified ones, probably due to the enhanced flexibility of the elongated internucleotide linkage.



R = CH_2NH_2

$COCMe_3$

$CH{=}CH_2$

CH_2OH

CH_2CH_2OH

26

Three C5′-modified nucleosides have been incorporated into oligonucleotides. A method for introducing 3′-O–P–S-5′ linkages has been reported based on a DMT-protected 5′-thionucleoside.[219] Oxidative hydrogen atom abstraction from the C5′-position results ultimately in strand cleavage, and one of the products of this process is a C5′-aldehyde-modified oligonucleotide. A phosphoramidite building block suitable for incorporation at the 5′-end of an oligonucleotide of an aldehyde has been described. The aldehyde group has little effect on duplex stability, and DNA duplexes containing the modification are cleaved very slowly.[220] Thermal stability studies of a C5′-ethynyl-modified uracil demonstrated that the stability depends on

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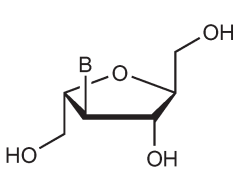
the chirality of the modified nucleoside (chiral at C5′). The L-*talo*-derivative has much less effect on duplex stability than the D-*allo*-derivative, the latter being quite destabilising.[221]

A number of alternative sugar units have been used in nucleotide building blocks. α-Anomeric nucleosides have been incorporated into DNA and it has been shown that they enhance the thermal stability of triplex strands,[222] and are still substrates for type IV endonucleases.[223] α-D-Arabino-oligonucleotides form antiparallel duplexes with themselves, but if partnered with normal DNA they only form stable duplexes in a parallel mode.[224] 2′-*O*-(2-Oxyethyl)arabinouridine is destabilising when base paired with complementary DNA but particularly destabilising with RNA.[225] The isonucleoside (**27**) has been incorporated into DNA as an antisense strategy; the presence of (**27**) caused some destabilisation of duplexes, but increased nuclease resistance, and the presence of (**27**) at the 3′-end gave better antisense effects than the unmodified control.[226] A molecular beacon (see Section 3.5) was found to be more selective when the stem structure was replaced by the homonucleoside (**28**).[227]



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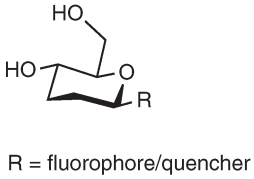

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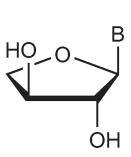
(3′–2′)-α-L-Threose nucleic acids (TNA) (**29**) is considered as an evolutionary precursor to DNA and RNA. It possesses the shortest backbone (four atoms in the sugar portion) and forms base pairs with DNA, RNA and TNA. The thermophilic DNA polymerase Therminator has been shown to be an efficient DNA-dependent TNA polymerase, synthesising TNA libraries in excess of 200 nt in length.[228–230] Hexitol nucleic acids (**30**) possess a six-membered sugar ring, which shows enhanced nuclease stability and a strong affinity towards RNA rather than DNA. Chimeric 2′-MOE-HNA oligonucleotides are able to inhibit gene expression by an antisense approach.[231] Cyclohexenyl nucleic acids (CeNA) (**31**) are analogues of HNA, but are DNA mimics. As their 5′-triphosphates they are substrates for various DNA polymerases, though only short sequences of CeNA are produced.[232] CeNA is conformationally flexible, and will adopt N- and S-type conformations depending upon the sequence environment.[233] Cyclohexyl nucleic acids (CNA), however, show poor base pairing with either CNA or with DNA and RNA.[234]



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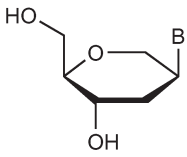

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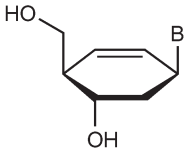

31

Since locked nucleic acids (LNA) were first described by Imanishi[235] and Wengel[236] they have been widely used in oligonucleotide applications. LNA oligonucleotides exhibit enhanced binding towards complementary ssRNA and ss- or ds-DNA compared with native oligonucleotides. LNA (**32**) contains a methylene bridge between the 2′-oxygen and the C4′-carbon, which results in a locked 3′-*endo* conformation, reducing conformational flexibility of the ribose ring, whilst

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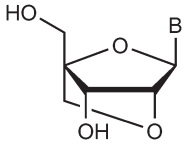
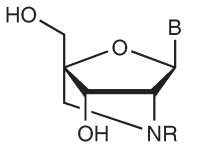
increasing the local organisation of the phosphate backbone. The incorporation of LNA into DNA oligonucleotides induces A-like duplex conformations.



32

There have been a few reports on thermodynamic and structural studies of LNA-containing oligonucleotides (see also Solution Structures, Section 4.2). LNA has been examined in duplexes[237–239] and in quadruplexes.[240] Due to their ability to stabilise duplex and higher order structures, and their enhanced stability towards nucleases, LNA-containing oligonucleotides find widespread use in cell-based applications. Thus LNA oligonucleotides have been used for the detection of microRNAs,[241] to stabilise siRNA,[242] for gene modification[243] and in antisense[244–246] and antigene[247] applications.

A number of LNA analogues have been investigated, the most studied analogue being 2′-amino-LNA (**33**). The incorporation of 2′-*N*-pyrenylmethyl LNA into DNA not only enhances duplex stability, but causes intense fluorescence.[248,249] It is proposed that the pre-organisation of the backbone by LNA forces the pyrene into the minor groove, where quenching of the pyrene fluorescence by nucleobases is minimised. The 2′-amino group has also been functionalised with *N*,*N*-bis (2-pyridylmethyl)-*β*-alanine;[250] positioning of this modification in complementary positions of a duplex causes further stability in the presence of divalent metal ions by formation of a zipper-motif. The analogue 2′-*N*-pyrenylmethyl-α-L-LNA,[251] when incorporated into a DNA duplex, also behaves as a zipper-motif, where considerable duplex stabilisation occurs.[252] The effect of inclusion of C-3′-modified LNA has been investigated. The C-3′-aminopropyl analogue (**34**, R = NH_2) was found to be protonated at physiological pH, where it enhanced duplex stability,[253] and was more stabilising than the corresponding hydroxypropyl derivative.



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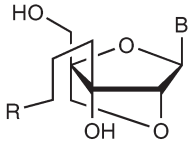

34

Various other locked nucleoside analogues have been studied. The C1′-O2′ locked nucleoside (**35**) has been studied in antisense oligonucleotides for enhancing duplex stability and increasing nuclease resistance.[254,255] It was shown that (**35**)-modified DNA was more effective at gene silencing than corresponding phosphorothioate oligonucleotides. C2′-C3′ Locked nucleosides have been incorporated into oligonucleotides; the piperazino-analogue (**36**) (R = *N*-methyl-*N*-carboxypiperazine) enhanced duplex stability at low salt conditions (40 mM), but was less stable at high salt 100 mM).[256] The O2′-C3′-α-D-nucleoside (**37**) showed enhanced stability towards parallel-stranded DNA.[257] The O3′-C4′ ethynyl derivative (**38**) caused destabilisation when incorporated opposite DNA, but exhibited enhanced stability with complementary RNA, particularly when incorporated into a zipper interstrand motif.[258] Synthetic procedures for incorporation of bicyclo[3.1.0]hexane carbosugars (**39**) have been described, though there are no further data reported.[259] The tricyclic-DNA purine analogues (**40**) are reported and it was shown that the analogues form

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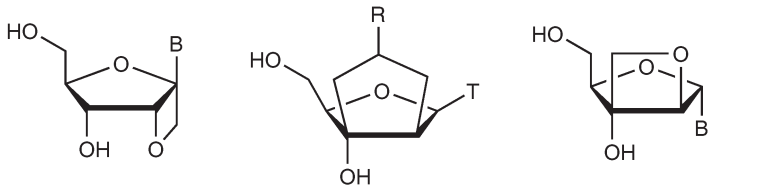
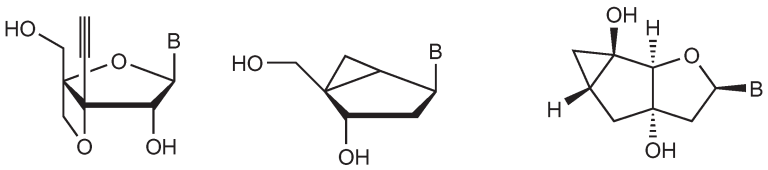
enhanced stable duplexes with pyrimidine DNA not only in Watson-Crick mode, but also by Hoogsteen base pairing.[260]



35 **36** **37**



38 **39** **40**

1.3.3 Oligonucleotides containing modified bases. The largest group of publications describe the use of modified base analogues in oligonucleotides, and they have varied applications. The main application is to study the effect of duplex stability with the analogue, but other applications include structural studies, base lesions, altered base pairing and novel base pairs. For fluorescent aromatic analogues, (*e.g.* pyrene), see also Section 3.5, and many other analogues are described in the section on conjugates (Section 3). In this review, pyrimidine analogues are described first, followed by purines, and finally a number of other analogues that include abasic sites, base pairing analogues and aromatic analogues.

There are two C2-modified pyrimidine analogues reported. 2-Thiothymidine has been used to improve the specificity of base pairing. The presence of the bulky 2-thio group causes a steric clash when paired with either diaminopurine or with the minor tautomer of isodG.[261] 2-Thio-dU has also been used to prepare 4-pyrimidinone for incorporation into oligonucleotides.[262] Various N^3-modified thymidine derivatives have been used to investigate N^3-dT-alkyl-N^3-dT inter- and intra-strand crossslinks. N^3-dT-Ethyl-N^3-dT interstrand crosslinks in a DNA duplex cause little perturbation as the ethyl group is accommodated between the major and minor grooves.[263] When present in a staggered conformation, the AT orientation is more destabilising than TA.[264] Increasing the alkyl chain from two to seven methylene groups causes a stepwise reduction in duplex stability,[265] whilst with four methylene groups it was shown that the alkyl chain caused significant widening of the major groove.[266] An N^3-dT-methyl red conjugate (**41**) has been observed to stabilise duplex DNA by an aromatic zipper formation between methyl red groups, stabilising the structure by stacking interactions.[267]

The main C4-modified analogue that has been studied is 4-thiouracil, used most often for crosslinking experiments. A synthesis of 4-thiouridine oligonucleotides using a convertible building block has been described.[268] 4-Thiouridine has been incorporated into RNA to study the active site structure of the hammerhead ribozyme[269] and the *E. coli* 16S ribosomal RNA.[270,271] The 4-thiouridine spin-labelled analogue (**42**) was used to measure the extent of docking of a tetraloop receptor upon magnesium-dependent docking of a GAAA tetraloop.[272] An O^4-caged photolabile thymidine analogue has been synthesised and incorporated into

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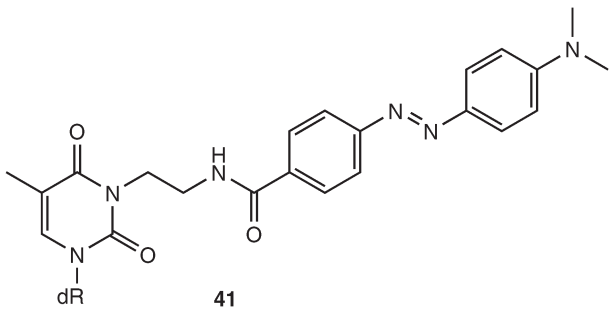

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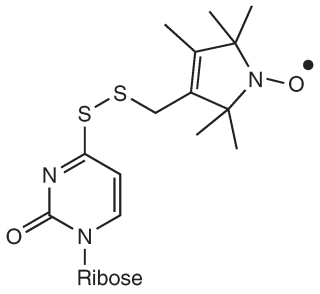
DNA where it was used as a switch for transcription.[273] Finally, a pyrrolo[2,3-d]pyrimidin-2(7*H*)-one analogue has been used for recognition of CG inversions in DNA triple helices.[274]



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C5-substitutions are the most common and numerous modifications to pyrimidines. C5-Aminopropynylation has frequently been used as a method to increase the stability of DNA duplexes, and this stabilisation in duplexes[275] and triplexes[276] has been reported. This stabilisation has been further studied by the synthesis of a series of 25 substituted propargylamino-derivatives.[277] 5-Bromo- and iodo-dU have been used in oligonucleotides to study crosslinking reactions. 5-Bromo-dU forms a uridinyl radical or anion when exposed to γ-irradiation. Formation of either radical or anion is suppressed in duplex DNA but is formed extensively in either ssDNA or at mismatch sites.[278] The uridinyl radical is also formed under UV irradiation, often leading to strand cleavage.[279] Strand cleavage occurs more frequently when BrdU is in a duplex bulge sequence than in a duplex.[280] DNA containing I-dU has been used to study protein-DNA crosslinking using mass spectrometry to characterise the products.[281] Br-dU has also been used as a probe for electron transfer in DNA.[282]

Thymidine glycol is an oxidation product of thymidine, and the synthesis and incorporation of the glycol phosphoramidite has been reported.[283] An oxidation product of cytidine, 5-hydroxy-dU has been shown to form stable base pairs with all four bases in a DNA duplex, providing a basis for its mutagenicity.[284] Thymidine will also undergo oxidative damage to form a (uridinyl)methyl radical under γ-irradiation. In order to further explore this reaction C5-(phenylselenyl)methyl-dU has been prepared and incorporated in DNA.[285] Under oxidative conditions (glutathione, O_2) the radical is generated and its crosslinking ability studied. The binding of protein kinases to Holliday junctions has also been studied by crosslinking reactions using DNA containing C5-azido-dU.[286]

The primary purpose for introducing a C5-modification is to introduce some new functionality, and many new analogues have been reported. Two new nitronyl nitroxide-modified analogues have been reported as spin labels for ESR studies and long range distance measurements.[287,288] The addition of an additional phosphate

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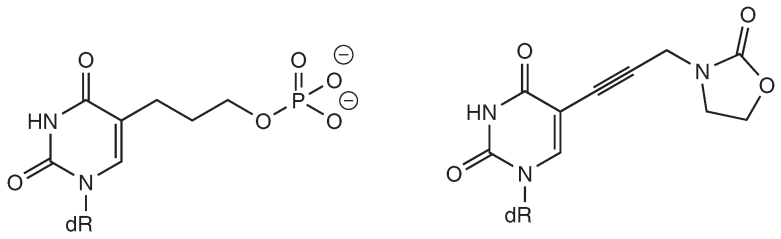
group attached *via* C5 (**43**) was found to greatly enhance chemical cleavage of DNA by Ce(IV)-EDTA.[289] A C5-dU-pyrene analogue has been reported that can be used in SNP detection as the fluorescence of the analogue is highly dependent upon its environment and which emits only when the analogue is opposite adenosine.[290] The adaptability of DNA binding domains has been examined by re-engineering it to recognise novel DNA bases. The analogue (**44**) was introduced into a known DNA binding domain, and mutations introduced into the Q50K homeodomain. A mutant protein was found that would bind selectively only in the presence of (**44**).[291] Incorporation of the analogue (**45**) into duplex DNA leads to cooperative lectin recognition, with enhanced binding depending upon the number of substitutions.[292] The effects of the hypermodified nucleosides ψ, mcm^5U and mcm^5s^2U in the anticodon loop of $tRNA^{Lys}$ has been examined using NMR spectroscopy.[293]



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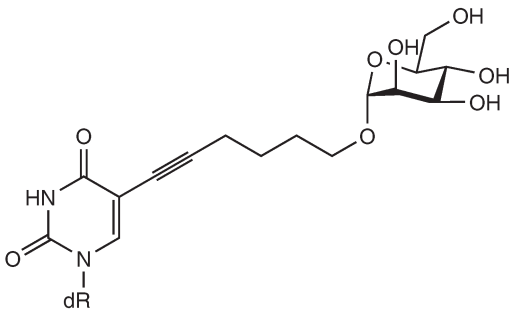

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There have been a number of reports of analogues bearing amino groups attached *via* C5 of uracil, which introduces a cationic species into the DNA duplex. Imidazole and amino groups are the most common modification; these have been introduced to add functionality for use in artificial ribonucleases,[294] to stabilise G–U wobble base pairs,[295] for attachment of other labels, such as biotin,[296] and to stabilise triplex structures.[297] The effect of introducing an aminopropylamino side chain into the Dickerson-Drew dodecamer revealed that each substitution decreases the duplex stability by removing waters of hydration, and inducing a slight bend in the duplex at each modified site.[298] The introduction of a guanidinium group on a side chain at C5 aided cellular delivery of oligonucleotides.[299] Spermine has been introduced onto C5 of uridine to probe critical residues of the hairpin ribozyme.[300]

5-Formyluracil in a DNA duplex forms a reversible Schiff base pair with 5-aminocytosine;[301] formation of the base pair stabilises duplex formation, but dissociates on heating at 90 °C. An interstrand crosslink may be formed under oxidising conditions between adenine and C5-(phenylselenyl)methyl uracil.[302] Under UV irradiation a thymidinyl radical is formed which reacts with the exocyclic amino group of an opposing adenosine. The analogue α-5-cyanovinyl-dU (**46**) has been used in a reversible photoligation process. It reacts with an adjacent thymidine at 366 nm, and is dissociated at 316 nm. This has been used in a template-directed

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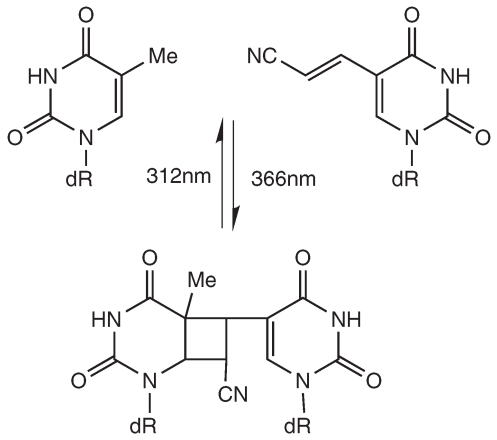
ligation reaction[303] and as a method for forming branched oligonucleotides.[304] The N3-methyl analogue of (**46**) will also react with an opposing adenosine under photolytic conditions.[305]



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One particular family of thymidine analogues that has been widely studied are the thymine dimers, which are formed as a result of UV irradiation. The most common thymine dimer is the cyclobutane derivative (**47**), but the (6-4) addition product, (**48**) as well as a Dewar photoproduct, also occurs. The extent of formation of thymine dimers (**47**) by UVA and UVB has been examined in human skin fibroblasts, and in particular in the *p53* tumour suppressor gene.[306] Repair of (**47**) has been examined; telomerase expression in skin fibroblasts has no effect on the nucleotide excision repair of (**47**),[307] and repair of the lesion by photolyase has been examined.[308,309] The lesion bypass synthesis by DNA polymerases η[310,311] as well as δ and ε from *S. cerevisiae*[312] are also reported. The formation and dissociation of thymine dimers (**47**) and (**48**), monitored by cyclic voltametry, revealed that the process occurs *via* formation of a dimer ion radical,[313] and dimer formation is enhanced when TpT is flanked by cytidine residues and diminished when flanked by guanosine residues.[314] In the latter case it is suggested that the flanking guanosine residues reduces the flexibility of the TpT step which limits dimer formation. Dimer formation is also significantly reduced in RNA compared to DNA.[314] The antibiotic distamycin A shows a preference for binding to DNA containing the 6-4 photoproduct (**48**).[315] A further thymine dimer (**49**), and its stereochemical formation has been examined.[316]

Only one C6-modified analogue has been described; C6-butyloxy-5,6-dihydro-dU has been used as a photochemical precursor for the generation of its C6-peroxy radical for studying its effect in DNA translesion synthesis.[317]

A few cytosine analogues have been studied during this review period. 5-Chloro-dC has been examined with methyl-CpG-binding proteins (MBPs) and shown that it mimics 5-methyl-dC by inducing binding by MBPs.[318] ^{125}I-labelled 5-iodo-dC has been incorporated into telomeric sequences to aid study by NMR and X-ray crystallography.[319] 5-Iodo-cytidine has also been incorporated into the hammerhead ribozyme for photocrosslinking studies.[269] 5-Bromo-dC can be used to induce crosslinks within DNA, and three different crosslinks with dA in a DNA duplex have been found following UV irradiation.[320] Also, crosslinking by the analogue (**50**), which generates a methyl radical upon UV irradiation, occurs through both inter- and intra-strand coupling.[321] 5-Methyl-2-pyrimidone incorporated into a parallel triplex strand will significantly stabilise all duplex base pairs.[322]

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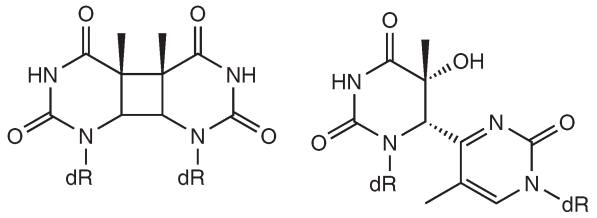

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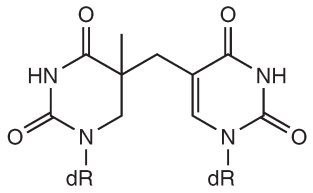

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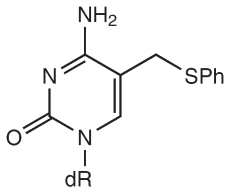

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Other cytosine analogues that have been studied are all modified at N^4. The tricyclic cytosine analogue (**51**), which is highly fluorescent, has been examined in DNA duplexes by physical methods, and it was shown that it does not perturb duplex structures,[323] nor is there significant fluorescent quenching of it by neighbouring bases.[324] The hybridisation properties of two N^4-modified cytosine derivatives have been examined. Analogue (**52**) causes duplex destabilisation until the DABSYL group is removed by UV irradiation.[325] A method of ligating two oligonucleotides has been described in which a DABSYL group acts as both the leaving group for the ligation reaction and as a fluorescent signal monitoring the reaction.[326] The C6-methyl derivative of (**52**), R = H, and the N^4-histaminyl derivative, have also been used in DNA to search for artificial ribonucleases.[294] The analogue (**53**) was designed such that it would form an intramolecular hydrogen bond, thus preventing Watson-Crick base pairing with guanine;[327] (**53**) was found to base pair indiscriminately. The repair-efficiency of the interstrand crosslink of N^4C-ethyl-N^4C shows differences at CpG and GpC sites, and using physical methods it was shown that the GpC site exhibits much greater flexibility, which may account for this difference.[266,328] Cytosine derivatives have been used as novel analogues in TFOs for recognition of the four duplex base pairs.[329,330] Two cytosine adducts have been reported. It has been shown that etheno-dC forms more readily in the presence of 4-oxo-2-pentanal when dC is opposed to an abasic site.[331] Translesion synthesis

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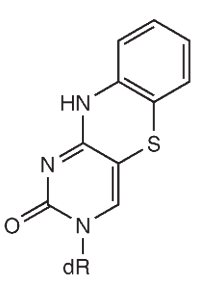
past the estrogen adduct (**54**) was shown to incorporate dCMP and dAMP, but never the correct base dGMP.[332]



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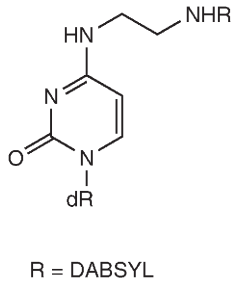

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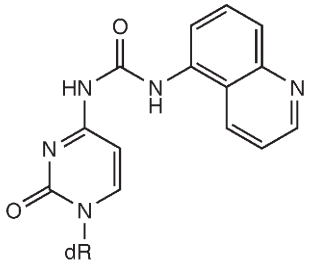

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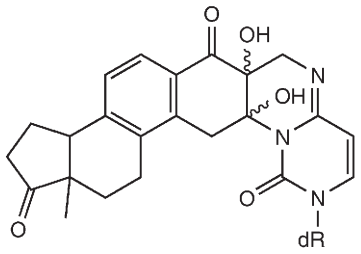

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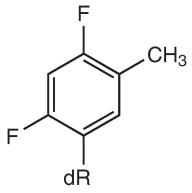
The analogue (**55**) first described by Kool and co-workers[333] was designed as a shape-mimic of the natural DNA nucleoside thymidine. In a DNA template (**55**) directs the incorporation of dAMP by DNA polymerases with almost the same efficiency as thymidine, yet it possesses no hydrogen bonding functionality. Analogues of (**55**) in which the fluorine atoms are substituted by H, F, Cl, Br and I increase the size of the nucleoside as the substituents increases,[334] and these have been used to probe for active site tightness of the Klenow fragment polymerase. It was found that the optimal size was reached with the dichloro-analogue, which exhibited a fidelity approaching that of thymidine.[335] However, with DNA polymerase β, NMR studies showed that the presence of (**55**) in the template strand prevents the polymerase adopting the required 'closed′ conformation.[336] The difluorophenyl analogue of (**55**) has also been used as a dU mimic to examine the mechanism of uracil DNA glycosylase.[337]



55

For the purine analogues there are more limited substitution sites. The minor modified base 1-methyladenosine has been shown to be a crucial modification for the structure and function of nematode mitochondrial tRNA.[338] Repair of 1-methyl-adenosine by *E. coli* AlkB has also been reported.[339] The most common C2-modifications of adenosine are 2-aminopurine (see also fluorescence, Section 3.5) and 2,6-diaminopurine. Both analogues have been used to study secondary

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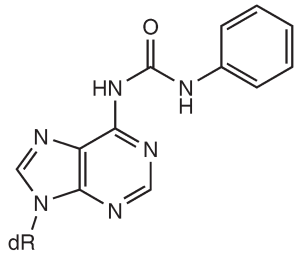
structures of RNA,[340] including the RNase III recognition site in *S. cerevisiae*,[341] the hammerhead ribozyme[269,342] and of hairpin loop structures.[343] 2-Hydroxyadenosine (2-OH-A) is an oxidative lesion of adenosine, and its recognition by the repair enzyme MUTYH is greatly impaired when it is opposed to guanosine, resulting in G:C to T:A transversions.[344] 2-Fluoroadenosine will form stable base pairs with uridine without perturbing the global RNA structure, and is therefore a useful tool for ^{19}F-NMR of RNA structures.[345]

Although the N6-position of adenosine is readily modified, there are surprisingly few N6-modified analogues reported. To aid in the understanding of the nature of the rigidity of DNA, N^6-methyl-dA has been incorporated into dT_n–dA_n duplexes. Introduction of the methyl group disrupts base stacking by hydrophobic interactions, thus demonstrating that the rigidity is as a result of base stacking.[346] The N6-modified analogue (**56**) in a DNA duplex results in base-flipping of the opposing nucleotide,[347] which, if the opposing strand is RNA, results in site-specific cleavage.[348]



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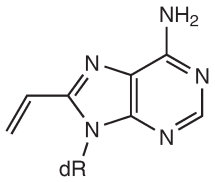
Three fluorescent C8-modified adenosine derivatives have been described. Two of these are pyrene derivatives, one linked by an acetylene unit,[349] the other through an amide linkage.[350] The former fluoresces when opposed to a C5-pyrene-modified dU, the latter only exhibits fluorescence when correctly paired with thymidine. 8-Vinyl-dU (**57**) absorbs and emits in the same range as 2-AP, but has a higher absorption coefficient than 2-AP, and is therefore about twice as sensitive.[351] 8-Methyl-dA has been incorporated into quadruplex-forming oligonucleotides where they were shown to form stable parallel-stranded quadruplexes, with stabilities comparable to unmodified sequences.[352]



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Two N2-guanine derivatives have been described. The acetaldehyde adduct N^2-ethyl-dG has been used to examine its repair by topoisomerase I (Top1). N^2-Ethyl-dG is unaffected by Top1, but in the presence of the anticancer agent camptothecin induced cleavage at the lesion site.[353] The C2 position of guanine has been used to attach a nitroxide spin label, which was introduced post-synthetically using 2-fluoro-dI.[354]

6-Thioguanine (6SG) has been used as a therapeutic agent for cancer and other diseases. When incorporated into a DNA in place of dG it causes duplex instability, equivalent to the loss of 1 kcal/mol per substitution. The lifetime of a 6SG:C base

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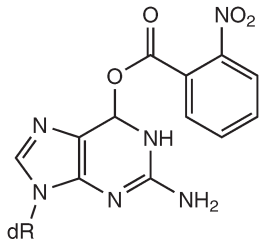
pair is of the order of 7 ms compared with 125 ms for a G:C pair, and these factors probably account for its destabilising effect.[355] 6SG in an oligonucleotide can be converted to *S*-nitroso thioguanosine by treatment with *S*-nitroso-*N*-acetylpenicillamine. In a DNA duplex opposed to dC, efficient nitroso-transfer occurs onto the exocyclic amine of cytosine, which rapidly leads to deamination.[356] O^6-Methylguanine (m6G) is an alkylated lesion that leads to mismatch incorporation of thymidine. Whilst m6G is efficiently replicated by Klenow fragment, a variant of the polymerase that lacks primer strand interactions is inhibited by the lesion, suggesting that minor groove recognition is critical for efficient translesion synthesis.[357] Removal of the proof-reading domain of *Pfu* DNA polymerase has little effect on the ratio of dCMP to dTMP incorporated opposite m6G.[358] m6G is also repaired by the recently discovered DNA alkyltransferase enzyme from *Ferroplasma acidarmanus*.[359]

Two caged guanine analogues are reported, each of which is used to control the structure of oligonucleotides. The photo-labile analogue (**58**) has been incorporated into RNA to study refolding[360] and into DNA to control quadruplex formation.[361] The second analogue is O^6-trichloroethylguanosine used to study RNA folding, removal of the trichloroethyl group being carried out by the action of zinc at pH 7.[362] ^{15}N7-Guanosine was used to prepare a hammerhead ribozyme motif for ^{15}N-NMR studies to understand the effects of divalent metal ion binding.[363]



58

The addition of substituents onto C8 of guanine nucleosides causes a conformational change around the glycosidic bond from *anti* to *syn*. It has been suggested that the instability of the base pair between 8-oxo-dG and dC is destabilising due in part to the steric bulk of the C8 oxygen. To this end a series of 8-halo-dG analogues were incorporated into DNA duplexes for thermal stability studies. It was found that as the size of the halogen was increased, so the stability of the duplex decreased.[364] Incorporation of 8-bromo-G into the loop of a hairpin structure actually enhanced the stability compared to the native hairpin.[365] 8-Bromoguanosine has been used as a photo-crosslinking agent to study the active site of the hammerhead ribozyme.[269] 8-Nitro-dG is an adduct derived from reactive nitrogen species, and is a blocking lesion to DNA synthesis. However, DNA polymerase η readily bypassed the lesion incorporating dCMP and dAMP.[366]

Various C8-aryl derivatives of guanine have been investigated. C8-Pyrene-modified dG is highly fluorescent, depending upon its environment, and can be used to distinguish single-strand, duplex, quadruplex[367,368] and Z-DNA.[369] 8-Aryl-dG has been investigated in duplex DNA[370] and in quadruplexes[371] where it was found to enhance stability. A novel porphyrin-fullerene dyad has been described in which the porphyrin is attached at C5 of dC and fullerene at C8 of dG. The system undergoes photoinduced electron transfer to produce a substantially long-lived charge separated state.[372]

8-Oxo-dG is probably the most common oxidative-damaged lesion of guanosine, and un-repaired it leads to G:C → T:A mutations. Thus most reports of this analogue deal with repair and translesion synthesis. Guanine can be oxidised by γ-radiation by a one-electron oxidation,[373] and by UVA irradiation in the presence of δ-aminolevulinic acid.[374] DNA containing the lesion can be crosslinked to single-

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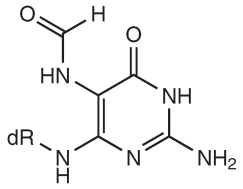
stranded binding protein under oxidative conditions.[375] Two clustered lesions results in decreased repair and hence an increase in point mutations[376] or persistent single-strand breaks.[377] When the lesion is present in telomeric DNA, this disrupts recognition by telomere repeat binding factors, resulting in cellular apoptosis or aging,[378] whilst its presence at methyl-CpG sites leads to inhibition of binding by methyl-CpG binding protein 2.[379] In certain DNA sequences, 8-oxo-dG will protect remote GG sites from oxidation.[380] In thermal melting studies, the oxidative lesion of inosine (8-oxo-dI) was compared to 8-oxo-dG and it was shown that 8-oxo-dG is more destabilising, and that 8-oxo-dI is replicated (with dATP) much more readily by Klenow fragment than 8-oxo-dG.[381]

The repair of 8-oxo-dG oligonucleotides has been examined using a number of different enzymes from the base excision repair and nucleotide excision repair pathways. Thus it may be repaired using MutT,[382,383] MutY,[384] the mismatch repair enzyme MutSα,[385] and the DNA glycosylase Ogg1.[386–388] APE1 is also able to remove 8-oxo-dG from the 3′-end of an oligonucleotide.[389]

Guanine may also undergo hydrolysis from a common radical precursor that leads to 8-oxo-dG to give formamidopyrimidine-dG (FaPy-dG), (**59**). In addition 8-oxo-dG may undergo further oxidation giving spiroiminohydantoin (**60**). A dinucleotide phosphoramidite building block has been synthesised to prepare DNA containing (**59**) for biological studies.[390] The presence of (**59**) in a duplex is highly destabilising, and it preferentially pairs with dC.[391] (**59**) is excised from DNA carried out by endonucleases III, VIII,[392] and IV,[393] but is also removed by Fpg.[394] The lesion (**60**) exists as *R* and *S* stereoisomers, and is highly mutagenic causing G → T and G → C transversions. Spermine has been shown to participate in the formation of (**60**) from 8-oxo-dG.[395] As yet the structural properties of (**60**)-containing DNA remain to be elucidated, but molecular dynamics simulations have been used to understand the structural and thermodynamic consequences of the lesion.[396,397] 8-Thio-dG has been incorporated into DNA for thermal stability studies.[398] It has been shown that the base pairs between 8-thio-dG and dC or dA are almost equivalent.



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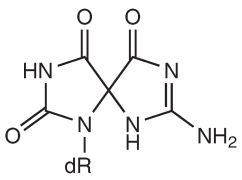

60

Common purine analogues are the 7-deazapurines, which have proven useful in structural studies as the analogues are unable to form Hoogsteen base pairs. They are also useful because substitution of N7 by carbon presents a new position for further functionalisation without affecting the base pairing properties of the analogue. The 7-deaza-2,6-diaminopurine analogue (**61**) forms stable duplexes opposite both dC and dG, and is therefore less discriminating than diaminopurine.[399] Duplex DNA containing either 7-deaza-dA or 7-deaza-dG strongly quenches the fluorescence of ethidium bromide in contrast to canonical DNA.[400] Fe(II) ions will bind to duplex DNA containing three or more successive guanosine residues. Substitution of one of these guanosine residues by 7-deaza-dG results in loss of Fe(II) ion binding, suggesting that it binds through N7.[401] Similar results are observed for Cu(II) ion binding at a helix-coil junction, where binding is removed when dG is replaced by 7-deaza-dG.[402] DNA polymerase ι a (member of the Pol Y family) is strongly inhibited by the presence of 7-deazapurine analogues in the template, suggesting that it requires recognition by Hoogsteen base pairing.[403]

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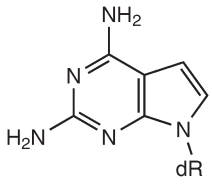
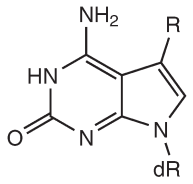


61

It is well established that the incorporation of propynyl groups at C5 of pyrimidines aids considerably in duplex stability. Propynyl groups at C7 of 7-deazapurines also enhances duplex and triplex stability.[404–406] Propargylamine substituents have a similar effect, with the 7-deaza-7-propargylamino-dA:dT base pair being comparable with a dG:dC base pair.[407] 7-Deaza-2′-deoxyisoguanosine (**62**, R = H) enhances both parallel and antiparallel duplex stability, though (**62**, R = H) exhibits significant keto-enol tautomerism. The 7-halogeno derivatives of (**62**, R = I, Br) shifts the tautomeric constant in favour of the keto form.[408] (**62**, R = H) when present in DNA duplexes also leads to quenching of ethidium bromide, though this is reduced with the halogeno derivatives.[409]



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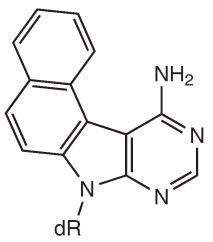
Fluorophores have been attached to C7 of 7-deaza-dA, where quenching of the fluorophore occurs if the analogue is opposed to thymidine, but not opposite any other nucleotide.[410] Conversely, the analogue (**63**) fluoresces when opposed to cytidine in a duplex, but not with any other nucleotide.[411] Analogue (**64**), when incorporated at the end of an oligonucleotide will undergo a photochemical ligation reaction with a complementary 5-vinyl-dU through a cycloaddition reaction.[412]



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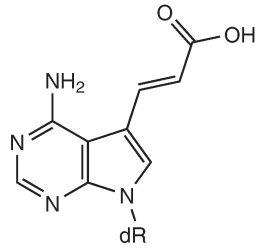

64

In addition to 7-deazapurines a number of other aza- and deazapurine analogues are reported. 1-Deaza-dG is acid-labile, and can therefore be used for the generation of abasic sites.[413] 3-Deaza-dG has been used to probe for essential hydrogen bonding between DNA and DNA polymerase I. It was shown that polymerase extension was significantly reduced, confirming an essential hydrogen bond with purine N3.[414] 3-Nitro-3-deaza-dA (**65**) possesses the hybridisation properties of dA, but is a photocleavable analogue that gives rise to chain cleavage.[415] The base pairing properties of a large number of 8-aza-7-deazaadenines linked through either nitrogen of the pyrazole ring are reported.[416] 8-Azainosine exhibits similar base

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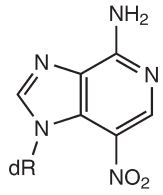
pairing properties as inosine,[417] and 8-azanebularine (**66**) has been used as a transition state analogue in the study of adenosine deaminase enzymes.[418] 7-Deaza-2,8-diazaadenine (**67**) preferentially base pairs opposite dG in a duplex.[419–421] Under prolonged heating with ammonia (**67**) cleaves to (**68**), which exhibits similar base pairing properties.



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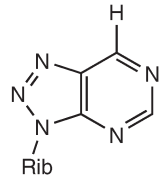

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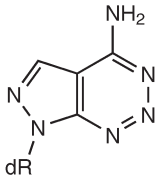

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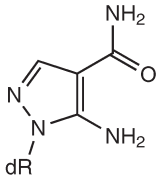
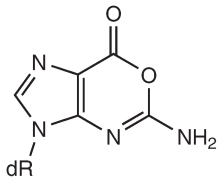


68

Xanthosine (dX), a NO-derived lesion, will act as a pausing lesion to many DNA polymerases, but whilst pol β preferentially inserts the correct dCTP opposite it, polymerases α, η and κ mis-insert dTTP.[422] dX is readily removed by endonuclease V.[423] Another NO-derived lesion is oxanosine (**69**): the synthesis of DNA containing it has been described,[424] and its thermodynamic properties in duplexes showed that it still preferentially base pairs with dC.[425] However, (**69**) is removed by endonuclease V opposite each of the natural bases with similar efficiency.[426] 2-Amino-8-oxopurine (**70**) forms base pairs with all of the natural bases, though it is generally destabilising.[427] 2-Amino-6-vinylpurine undergoes hybridisation-promoted crosslinking with cytidine.[428]



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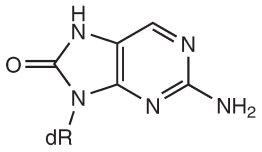

70

Guanine is the nucleobase that is most susceptible to modification by environmental mutagens, and a number of these have been examined. These include adducts formed by simple reactive aldehydes to a range of polyaromatic hydrocarbons (PAHs). Reaction of dG with malondialdehyde (derived from lipid oxidation) generates the adduct (**71**, M_1dG), which is a miscoding lesion, and exists *in vivo* in equilibrium with the N2-acyclic derivative. Translesion synthesis using Klenow fragment was found to be more efficient with the acyclic derivative, and dCTP was preferentially incorporated opposite both, followed by dTTP.[429] The restriction enzyme *Eco*RI only cleaves 60% of the strand containing (**71**) in the recognition site,[430] though cleavage by DNA topoisomerase IIα is enhanced in the presence of the lesion.[431] Reaction of dG with acrolein yields the isomeric adducts (**72**, **73**), and this is accelerated in the presence of polyamines,[432] and can also give rise to interstrand crosslinks with neighbouring guanine residues.[433] These two lesions are

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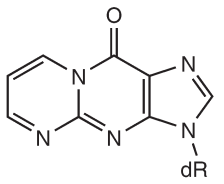
thermally destabilising in telomeric quadruplexes.[434] Epoxides, such as diepoxybutane, react at N7 of guanine residues, resulting in strand cleavage.[435] Exposure of DNA to alkylating agents such as vinyl chloride leads to formation of etheno-adducts of dA, dC and dG. These lesions are substrates for AlkB repair protein, which is an α-ketoglutarate dioxygenase, removing the alkyl chain from the lesions,[436,437] and also repairs 1-methyl-guanine and -adenine derivatives.[339,438]



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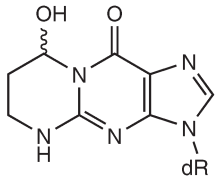

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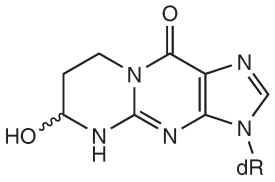
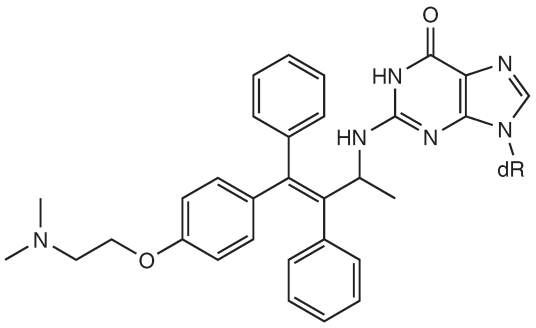


73

Tamoxifen is a drug widely used in cancer chemotherapy, and its toxicity is associated with adduct formation with guanine residues (**74**), and is a blocking lesion to DNA polymerases. Oligonucleotides containing one diastereoisomer of (**74**) have been described.[439] The effects of (**74**) in different cells showed that if formed in the liver, being mitotically quiescent, it has less effect than in highly proliferative organs.[440] Nucleotide excision repair (NER) is believed to be the major route for excision of the lesion.[441]



74

Benzo[a]pyrene is a known carcinogen present in cigarette smoke, which reacts with the exocyclic amino group of guanine to give the lesion (**75**, (−)-*trans*-*anti*-[BP]-N^2-dG isomer shown). (**75**) occurs frequently at CpG sequences where the reactivity towards adduct formation is enhanced by methylation of the dC. Methylation causes a conformational switch of the adduct from residence in the minor groove to intercalation and subsequent base displacement.[442] The presence of (**75**) at CpG sites, however, results in decreased methylation and greatly reduced cleavage by *Eco*RII methyltransferase and endonuclease.[443] The lesion causes G → T and G → A mutations, but the mutation rate is reduced at CpG steps if the cytosine is

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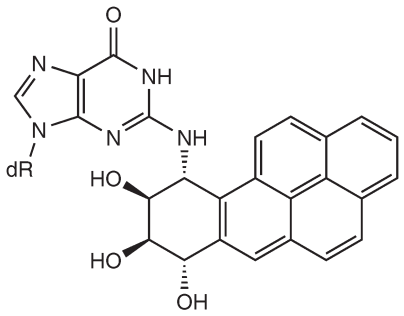
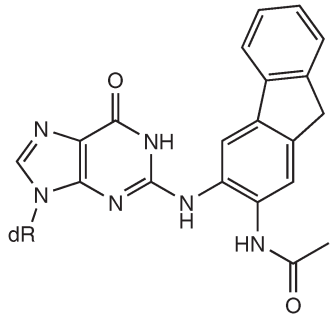
methylated.[444] The large adduct also affects translesion synthesis by human DNA polymerase η, the efficiency of which decreases with increasing size of lesion.[445]



75

N-Acetyl-2-aminofluorene is another environmental mutagen, and it reacts predominantly at C8 of guanines (**76**). The chemical synthesis of oligonucleotides containing (**76**) has been described by Gillet *et al*.[446] (**76**) frequently gives rise to a -2 frameshift deletion,[447,448] though DNA polymerases η and κ insert the correct base opposite along with low level misincorporation of dAMP.[449] (**76**) is a substrate for the translesion DNA polymerase V[450] and the human replication protein A.[451] The chemical synthesis of oligonucleotides containing the C8 adduct of the dietary mutagen IQ has been described, though no biochemical data are presented.[452]



76

Kool and co-workers have examined two sets of analogues that retain the hydrogen bonding potential of the normal DNA nucleosides, but have a phenyl ring inserted into the structure, and are therefore larger than their native counterparts. One series of analogues has been termed expanded DNA or xDNA,[453–455] (**77–80**), the other as wide DNA or yDNA,[456–458] (**81–83**). In both cases, xDNA and yDNA are 2.4 Å larger than natural DNA, and, due to the insertion of the phenyl ring into the nucleobase, these analogues are naturally fluorescent. The size-expanded analogues form selective, stable base pairs with their corresponding complementary native DNA base, and whilst the new analogues are generally more stable, there are sequence contexts in which they are destabilising. They have also been shown to form stable triplexes in the same way that native DNA does. A further extended guanine analogue (**84**) has also been described for incorporation into TFOs for recognition of an A:T inverted base pair.[459]

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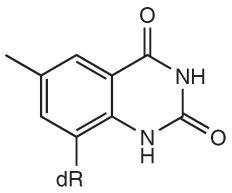

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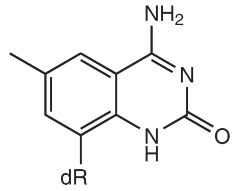

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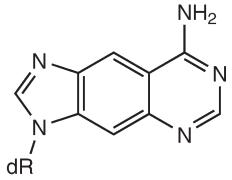

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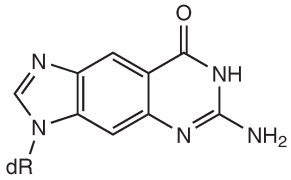

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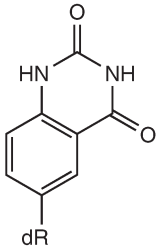

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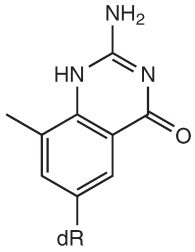

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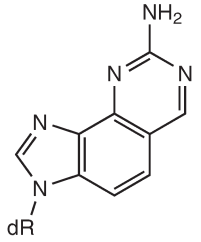

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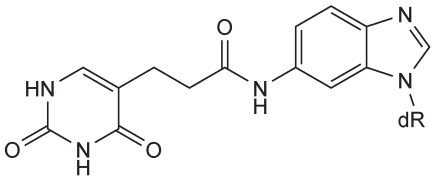

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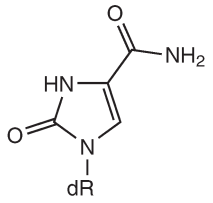
Other analogues that have been described include methyl indole used as an adenine mimic in the role of uracil DNA glycosylase, in which the enzyme is more efficient when dU is opposed to the non-hydrogen bonding analogue than dA.[460] A pteridine has been incorporated into an oligonucleotide to study photooxidative damage.[461] Imidazole *C*-nucleosides have been used as a probe for acid-base catalysis in the VS ribozyme.[462,463] The 2-oxo-imidazole-4-carboxamide (**85**) in a DNA duplex favours base pairing with the purines rather than pyrimidines,[464] and primer extension past the oxadiazole carboxamide (**86**) occurs with incorporation of each of the natural dNTPs.[465]



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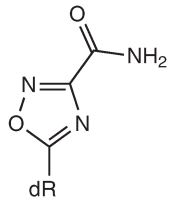

86

Abasic sites are highly abundant lesions in DNA that usually occur as a result of a depurination event. It has been estimated that the basal level of abasic sites is of the order of 70–100 000 per genome.[466] There are four different kinds of naturally occurring abasic site, the non-oxidised abasic site (AP), (**87**) C2-AP (**88**), which is a

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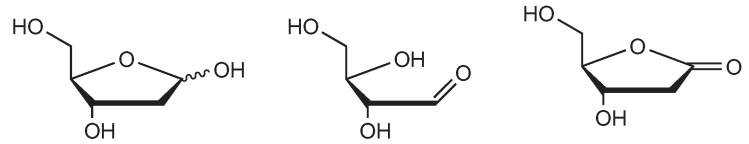
C2′-oxidised abasic site and arises as a result of γ-radiolysis, the C1′-oxidised abasic site 2-deoxyribonolactone (**89**) and the C4′-oxidised lesion C4-AP (**90**). In addition to these there is a chemically stable abasic site that does not occur naturally, but has been used to chemically synthesise oligonucleotides containing abasic sites, usually denoted as F (**91**). Also, the analogue (**92**) has been used as a method of introducing the ribonucleoside derivative of (**87**) abasic site into RNA following photolysis.[467] The ribosyl-derivative of (**87**) is readily by-passed by HIV-1 RT, preferentially incorporating dAMP opposite it.[468] A carbocyclic analogue of (**87**) has also been synthesised, where it was used for structure determination by NMR.[469] A chemically stable analogue of (**87**), (**93**) containing a methylenephosphinic acid group, has been introduced into DNA.[470] The analogue is stable under basic conditions, but the hemiacetal centre is still fully functional.



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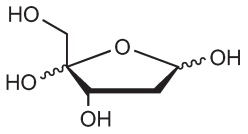

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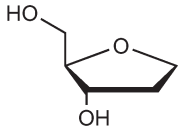

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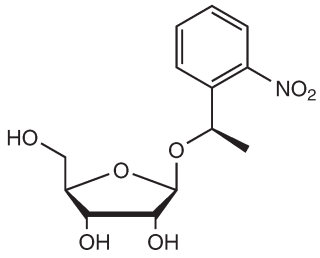

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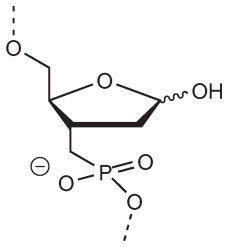

93

(**87**) sites are readily introduced into DNA by treatment of 2′-deoxyuridine-containing oligonucleotides with uracil DNA glycosylase, or various endonucleases, thus allowing biochemical studies of abasic sites. (**87**) has been introduced into the hairpin ribozyme for functional analysis,[471] and to help characterise Exonuclease-3 enzyme from *C. elegans*.[472] Abasic sites in DNA are mutagenic, preferentially following the 'A-rule',[473] though *E. coli* DNA polymerase η preferentially inserts dCMP.[474] Pyrene nucleotide,[475] however, is incorporated opposite an abasic site with almost the same efficiency as a normal base pair, and the kinetics of this has been investigated using yeast DNA polymerase η.[476] The repair of (**87**) by apurinic/apyrimidinic endonuclease[477] and at clustered damage sites with nuclear extracts[478] are reported.

The chemically-stable abasic site (**91**) has also been used in translesion synthesis. Translesion synthesis by HIV-1 RT is facilitated by the Vif auxiliary factor.[479] Human DNA polymerase Q inserts dAMP opposite (**91**),[480] whilst human DNA polymerases λ and β generate -1 frameshift mutations.[481] A number of aromatic non-nucleoside triphosphate derivatives are also incorporated opposite (ab5) by

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DNA polymerases λ and β.[482] A comparison of (**87**) and (**91**) in translesion synthesis has been reported by Greenberg.[483,484]

The C2′- and C4′-abasic sites (**88**, **90**) have been less well studied. Methods for chemically introducing them into oligonucleotides have been described,[485,486] whilst two reports describe translesion synthesis of them. (**88**) and (**90**) are replicated by Klenow fragment according to the 'A-rule',[487] though a −3 frameshift deletion also occurs with (**90**).[488] Less is known about the lesion (**89**), though methods of detecting it in DNA are reported.[489,490]

For some time there has been interest in developing new base pairing systems to expand our genetic code (for a review see Wang and Schultz[491]), and an altered or expanded genetic code will allow for many new applications available to molecular biologists. A number of new base pairing systems and their applications have therefore been described. One of the earliest such systems is the base pair between isoguanine (^{iso}G) and isocytosine (^{iso}C), and this is readily tolerated by DNA polymerases. DNA syntheses using A, T, C, G, ^{iso}G and ^{iso}C were found to be replicated well, though regions of high ^{iso}G and ^{iso}C content were less well tolerated.[261,492] Also, the base pair between 2-thiothymidine and diaminopurine is selective in a six base pair system, and is well tolerated by DNA polymerases[261] and similar results are observed using 6-thiopurine and 5-methyl-2-pyridinone as a third base pair.[493]

The size-expanded nucleoside analogues (**77–80**) have the potential to act as an alternative base pairing system, which has been developed further by Liu *at al*.[494] An alternative size-expanded system, (**94–97**) has also been considered, though only their base pairing properties have been reported so far.[495] Another potential base pair is that between an abasic site and either phenanthroline or pyrene, though again only their thermal stabilities are described.[496] Romesberg and co-workers have examined a number of aromatic systems based on isocarbostyril, naphthyl and indole as self-pairing systems for a third base pair.[497] The analogue that has received most attention is an isocarbostyril analogue (PICS) that forms stable self-pairs in a DNA duplex, but is a very poor substrate for DNA polymerases. To overcome this they have started to evolve novel polymerases using phage display to acquire polymerases capable of replicating beyond the analogue.[498] In addition, they have devised a model base pairing mimic (**98**) to study tautomerism and solvation within a DNA duplex.

The novel base pair that has been most widely studied is that between a 6-thienyl- or 6-thiazolyl-purine (**99**) and 2-oxo(1H)pyridine (**100**). (**99**) and (**100**) form a selective and stable base pair, and are replicated by DNA polymerases[500] and RNA polymerases.[501,502] They have also been used for site-specific fluorescent[503] and biotin[504] labelling of RNA during transcription.[499]

Another class of analogue that has been investigated are universal bases. These are so called because they are able to pair with each of the natural DNA bases without discriminating between them. They are generally planar aromatic non-hydrogen bonding analogues, and the most widely studied universal bases are 3-nitropyrrole (**101**)[505] and 5-nitroindole (**102**).[506] The 2′-*O*-methyl ribonucleoside derivative of (**102**) has been described, though no data have been reported.[507] The efficiency of incorporation of indolyl-2′-deoxyriboside 5′-triphosphate opposite an abasic site is 3600-fold lower than for the nitroindole derivative, suggesting that stacking interactions are more important than desolvation.[508] A series of 5-substituted indoles has been used to probe the contributions of shape complementarity and π-electron surface area during DNA polymerisation. The larger 5-phenyl derivative is incorporated more efficiently than 5-nitro-, 5-fluoro- and 5-amino-indole, suggesting that π-electron surface area is more important than shape complementarity.[509] Incorporation of these analogues opposite an abasic site prevents incorporation of other dNTPs and hence selectively inhibits translesion synthesis.[510] The analogue 7-nitroindole has previously been used as a photocleavable analogue, but it exhibits very similar universal base properties to (**102**).[511]

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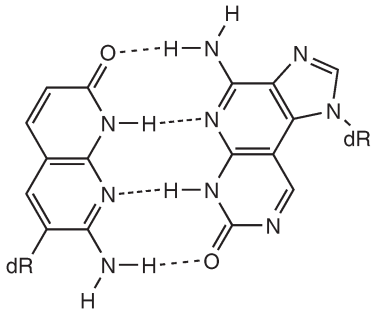

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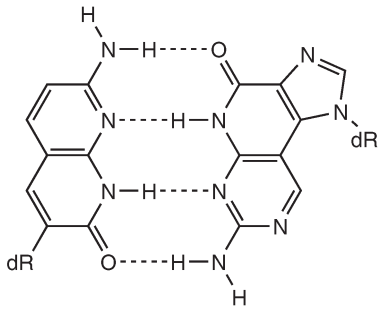

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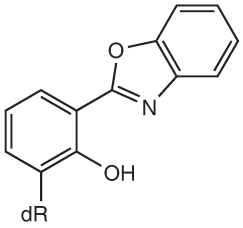

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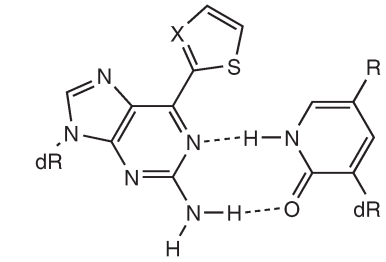
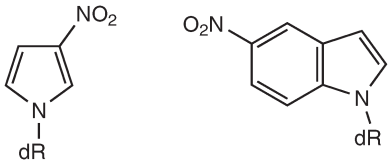


X = CH or N

99 100



101 102

The cytidine analogue (**53**), despite having the potential for forming Watson-Crick hydrogen bonds, behaves as a universal base, though with reduced stability compared to a G:C base pair.[327] 2′-Deoxyxanthosine when present in TFOs also behaves as a universal base,[512] and the analogues (**103**)[417] and (**104**)[416] behave as universal bases in duplex DNA.

In addition to all of the above-modified nucleoside derivatives are a series of analogues whose main common feature is that they are derived from aromatic hydrocarbons. The phenol nucleoside (**105**) introduced into duplex DNA undergoes

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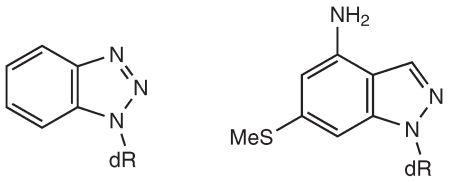
a photolytic crosslink with a complementary adenine residue,[513] and the thiophenol C-nucleoside (**106**) has been used as a redox-active crosslinking nucleoside.[514] The *C*-nucleosides derived from biphenyl, pentafluorobiphenyl and bipyridyl as self-complementary pairs form a stabile zipper-like motif, stabilised by stacking interactions.[515–517] The azobenzene analogue (**107**) can be used as a photo-trigger for duplex hybridisation. In duplex DNA (**107**) is present in the *trans*-form, which aids duplex stability. After UV irradiation, the analogue isomerises into the *cis*-form, which is destabilising and leads to separation of the DNA strands. This has been used as a method for regulating RNase H-mediated digestion of RNA in which (**107**) is present in the sense strand, and on isomerisation the antisense strand hybridises to the RNA, triggering RNase H activity.[518] The *C*-nucleosides of 2-aminoquinoline and 2-aminoquinazoline form stable Hoogsteen base pairs with an A:T base pair in TFOs.[519,520]



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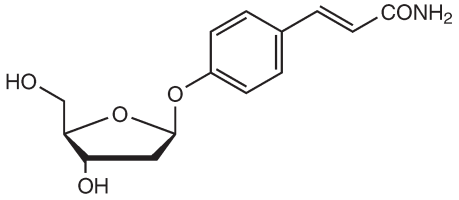

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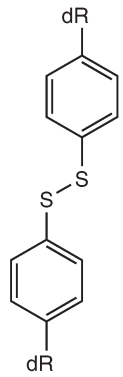

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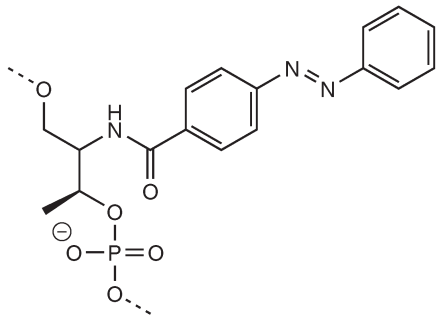

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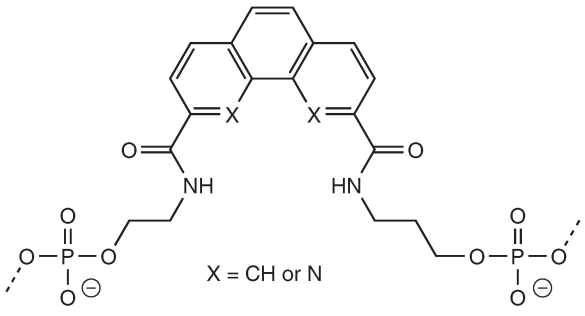
Oligonucleotides bearing anthracene units on their neighbouring 5′- and 3′-termini undergo photolytic ligation *via* anthracene cyclodimer formation.[521] Phenanthroline and phenanthrene linkers (**108**) form stabilising zipper-like structures when they are complementary in duplex DNA.[522,523] Phenanthroline is more stable than phenanthrene, the latter being considerably stabilising when used as an end-cap for duplex DNA.[524] Pyrene is frequently incorporated into oligonucleotides for its fluorescent properties (see Section 3.5), but can also be used for its stacking potential. Intercalating nucleosides derived from pyrene are able to strongly stabilise TFOs.[525,526] Oligonucleotides containing multiple substitutions of the *C*-nucleosides derived from pyrene, terphenyl and terthiophene have been shown to exhibit bright fluorescence with large Stokes shifts. The fluorescence can be readily tuned to give desirable colours by varying the *C*-nucleoside and the number of substitutions.[527,528] Perylene has been used to stabilise duplex and triplex DNA. As an intercalating base it is most stabilising when two perylene units are incorporated into a TFO,[529] but when incorporated into a self-complementary pair then the resultant duplex can also exist as two hairpin structures, with the stacked perylene units holding the two hairpins together.[530] Finally, neutral porphyrin has been incorporated onto the 5′-terminus of oligonucleotides.[531] In duplex structures it is destabilising, but ssDNA interacts strongly with the porphyrin.



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A number of fluorinated *C*-phenyl and benzimidazole derivatives have been incorporated into RNA duplexes to study their base-stacking properties. Generally it was found that self-pairing was more stable than pairing with a natural base, with 4,6-difluorobenzimidazole being the most stabilising analogue.[532] Molecular dynamic calculations have been used to examine the effect of pairing adenine with the *C*-nucleosides of phenyl and 2,4-difluorophenyl in duplex RNA.[533] Whilst calculations predict a stable A-form structure, they also showed localised mobility at the site of the analogue, and no stable analogue-adenine base pair was observed. The incorporation of the triphosphate derivatives of benzene, indole, 2,3,4,5-tetrafluorobenzene and 4,5,6,7-tetrafluoroindole nucleosides to form self-pairs by Klenow fragment has been used to study hydrophobic effects and stacking interactions in a polymerase active site.[534] The self-pairs were formed up to two orders of magnitude more efficiently than the formation of an analogue pair with a natural dNTP, with the fluorous analogues forming the most efficiently.

2. Aptamers and (deoxy)ribozymes

Aptamers are nucleic acid (or peptide) molecules that have been selected to bind a specific target molecule. Aptamers are usually created by selecting them from a large random sequence pool, and the usual method for this is SELEX, though other methodologies are being used. Aptamers may also be designed to carry out a chemical reaction, *e.g.* ligation or cleavage reactions, in which case they are termed

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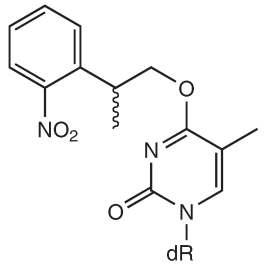
ribozymes (RNAzymes) (or deoxyribozymes, DNAzymes). For aptamer-based nanodevices see Section 3.6.

A number of binding aptamers have been evolved, most of which bind proteins. Aptamers binding to neuropeptide Y,[535] fibronectin,[536] Ff gene 5 protein,[537] archaeal chromosomal MC1 protein[538] and HIV-1 Rev protein[539] have been described, as has a quadruplex aptamer that is a potent inhibitor of HIV-1 integrase protein.[540] However, most DNA aptamers have been designed for specific applications. Thus the thrombin-binding aptamer has been used as a sensor for detection of thrombin in blood serum,[541] as a method for detection of DNA invoked by the formation of the complex between the aptamer and thrombin,[542] and *in silico* methods have been used to devise novel thrombin-binding aptamers.[543]

Aptamers that emit a fluorescent signal on binding to their target are known as signalling aptamers. A method for selection of such signalling aptamers has been reported,[544] and fluorescent signalling has been used to monitor enzyme activity.[545] Aptamers have been attached to gold surfaces[546,547] and electrode transducers[548] for electrical signalling. Circular aptamers have the advantage that they are then substrates for rolling-circle DNA synthesis, allowing for amplification of signal in real time.[549]

Various analogues have been used in the selection or optimisation of aptamers. Phosphorothioate aptamers have been selected against NF-κB transcription factors[550] and the RNase H domain of HIV-1 RT.[551] An anti-thrombin aptamer modified by the caged thymidine (**109**) allows for the aptamer to be switched on following UV irradiation,[552] and an aptamer incorporating (**110**) fluoresces on binding ATP or argininamide.[553] 7-Deaza-dG has been incorporated into aptamers to disrupt a quadruplex formation in the aptamer active site.[554] Molecular beacon aptamers,[555,556] quantum dot beacon aptamers[557] and quartz crystal microbalance aptamers[558] have each been used for the detection of protein-binding.



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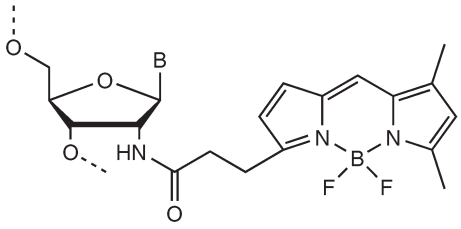

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A more important class of aptamer are those that carry out chemical reactions, sometimes, though not always, catalytically. The scope of chemical reaction that could be carried out is without limit, and a number of different types of chemical reactions have been used to design aptamers, though more so with RNAzymes (see later). Deoxyribozymes were initially designed to site-specifically cleave RNA, and are still a subject of much interest, though are more concerned with characterisation of the DNAzymes. These DNAzymes are usually selected under conditions containing magnesium ions, yet many of them are found to act independent of Mg(II) ions[559] or any divalent metal ions.[560] Other RNA-cleaving DNAzymes have been selected to work in the presence of Pb(II) ions.[561] Selection of fast-acting cleaving DNAzymes yielded aptamers that worked on a second, rather than hour, timescale,[562] whilst other DNAzymes work under photolytic control[563–565] or at low pH (pH 3.8).[566] A DNAzyme that cleaves the mRNA for the enzyme ornithine decarboxylase is able to mediate gene silencing.[567] Conjugation of RNA-cleaving DNAzymes with polyamines or peptides increases the aptamer's resistance to cleavage by DNase I, and enhances cellular uptake.[568]

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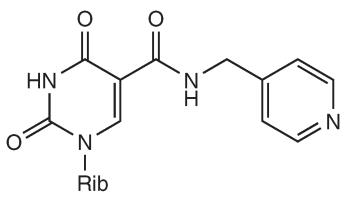
Another common chemistry used to design DNAzymes is to mimic the action of ligases. DNAzymes are able to ligate RNA with native 3′–5′[569–571] and unnatural 2′–5′ linkages.[572,573] A ligation DNAzyme has been coupled with rolling circle DNA amplification as a sensitive sensor for ATP.[574] Another ligase DNAzyme generates lariat RNA by formation of a 2′–5′ linkage at the branch site,[575] and this has been further developed to generate DNAzymes that mimic RNA splicing.[576,577] A final DNAzyme acts as a kinase for phosphorylation of DNA.[578]

Whilst there are fewer reports on RNA aptamers and RNAzymes than for DNA, nevertheless the scope of aptamers is broader. There are reports of allosteric aptamers, and RNAzymes that catalyse a broader range of chemical reactions, such as Diels-Alder reactions. As with DNA aptamers, there are many RNA aptamers selected for binding to specific targets. A system has been devised for the automated development of aptamers, using peptide P as an example.[579] Aptamers have been selected for small molecules, such as NTPs,[580,581] flavin mononucleotide,[582] theophylline[583] and malachite green.[584,585] Aptamers have also been developed that require the presence of particular metal ions, for example a Co(II) ion binding aptamer.[586] Other binding aptamers include the receptor activator of NF-κB,[587] ADP-ribosylation factors,[588] the *B. subtilis tyr S* T box antiterminator,[589] an HCV IRES domain III-IV aptamer[590] and an HBV RNA encapsidation signal aptamer.[591] Other therapeutically-based aptamers include an aptamer that inhibits angiogenesis by targeting the heparin binding domain of VEGF[592] and the use of an oligonucleotide as an anti-aptamer to control the effects of an anticoagulant aptamer.[593]

Allosteric regulation requires an effector molecule bound to the allosteric site to enhance or activate the required activity. This has been successfully applied to aptamers, and a number of allosteric aptamers have been described. Aptamers have been designed to require the presence of small molecules, such as guanine analogues,[594] boronic acid derivatives[595] and metal ions[596] in order to 'switch' on the activity of the aptamer. A ligand-dependent RNA transcriptional activator has been selected that is 10-fold more active in the presence of the dye tetramethylrosamine.[597] In addition, oligonucleotides have been used to hold the aptamer in an 'off' position, the aptamer then being activated by its desired target.[598,599]

Fewer analogues have been assayed in RNA aptamers. The pyridyl-modified analogue (**111**) when incorporated into an aptamer controls the rate and shape of growth of palladium particles.[600] Replacement of (**111**) with uridine leads to complete loss of RNA activity confirming that (**111**) is critical for nanoparticle growth. A 2′-*O*-methyl aptamer against VGEF is found to be stable in plasma and to autoclaving.[601] Replacement of all sugar residues of an aptamer towards NF-κB by a 4′-thiosugar resulted in loss of binding, but at selective positions retained aptamer binding and enhanced cellular stability.[602] Similar results are found when an aptamer against HIV-1 TAR RNA are fully replaced by hexitol nucleic acids (HNA) (**30**), and again RNA-HNA mixmers retain binding with improved nuclease resistance.[603] Mixed 2′-*O*-methyl-LNA (**32**) chimeras of the tenascin-C binding aptamer exhibit enhanced binding and cellular properties.[604] Binding aptamers using L-nucleotides (termed Spiegelmers) have also been reported, and these show enhanced cellular stability.[605]



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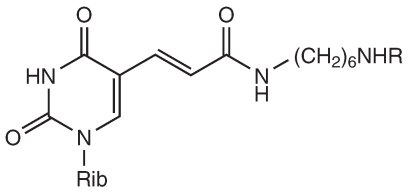
The scope of chemical reactions is far greater with RNAzymes than with DNAzymes. One report describes a fusion of an aptamer with the hammerhead ribozyme in order to reduce the self-cleavage reaction of the ribozyme in the absence of its target sequence.[606] There are reports of two RNA ligases[607,608] and two kinases,[609,610] as well as two RNAzymes that will aminoacylate tRNA.[611,612] A twin ribozyme containing the analogue (**112**, R = fluorescent dye) has been designed which will mediate the exchange of a patch of substrate RNA with a separate synthetic RNA fragment, in this case containing (**112**).[613] A fast-acting RNAzyme has been selected carrying out the action of a purine nucleotide synthase.[614] The ribozyme will synthesise 6-thioguanosine monophosphate from a substrate 5-phosphoribosyl 1-pyrophosphate and 6-thioguanine.



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There have been four reports of Diels-Alderase ribozymes, based on a ribozyme first described by Seelig and Jäschke.[615] One report describes the analysis of the catalytic pocket,[616] whilst the same group has selected an allosteric Diels-Alderase under the control of theophylline,[617] and another group has mutated the RNAzyme to improve its catalytic efficiency.[618] The final report compares the selection of a Diels-Alderase ribozyme derived using two different methods. The first is using SELEX, which is the most common method employed for aptamers. The second uses the method of *in vitro* compartmentalization (IVC).[619] Ribozymes selected using SELEX alone all contained a common catalytic motif, whereas use of SELEX followed by IVC gave greater variation within the catalytic motif, as well as novel motifs.[620] The final ribozyme catalyses a Zn(II) dependent Aldol reaction, which shows a 4300-fold increase in activity over the uncatalysed reaction.[621]

3. Oligonucleotide conjugates

The range of cargoes that have been attached to oligonucleotides is quite exceptional. This section has been broken down into a number of sections to cover the broad range of oligonucleotide conjugates, starting with oligonucleotide-peptide conjugates, which are primarily used to attempt to aid cellular delivery of oligonucleotides. Template-directed synthesis has seen fewer publications, but is nevertheless an important area, whilst metal conjugates and charge transfer continues to be an expanding area of research. Fluorescent applications have expanded considerably, and many applications are described. There is also the rapidly emerging area of nanodevices, for which oligonucleotides play a key role.

3.1 Oligonucleotide-peptide conjugates

Oligonucleotide-peptide conjugates are an important class of analogue as they are widely used as a means of delivering oligonucleotides into cells or cellular components. Traditionally this has been used as a method for delivering antisense oligonucleotides, but this has now broadened to include triplexes and siRNA. Most of the reports of oligonucleotide-peptide conjugates in this review period deal with their synthesis. In addition, there are two reports on the chemistry of conjugation of

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amino acids to RNA to study translation,[622] in one case incorporating an unnatural amino acid.[623]

Various methods have been examined for the conjugation of peptides and oligonucleotides. Generally, these are prepared by conjugation of the two parts because there is as yet no general strategy for the stepwise synthesis of conjugates *de novo* because of the incompatibility of the two classes of compound. However, methods have recently been reported which use 2-(biphenyl-4-yl)propan-2-yloxycarbonyl (Bpoc) as an amino acid protecting group, which is removed under the same conditions as dimethoxytrityl from an oligonucleotide. Amino acid amino groups are also protected with base-labile protecting groups, and may be removed using ammonia at the end of the conjugate synthesis.[624] In a second method, the oligonucleotide is synthesised terminating in a 2′-amino-dU building block, and this may then be used for the stepwise addition of benzyl-protected lysine, where the ester groups are removed under phase transfer conditions using palladium nanoparticles.[625] Fmoc-protected amino acids have also been synthesised onto the 5′-end of an amino-modified oligonucleotide on solid support.[626] A C5-modified dU analogue bearing a cysteine has been prepared for oligonucleotide synthesis followed by coupling of a peptide by native ligation.[305]

A number of different conjugation chemistries have been attempted to conjugate peptides and oligonucleotides. The synthesis of labile conjugates has been carried out using disulfide bridges between a peptide bearing a terminal cysteine and an oligonucleotide with a thiol-modifier.[627–629] Oxime formation has also been used to synthesise conjugates between aminooxy-modified peptides and oxidation of a diol-modified oligonucleotide[630,631] or a glyoxal-modified oligonucleotide.[632] Using an aminooxy-modified oligonucleotide, glycopeptide-oligonucleotide conjugates have also been prepared.[633] Fluorescently-labelled 3′-amino-oligonucleotides have also been conjugated to peptides through amide bond formation.[634] Conjugation of arginine-rich peptides to steric blocking morpholino oligomers enhances antisense activity 3–25-fold compared to non-conjugated oligomers.[74]

The remaining reports in this area deal with the delivery of oligonucleotides by peptide conjugates, but see also Section 1.3 on PNA-oligonucleotide conjugates. Oligonucleotides are frequently conjugated to the nuclear localisation signal peptide (NLS), and this has been used to deliver DNA cargoes as antisense agents.[635–637] An antennapedia peptide is also frequently used, and has been reported for the delivery of triplex-forming oligonucleotides (TFOs).[638] TFOs have also been targeted to the liver by conjugation to mannose-6-phosphate bovine serum albumen,[639] whilst Tat peptide has been used for the cellular uptake of siRNA.[640]

3.2 DNA-templated organic synthesis

The first example of DNA-templated organic synthesis is accredited to Naylor and Gilham,[641] and this field has been extensively researched by Liu *et al*., amongst others. DNA-templated synthesis generates organic products individually linked to oligonucleotides which encode and direct their synthesis. A series of Staudinger transformations, converting templated azides with templated arylphosphines have been reported, increasing the scope of template-directed syntheses.[642] Liu *et al*. have demonstrated template-directed multistep syntheses[643,644] as well as a method for carrying out asymmetric catalysis using DNA bearing the aminoacridine derivative (**113**). DNA carrying (**113**) was used to carry out Cu(II)-catalysed Diels-Alder reactions.[645]

Using the techniques for template-directed multistep syntheses,[643,644] Liu and co-workers have developed a method for the synthesis of macrocycles.[646] Using a ‘codon’ approach, short oligonucleotides (10–12mers) coding for specific building blocks have been used to direct organic synthesis in the presence of an ‘anticodon’ template oligonucleotide. By this method, macrocylic structures composed of four building blocks have been ‘translated’. They have also combined DNA-templated

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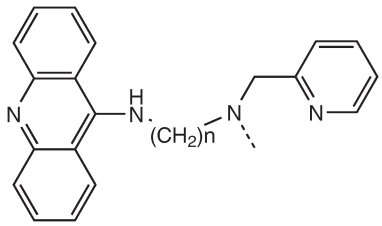
synthesis with *in vitro* selection methods to discover a C–C bond-forming reaction of an enone from an alkyne and alkene in the presence of a Pd catalyst.[647] Oberhuber and Joyce have used DNA-templated synthesis to describe an aldol reaction for the formation of pentose sugars, which they describe as a potential model for synthesis in the RNA world.[648]



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3.3 Oligonucleotide-metal conjugates

Oligonucleotide-metal conjugates cover a variety of different applications, as well as a number of different metals. The most widely used application is the attachment of oligonucleotides to solid surfaces by attachment to gold, often to gold nanoparticles. A new method for the attachment of oligonucleotides to gold surfaces *via* a Diels-Alder reaction has been described.[649] The thermodynamics of DNA hybridisation[650–652] and the binding properties[653] of DNA on gold nanoparticles have been examined. The analyses of detection of DNA and RNA attached to gold surfaces has also been studied.[654–658] The detection of DNA attached to gold nanorods, which exhibit fluorescence properties,[659] and gold nanoelectrodes for electrochemical detection[660–663] are also reported. Gold-supported oligonucleotides have also been used as optical rulers by FRET measurements.[664,665]

Other reports of oligonucleotide-gold conjugates describe various applications. They have been used for detection of SNPs[666–668] and DNA lesions,[661] to study aggregation[669–671] and the assembly of G-quartets.[672,673] It has been reported that the use of DNA-gold nanoparticles enhances specificity of multiplex PCR reactions.[674] DNA attached to gold nanorods may be released in a controlled manner without degradation of the DNA using pulsed near-infrared irradiation.[675] Oligonucleotides attached to magnetic particles have been used as a method to assay for telomerase activity for rapid detection of cancer cells.[676]

Amongst the many applications of oligonucleotide-metal conjugates, they have been used to generate alternative base pairing systems (see also Section 1.3.3). A thymidine–thymidine mismatch in duplex DNA is significantly stabilised in the presence of Hg(II) ions.[677–679] The pyridyl-pyrimidone (**114**) forms a stable self-pair in duplex DNA in the presence of Ni(II) ions, which is as stable as a G-C base pair.[680] The purine analogue of (**114**), (**115**) also forms a stable base pair, being more stable than a G-C base pair, and both (**114**) and (**115**) require Ni(II) ions for duplex stabilisation. In the absence of Ni(II) the analogues are considerably destabilising.[681] A metallo-base-pair derived from the ligand *N*,*N*-bis(salicylidene)ethylenediamine (salen) has been prepared which is considerably stabilising in a DNA duplex in the presence of various divalent metal ions, but particularly in the presence of Cu(II) ions, but also with Mn(II) ions.[682,683] Stabilisation of DNA duplexes by as much as 40 °C is reported in the presence of Cu(II). Cu(II) ions are also stabilising in the metallo-base-pair (**116**) which contains a three-carbon backbone, and (**116**) is more stabilising than its corresponding 2′-deoxyribosyl analogue.[684]

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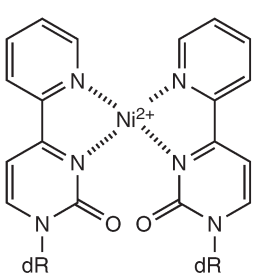

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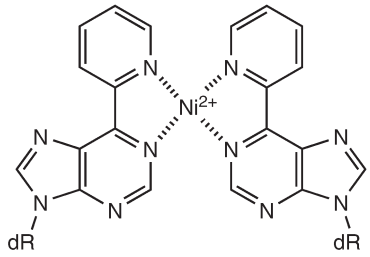

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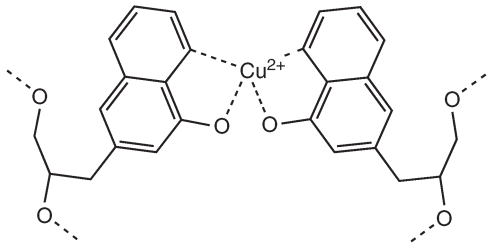

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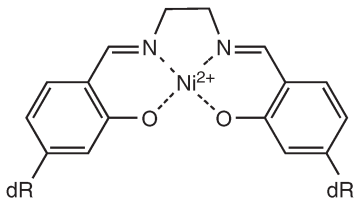
The nickel-salen analogue (**117**) has also been incorporated into a single-stranded oligonucleotide which when paired with complementary DNA effects oxidative cleavage of the complementary strand.[685,686] An unsymmetrical nickel-salen analogue has been prepared using salicaldehyde and a histidine residue. The histidine residue was attached to the N-terminal of PNA, and the resultant PNA-salen conjugate undergoes crosslinking to a DNA target, preferentially crosslinking to guanine residues.[687] Triazacyclododecane-modified oligonucleotides also effect strand cleavage in the presence of Zn(II) ions.[688]



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A common ligand for coordinating metal ions in oligonucleotides is the pyridyl group. Strömberg *et al*. have used such modified nucleosides as artificial nucleases. Incorporation of the phenanthroline derivative (**118**) (L = linker) to C5 of dU yields an analogue that, when targeted towards bulged regions of complementary RNA, leads to cleavage of the RNA in the presence of Zn(II) ions.[689,690] Terpyridine derivatives, *e.g*. (**119**, D-serinol derivative shown), have also been used as artificial nucleases,[691] though other applications include stabilisation of hairpin structures. In the latter case the terpyridine was incorporated into the loop of the hairpin, where coordination by various divalent metal ions led to an increase in stability.[692] Terpyridine conjugates have also been used to control structure of oligonucleotides.

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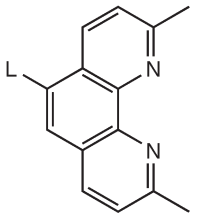
In one case a single-stranded oligonucleotide with terpyridine moieties at each terminus forms a duplex with a complementary strand of DNA in the absence of divalent metal ions. In the presence of metal ions (Zn(II) or Fe(II)) the duplex is denatured by formation of a single-stranded metal-coordinated cyclic oligonucleotide.[693] Bipyridine-ruthenium conjugates have been used in a similar manner.[694] A further example describes the synthesis of DNA triangles with terpyridine residues forming the vertices.[695]



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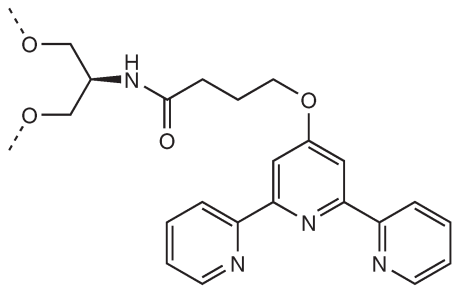

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Lanthanide-oligonucleotide conjugates may be synthesised using pyridyl groups. Ruthenium complexes have been attached to oligonucleotides for use as fluorescent probes, with the ruthenium coordinated *via* phenanthroline-dipyridophenazine ligands.[696] Luminescent lanthanide chelates have also been prepared using pyridyl ligands.[697] Acridine and other polyarenes have also been used to prepare lanthanide-coordinated oligonucleotides.[698,699] A Ce(IV)-EDTA complex was able to cleave gap sites in duplex DNA.[700]

Platinated oligonucleotides are of particular interest because of their use as antitumor agents (see also Section 4.2). *Cis*-platinated GTG sites have been shown to inhibit double-strand breaks by non-homologous end-joining when it is close to the strand break.[701] Crosslinking of guanines in telomeric DNA has been examined with *trans*-platin, and shown that the crosslink occurs between two guanine residues from the same G-quartet.[702] The crosslinking by *cis*-platin has been compared with platinum-acridine conjugates at TATA sites: it was shown that the DNA damage caused by Pt-acridine conjugates is similar to that found for *cis*-platin.[703,704]

Ferrocene-modified oligonucleotides have found use in studying redox reactions. Further reports have been described for the synthesis and characterisation of oligonucleotides bearing ferrocene residues. Ferrocene has been attached to C5 of dU,[705] where it was attached to silicon-modified electrodes, to N3 of thymidine for electrochemical labelling[706] and as a linker unit for incorporation at any position within an oligonucleotide.[707] Porphyrin has also been conjugated to oligonucleotides. A porphyrin residue bearing four maleimide groups has been conjugated to the phosphate backbone of four complementary strands of DNA to generate double-helical structures.[708] Energy transfer between two different porphyrin units (Zn-porphyrin and H_2-porphyrin) was observed. Porphyrin has previously been shown to bind to quadruplex structures, and the binding of a copper-porphyrin adduct has been examined, and shown to behave similarly to other porphyrins.[709] A hemin-DNA adduct has also been used to generate novel artificial heme enzymes.[710]

3.4 Charge transport

DNA is able to transport electrons over long distances, and is usually mediated by oxidation of guanine residues, generating guanine radical cations. Electron transport occurs in a multistep hopping process with guanines acting as carriers of the positive charge. The rate of the hopping step decreases with the distance between guanine residues, and mismatches, guanine-oxidation products and single-stranded regions

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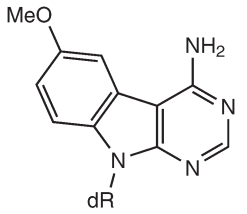
also decrease efficacy of charge hopping. In the absence of a guanine residue, adenine can also act as charge carrier.

Publications on charge transport in DNA may be broadly categorised as mechanism of action, examples of charge donor/acceptor, purine analogues and pyrimidine analogues. Finally there are applications of charge transport. Charge transport through DNA is assumed to occur through the base pairs, rather than through the sugar-phosphate backbone. This assumption has been confirmed by studying charge transfer along nicked DNA duplexes, where little effect was observed.[711] The damaging effects of low-energy electrons on DNA on monolayers revealed that duplex DNA does not capture electrons as efficiently as ssDNA, but once captured on dsDNA the electrons are more strongly bound.[712] The effect of linker length tethering oligonucleotides onto a gold surface,[713,714] absolute rates of hole transfer in DNA,[715] long-range charge transport,[716,717] and base repair by the enzyme MutY[718] have also been reported.

Quinone derivatives are frequently used as charge donors. 2-Methyl-1,4-naphthoquinone when used as donor leads to photocrosslinking of the quinone to DNA.[719] The use of naphthacenedione as charge donor yields results almost identical to the more commonly-used anthraquinone.[720] Anthraquinone has also been used attached to C8 of an adenosine,[721] and the effect of charge transport from anthraquinone by spermine derivatives has been shown to lead to protection of the DNA, presumably by formation of a hydrophobic layer on the DNA surface.[722] Other commonly used charge donors are pyrene,[723,724] phenothiazine[725,726] stilbenes[727] and phenanthridium.[728] A terthiophene-modified dG has been introduced into DNA duplexes as the radical cation it forms on one-electron oxidation has a long lifetime.[729]

Few analogues have been reported for use in charge transport; among them are methylindole[730] N^2-cyclopropylamine guanosine,[731] and 8-bromo-dG,[732] each of which act as radical traps. The effects of DNA nucleobase mobility has been studied using photoexcited 2-aminopurine at low temperatures (77 K)[733] and through purine (A, G and I) bridges.[734] Whilst pyrimidines are generally poor acceptors in charge transport, 5-bromo-dU[282,735] and 5-bromo-dC[736,737] may be used as a electron donor, and N^4-cyclopropylctosine as a radical trap.[738]

Applications of charge transport have so far been limited. However, as charge transport is strongly reduced by DNA mismatches this has been used as a method for detecting SNPs.[739] In addition, the analogue (**120**) exhibits enhanced mismatch discrimination compared to a normal mismatch, and this phenomenon has been used to devise a DNA logic gate[740,741] (see also nanodevices, Section 3.6). Finally, charge transport resulting in the remote oxidation of thiols has been used to form a disulfide bond in a nicked DNA duplex.[742]



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3.5 Fluorescence

There have been many reports regarding the use of fluorescently-labelled oligonucleotides, and many different fluorophores have been assessed. Fluorescent-labelling is rapidly overtaking radioisotope-labelling, so the number and variety of applications is large. There are also many specific applications including fluorescence

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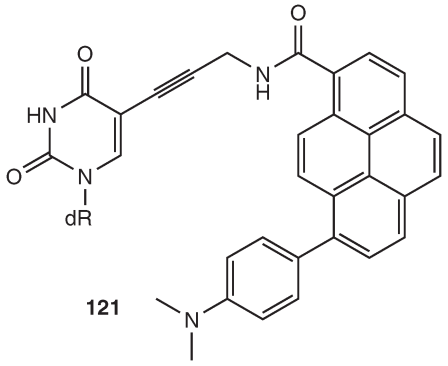
resonance energy transfer (FRET), molecular beacons, single molecule detection and quantum dots. There are a large number of publications in this area, though a detailed report of these applications is beyond the scope of this review.

A commonly used fluorophore is 2-aminopurine (2-AP), which is naturally fluorescent, and causes minimal perturbation when substituted in place of adenine in oligonucleotide structures. 2-AP has been substituted into a GAAA RNA tetraloop to monitor the binding of small molecules, in particular aminoacridine, which is found to bind with 1 : 1 stoichiometry.[743] It has been used to monitor base flipping by complementary surrogate bases as its fluorescence decreases when it is forced extrahelical.[744] 2-AP has proven to be particularly useful at monitoring protein-DNA interactions, for example, base flipping by M.HhaI[745] and *E. coli* Dam DNA methyltransferase,[746] stacking interactions between 2-AP and tryptophan in a RNA-transcriptor antiterminator N protein[747] and DNA mismatch-extension by T4 DNA polymerase[748] and RB69 DNA polymerase.[749] Also, the kinetics of ligand binding by an adenine-sensing riboswitch were monitored using 2-AP.[750] 2-AP was used to monitor the release of N7-alkylguanine from duplex DNA on treatment with the anticancer agent leinamycin.[751]

Pyrene is also a commonly used fluorophore for probing oligonucleotide interactions, and has been incorporated onto the C5 of dU, *via* C2′ as a *C*-nucleoside and as a backbone linker. Pyrene has been incorporated as an endcap, where it was used to probe base mismatches.[752] In the presence of a T–T mismatch stabilised by Hg(II) ions, pyrene fluorescence was enhanced,[678] acting as a probe for mercury ions. The pyrene analogue (**121**) exhibits dual fluorescence, strongest in ssDNA, and has been used as a probe for hybridisation.[753] A 2′-bis-pyrene-modified oligonucleotide has been reported to exhibit strong fluorescence in duplex DNA,[754] but in contrast to this, two reports describe only weak fluorescence when pyrene is attached to O2′ in DNA, but strong fluorescence in RNA structures.[755,756] DNA oligonucleotides have been synthesised incorporating pyrene, terphenyl and thiophene as their *C*-nucleoside derivatives.[527] Such oligonucleotides exhibit a broad range of fluorescence spectra depending upon the composition of the DNA. Pyrene attached to the DNA backbone either at the termini or internally have been examined; it was used to study mismatch DNA,[757,758] and as a probe for K(I) ions in a G-quadruplex structure[759] and duplex structures.[760]



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A number of other fluorescent analogues have been synthesised and studied with oligonucleotides. Thiazole orange tethered to the 5′-end of an oligonucleotide exhibited enhanced fluorescence when hybridised to complementary sequences on the surface of optical fibres.[761] The dU analogue (**122**) was synthesised and used to map the dielectric constants on the interior of DNA-binding proteins.[762] C5-furano-dU is a fluorescent analogue, and has been used to detect the presence of abasic sites.[763] The effects of incorporation of the fluorescent cytosine analogue (**51**) in duplex DNA has been examined, and shown that it does not perturb the

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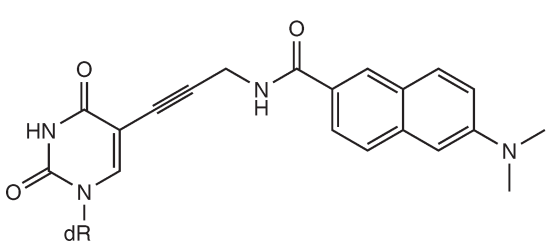
structure.[323,324] The influence of Watson-Crick hydrogen bonding within duplex structures has been studied using 2-aminopyridine nucleoside,[764] and the effects of base stacking studied using methyl red and naphthyl red dye conjugates[765] and perylene linkers.[766] Metal-sensing has been examined using fluorescence with a T–Hg–T base pair[679] and with a copper-chelating analogue (**123**) which, in the presence of Cu(II), quenches fluorescence from a proximal fluorophore.[767] Primer extension reactions with Klenow fragment have been monitored using a caged fluorescent template,[768] and a caged fluorophore has been activated by means of the Staudinger reaction using a neighbouring azido-modified oligonucleotide.[769] Fluorescently-labelled DNA on a gold surface has been used to generate a photocurrent under the influence of an electrical potential and incident irradiation, which was used to reduce NADP to NADPH.[770]



122 **123**

The diversity of applications of fluorescent-labelling and detection increases each year, as fluorescent-labelling has none of the hazards associated with radioisotope usage, and is at least as sensitive. It has been used for the detection of SNPs,[771,772] small molecules,[773] in conjunction with nucleobase analogues,[774] to study kinetics[775] and other microenvironmental changes.[776,777] A common use is the study of oligonucleotide-protein interactions.[778–784] Fluorescence techniques with enhanced sensitivity have been reported, including the use of magnetic microparticles,[785] dual-colour fluorescence[786] and two-colour dyes.[787] Organic chromophores have also been used as nanostructures for oligonucleotide structures.[788]

Molecular beacons (MB) are hairpin oligonucleotides with an internally quenched fluorophore, whose fluorescence is restored on binding to target oligonucleotides, and are useful for the detection of oligonucleotides. For a review on molecular beacons and related strategies see Ranasinghe and Brown.[789] A new non-fluorescent quencher (**124**) has been synthesised for incorporation at the terminii of MBs or attached to C5 of dU.[790] It may be used with a number of fluorescent dyes, and has the advantage that it aids duplex stabilisation with target DNA. MBs have been used for the detection of antisense binding sites in mRNA,[791] transport of mRNA,[792] to probe RNA unfolding,[793] detection of low abundance oligonucleotides[794] and transport of DNA through permeable membranes.[795] Bead-based MBs have been used for detection of nucleic acids using flow cytometry,[796] and, in enzyme-based assays using a phosphorylation-ligation coupled reaction, MBs have been used to monitor nucleic acid phosphorylation.[797]

A number of modified oligonucleotides have been studied for use in MBs. MBs have been synthesised with inversion sites at each end of the target-binding region, which leads to improvement in selectivity as the hairpin arms no longer bond to the target.[798] The use of LNA (see Section 1.3.2) in MBs has been demonstrated to improve their stability without loss of specificity,[799] whilst MBs synthesised from homo-DNA (see also Section 1.3.2) (**125**) in the hairpin stem leads to improved target selctivity.[227] MBs have been attached to gold surfaces,[800] allowing their use in microarrays, and have been linked to tRNA transcripts where they are readily transported from nuclei into the cytoplasm.[801]

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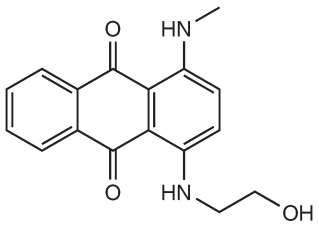

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Fluorescence resonance energy transfer (FRET) involves the non-radiative transfer of energy from a fluorophore in an excited state to a nearby acceptor fluorophore. FRET has proven to be a useful tool for measuring distances of 10–100 Å, and for monitoring conformational changes as a consequence of oligonucleotide- or protein-induced bending. FRET has been used to study the aggregation of a polyfluorene analogue, in which energy transfer to Texas-red labelled DNA is monitored.[802] The binding of metals,[677] drugs[803–805] and intercalating polyaromatic structures[806] in duplex DNA has been examined using FRET. A duplex which adopts either Watson-Crick or Hoogsteen structures has been used as a pH sensor in living cells, monitoring the interconversion with FRET.[807] In SNP detection, non-fluorescent probes have been used using SYBR green as the energy donor.[808] Oligonucleotides have been conjugated to coloured nanoparticles for SNP detection.[809]

Quadruplex structures have been examined using FRET to monitor the effects of binding small molecules including potassium ions,[810] osmolytes[811] and telomerase inhibitors,[805] as well as the binding of aminoglycosides to a T box antiterminator RNA.[812] Folding of RNA structures is ideally suited to monitoring by FRET, and the folding of a four-way junction,[813] the hepatitis delta virus ribozyme[814] and the hairpin ribozyme[815] have been reported. The main area of study using FRET is in the interaction of oligonucleotides with protein. These include the synthesis of DNA by Klenow fragment,[816] conformational studies of $tRNA^{Asp}$ bound to *B. subtilis* RNAse P,[817] a complex between DNA and retroviral integrase[818] and an integrase-Holliday junction complex,[819] the interaction of DNA with *E. coli* DNA polymerase clamp loader complex[820] and interaction of DNA with exonuclease III.[821]

Due to significant advances in microscopic techniques, the field of single-molecule detection using fluorophores has enabled the study of individual molecules, which can provide specific, rather than average, information on distribution and time trajectories (for a review on single molecule microscopy see Tinnefel and Sauer[822]). A number of studies using single molecule FRET (smFRET) have been reported, including the docking of a tetraloop-receptor motif to target RNA,[823] conformation of telomeric DNA,[824] cleavage and ligation reactions of a hairpin ribozyme[825,826] and several reports concerning the junction dynamics of Holliday junctions.[827–829] There are also reports on oligonucleotide-protein interactions, including conformational fluctuations in nucleosomes,[830] translocases[831] and helicase motion on DNA.[832]

A variety of microscopic techniques have been used to study fluorescently-labelled single molecules. Systems that have been studied are quite varied, including hybridisation-detection,[833] conformation of stretched DNA,[834] the use of

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oligonucleotides as nanometer rulers,[835] electrophoretic transport[836,837] and nucleic acid dynamics.[838] Dynamics of DNA in live *E. coli* cells has also been studied.[839] Conformational studies of Holliday junctions including branch migration have been reported.[840–842] Studies of a number of protein-oligonucleotide dynamic systems are also described, including tRNA dynamics on the ribosome during translation,[843,844] and the motion of RNA polymerases on a DNA template.[845,846]

A quantum dot is a semiconductor nanostructure that confines the motion of conduction band electrons in a spatial direction due to the presence of a semiconductor interface. Quantum dots have discrete quantised energy spectra, and the material of construction defines its intrinsic energy spectrum. The larger the dot, the redder the fluorescence. Quantum dots are particularly useful for optical applications due to their theoretically high quantum yield. There are a number of emerging techniques involving the use of quantum dots with oligonucleotides. They have been used to detect mRNA[847] by fluorescent *in situ* hybridisation (FISH), to monitor the delivery of siRNA,[848] and multicolour quantum dots have been used in single-molecule detection of oligonucleotides.[849] It is reported that the use of quantum dots is more sensitive than organic fluorophores.

Quantum dots have also been used in conjunction with organic fluorophores[850,851] which results in significantly improved FRET efficiency. When in close proximity to gold surfaces, the fluorescence of quantum dots is quenched, and this may be used as an alternative biosensing method.[852,853] Oligonucleotides have been used for the construction of nanostructures conjugated to quantum dots[854] and combined with gold nanoparticles.[855]

3.6 Nanostructures and nanodevices

Over recent years there has been a rapid increase in research in nanostructures and nanodevices, and oligonucleotides have made a significant contribution in this field. This section is divided into three broad categories covering the use of nanoparticles, self-assemblies and finally examples of oligonucleotide nanodevices.

DNA nanotubes have attracted much attention, with wide ranging applications such as gene delivery vehicles, DNA sensing and DNA separations and nanoscale components. There are principally two types of DNA nanotubes, one is a programmed self-assembly DNA 'tile', the other DNA-coated nanotubes, of which the most common are carbon nanotubes. The design and characterisation of DNA nanotubes has been investigated, leading to tubes of 7–20 nm in diameter, and as long as 50 μM.[856–858] The electrical properties of DNA-wrapped carbon nanotubes have been examined.[859] DNA nanotubes have also been prepared using a porphyrin module as a four-way connector.[860] A five layer DNA nanotube prepared by successive hybridization on a diorganophosphate zirconium surface has been prepared.[861] Gold surfaces have also been used for DNA nanotube construction. These have been designed as artificial ion channels, where the bore size is determined by the size of the oligonucleotide attached to the wall,[862] and the selective permeation is controlled by hybridisation of the transportor strand.[863]

Carbon nanotubes have been widely used for functionalisation by DNA, making them compatible with aqueous environments and amenable to a broad range of applications. Nanotubes are frequently used as vehicles for delivery of genetic material. They have been used for delivery of oligonucleotides,[864] siRNA,[865] PNA,[866] aptamers[867] and plasmid DNA.[868,869]

Oligonucleotides have been used to synthesise nanowires. Using the affinity of DNA for Ag(I) ions, silver clusters are deposited on DNA, which are then photoreduced yielding silver nanowires.[870] In a similar manner, DNA has been coated with ferric oxide yielding magnetic DNA wires, which are observed using AFM,[871] and may be used in magnetic resonance imaging.[872] When oligonucleotides are coated with $Mo_{21}Ge_{79}$, the resulting DNA wires are superconducting at low temperatures.[873]

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Oligonucleotides may be used to tag or 'barcode' other biomolecules, including DNA, or may be tagged with other coding devices for characterisation. Thus genomic DNA has been barcode-tagged to analyse the diversity and sequence redundancy in genomic DNA,[874] and molecular beacons have been devised that would be suitable as tags for pharmaceutical products.[875] A method for detection of SNPs has been described in which each nucleoside is tagged with a different metal sulfide. The resulting oligonucleotide exhibits a characteristic voltammetric signature that can then be used to detect and identify mismatch sequences.[876] Dendrimer-like DNA based barcodes, which are fluorescence-intensity coded, have been used for the specific detection of pathogen DNA.[877]

By use of the pairing properties of oligonucleotides it has been possible to generate various self-assembly structures capable of adopting a pre-designed structure or network. A number of different oligonucleotide-based tiles have been generated, including DNA triangles and hexagonal tiles[878–881] and pegboard tiles.[882–884] Self-assembly arrays have also been produced using carbon nanotubes,[885,886] gold microarrays[887] and aptamers.[888]

There have been a number of new nanodevices reported which make use of oligonucleotides. AND/OR logic gates have been devised,[889,890] including one which uses the base analogue (**120**) which has been used for hole transport in DNA[741] (see Section 3.4). Two reports have appeared of a DNA device which is able to 'walk' along an oligonucleotide track, making using of short, partially complementary oligonucleotides, and single-stranded (complementary) strands along the track.[891–893] Using similar technology, a pair of DNA circles are able to continuously roll over each other as molecular gears.[894] Various DNA motors are described,[895,896] including some which are driven by enzymes,[897,898] as well as switching devices.[899,900] Finally, nanomachines are described that make use of a duplex-triplex transition,[901] and one which mimics translation by addition of DNA set strands.[902]

Aptamers (see Section 2) have also been used for the construction of nanodevices. Aptamers are able to link proteins to periodic sites of self-assembled DNA structures,[903] and DNAzymes have been coupled to carbon nanotubes.[904] A DNA-aptamer nanoswitch can be coupled to an enzymatic reaction to create a hybrid DNA-enzyme nanoengine transporting an antisense DNA molecule between two specific destinations,[905] another DNA-based machine is able to cyclically bind and release thrombin.[906] Aptamer devices are able to proof-read nanomaterial assemblies using DNAzymes to specifically locate and remove errors in DNA-templated gold nanoparticle assemblies.[907] Aptamers have also been used in DNAzyme-based logic gates,[890,908] deoxyribosensors[909] and in devices that 'walk' along an oligonucleotide track.[893]

3.7 Miscellaneous conjugates

The range of 'cargoes' conjugated to oligonucleotides is quite extensive, and will be dealt with in this final section of miscellaneous conjugates. A few new synthetic methods for the synthesis of oligonucleotide conjugates are described (see also oligonucleotide-peptide conjugates, Section 3.1) Two methods for incorporating aldehyde functions into oligonucleotides have been reported that are suitable for further chemical modification.[910,911] In addition, there is a method for preparing 3′,5′-bifunctionalised oligonucleotide conjugates by selective oxime formation.[912] A method for synthesising branched oligonucleotides makes use of a 5′-aldehyde-modified oligonucleotide that is reductively linked to a terminal amino-modified oligonucleotide.[913] Synthesis of various 5′- and 3′-conjugated oligonucleotides linked through either a phosphodiester or phosphoramidate bond has been described.[914]

Various reporter groups have been used to label oligonucleotides including biotin,[915–919] and a biotin-phenyldiazomethane conjugate which can be used for labelling phosphate groups in oligonucleotides.[920] An oligothiophene

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phosphoramidite has been synthesised as a fluorescent label,[921] and a tetraarylporphyrin which may be conjugated to a terminal 3′-aminonucleotide has been used in CD studies of DNA duplexes.[922] Flavin has also been conjugated to oligonucleotides, which allows monitoring of hybridisation by amperometric determination.[923,924] A hydrazide linker has been introduced for post-synthetic labelling of oligonucleotides.[925]

A number of papers have been published on attachment of oligonucleotides to solid surfaces (see also microarrays, Section 1.1.2). Oligonucleotides have been attached to silicon surfaces to use potentiometric detection of SNPs,[926,927] and for submicron patterning with feature sizes of 500 nm,[928] and in a further report, structures smaller than 10 nm have been patterned.[929] PCR amplification has been carried out with single DNA molecules on magnetic beads[930] and on a quartz crystal microbalance.[931] A quartz crystal microbalance has also been used to study cleavage reactions by an ATP-dependent deoxyribonuclease.[932] The interactions of DNA at a quartz/water surface have also been studied using second harmonic generation.[933] DNA bound to a microplate has been used to detect cellular mRNA,[934] and bound to a gold electrode to study the redox activity of DNA repair glycosylases.[935]

A number of sugar and carbohydrate analogues have been conjugated to oligonucleotides. Sucrose has been conjugated to the 3′- and/or 5′-end of DNA as a phosphoramidite derivative.[936] The presence of the carbohydrate increased the chemical and enzymatic stability of the oligonucleotides without perturbing the stability of duplexes or quadruplexes. By using an orthogonally-protected linker, DNA bearing three different sugars could be synthesised.[937,938] In order to aid intracellular delivery of siRNA, lactosylated-PEG-RNA has been prepared,[939] and a glycolipid conjugate was used to transfer DNA across a phospholipid membrane.[940] A polysaccharide carrier has been used to deliver CpG oligonucleotides for enhanced cytokine secretion.[941] The aminoglycoside antibiotics daunomycin and doxorubicin have been conjugated to DNA. Daunomycin-DNA conjugates were used as TFOs targeting the polypurine tract of HIV-1,[942] whilst doxorubicin was used to aid stabilisation of an antisense oligonucleotide to assay for multidrug resistance in a human carcinoma cell line.[943]

Cholesterol and lithocholic acid have been conjugated to oligonucleotides to enhance cellular delivery for improved antisense effects,[944,945] and lithocholic acid conjugation has also been used to enhance uptake of siRNA.[946] Other lipid conjugates that have been used to aid transport across phospholipid bilayers include cholic and deoxycholic acids,[947] oleylamine,[948] PEG,[949–951] polyamide,[952] ethylene glycol[953–955] and dienes.[956–958] In addition to lipids, polyamidoamine (PAMAM) will direct delivery of DNA to cancer cells,[959] and a DNA-HEG-DNA construct is shown to increase the efficiency of triplex formation.[960]

Another application of polymer-conjugated oligonucleotides is for detection. Polyphenylethynylene-conjugates may be used for fluorescence detection of DNA,[961] and PEG[962] and norbornene[963] conjugates for electrochemical detection of DNA. Block copolymers have also been used for DNA detection on microarrays.[964] Polymethyl methacrylate polymers enable printing of DNA features with a 40nm resolution, with coverage up to 100 μm^2.[965]

Aromatic molecules are frequently conjugated to oligonucleotides for applications such as cleavage, crosslinking and structure stabilisation. Conjugation to the 5′-end of an oligonucleotide by 2-methyl-1,4-naphthoquinone leads to selective oxidation of 5-methylcytosine to 5-formylcytosine, which leads to strand cleavage.[966] The *bis*-imidazole (**126**) conjugated at the 5′-terminus of an oligodeoxyribonucleotide targeted towards tRNA effects site-specific cleavage at a CA site under physiological conditions.[967] Psoralen is frequently used to promote crosslinking in oligonucleotides, and three reports describe the use of psoralen attached to TFOs to effect DNA crosslinks.[968–970]

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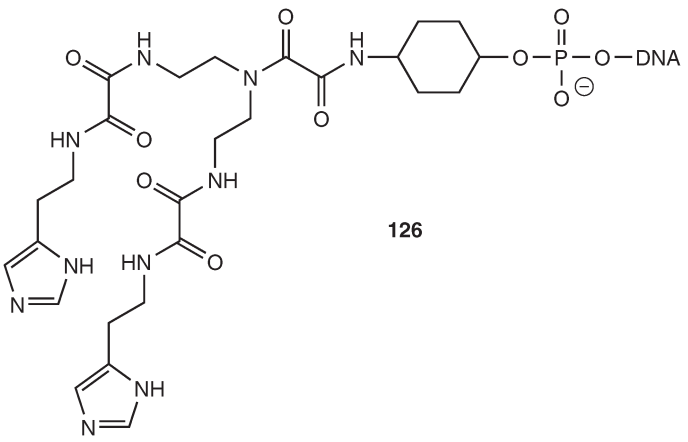

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The remaining aromatic conjugates were used to stabilise oligonucleotide structures. Perylenediimide-linkers with DNA tails undergo self-assembly in lipid environments.[971] Duplex DNA may be stabilised by chromone,[972] aminonaphthalene[973] and acridine.[974] Pyrrolobenzodiazepine,[975] etoposide analogues[976] and camptothecin[977] have each been used for the stabilisation of triplexes. Stilbene dicarboxamide has been used to replace the loop structure of TAR RNA to study the effects of binding with Tat peptide.[978]

4. Nucleic acid structures

Nucleic acid structures are another area that has seen significant expansion. Not only are there more structures being solved either by X-ray crystallography or by NMR, but there are now many new techniques that are being explored to aid structure determination, in particular of larger and more complex nucleic acids.

4.1 Crystal structures

Amongst the many crystal structures reported, there are a number involving either protein-nucleic acid or macromolecular RNA structures that are too complex to discuss in detail in this review, but are noted for completeness of this review. These include nucleic acid structures complexes with DNA polymerases,[979–985] RNA polymerases,[986–988] HIV-1 reverse transcriptase,[989] transcription factors,[990–993] ribonucleases,[994–998] endonucleases,[999] methyl transferases and[1000,1001] repair enzymes.[1002–1006]

There are nucleic acid structures with human DNA ligase I,[1007] λ integrase,[1008,1009] Ro autoantigen,[1010] a resolvase,[1011] a topoisomerase,[1012] an ATPase,[1013] the mRNA elongation factor SeIB,[1014] a nuclear effector,[1015] the thymidylate kinase from *M. tuberculosis*,[1016] the partition factor ParB[1017] and a poxvirus protein bound to Z-DNA.[1018] In addition, there are a few RNA structures including tRNA,[1019,1020] tRNA synthetases,[1021,1022] siRNA,[1023,1024] a riboswitch,[1025] a group I ribozyme from phage Twort,[1026] ribosomal RNA[1027–1034] and nucleosome structures.[1035,1036]

There have been a few oligonucleotide crystal structures reported. The oligonucleotide d(GGACAGATGGGAG) self-assemblies into a 3-D lattice structure through base pairing and stacking interactions. The structure of this DNA lattice has been solved at 2.1 Å, which consists of stacked parallel helices, with adjacent layers linked through the parallel-stranded base pairing.[1037] The oligonucleotide d(ATATATATATAT) forms duplexes with single-stranded overhangs which can associate with neighbouring molecules. The outcome is a rigid coiled-coil structure.[1038] Crystal structures of duplexes containing extended A-tracts differ from those containing shorter ones. Extended A-tracts show disordered hydration

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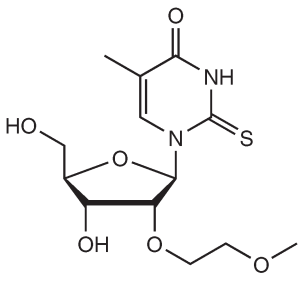
patterns, as well as bifurcated hydrogen bonding between bases that are not base-paired.[1039] Two crystal structures have been reported involving Z-DNA structures. The duplex d(CGCGCA)·d(TGCGCG) adopts a Z-DNA structure in the presence of cobalt hexamine, which also results in the adenine base forming a base pair in its imino tautomer.[1040] When B-DNA turns into Z-DNA, two B–Z junctions are formed. A crystal structure of a 15-mer duplex containing a B–Z junction reveals that continuous base stacking occurs throughout the duplex except at the junction where the bases are extruded.[1041]

A crystal structure of I–C and I–A wobble base pairs in the ribosomal decoding centre revealed that the I–A base pair adopts the conformation predicted by Francis Crick, *viz* an I_{anti}–A_{anti} wobble pair.[1042] Riboswitches are genetic regulatory elements located in the 5′-untranslated regions of mRNA. Many genes involved in purine metabolism contain a guanine-responsive riboswitch which binds guanine or guanine analogues to terminate transcription. The crystal structure of the guanine riboswitch from *B. subtilis* has been reported bound to hypoxanthine.[1043] Hypoxanthine acts to stabilise the structure and promotes the formation of a downstream transcriptional termination factor. A crystal structure of a luteoviral RNA pseudoknot has been reported to aid the understanding of structural elements of RNA psuedoknots.[1044] The structure defines a minimal 22 nucleotide motif which is capable of stimulating −1 type ribosomal frameshifting. The final RNA structure is also a pseudoknot but is derived from a ribozyme evolved to catalyse carbon–carbon bond formation by a Diels-Alder reaction.[1045] The pseudoknot has a hydrophobic pocket which is complementary to the shape of the reaction product.

There are very few X-ray crystal structures involving analogues. The crystal structure of the Dickerson-Drew dodecamer, where the thymidines are replaced by C5-propylamino-dU, has been studied to determine the effect of tethered cations in the major groove.[1046] Only one of the cationic groups, displaced towards the 3′-end of the duplex, showed any effect on duplex structure, resulting in displacement of the backbone. The binding of the self-complementary duplex $d(CGATCG)_2$ complexed by the disaccharide anthracyclin MAR70 was in the minor groove of the structure, as has been observed with other anthracyclin analogues.[1047] The sequence $d(CCXGTA^{5-Me}CGG)$ will adopt a four-stranded DNA Holliday junction when X is inosine, but when X is diaminopurine it adopts a regular duplex.[1048] RNA duplexes containing 2′-aminocytidine still form A-form duplexes, though there is a strong interaction between the protonated amine and the 3′-phosphodiester.[1049] The substitution of uridine by the 2′-*O*-[2-(methoxy)ethyl]-2-thiothymidine analogue (**127**) was shown to be more stable due to enhanced base overlap and a van der Waals interaction between adjacent (**127**) substitutions.[1050] A hybrid duplex between RNA and hexitol nucleic acid (HNA), (**30**), shows a modified A-form duplex with four duplexes in the asymmetric unit. It exhibits extensive backbone hydration which may account for the enhanced stability of the duplex.[1051] The X-ray structure of a PNA decamer self-complementary duplex exhibits a right- and a left-handed helix, allowing the formation of a $(PNA)_3$ triplex structure.[1052]



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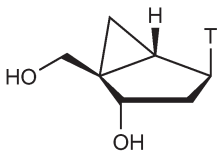
4.2 Solution structures

A number of solution structures have been reported during this review period, many containing modified nucleoside analogues. One DNA duplex structure demonstrates that by measuring imino proton resonances, the binding of uracil DNA glycosylase (UDG) to a T–A base pair increases the equilibrium constant for opening of the base pair by two orders of magnitude.[1053] Four i-motif structures have been solved.[1054–1056] Amongst native DNA structures, most deal with quadruplex structures. An aptamer which inhibits HIV-1 integrase has been shown to exist as a dimeric parallel-stranded quadruplex,[540] as does a G-quadruplex element in the human c-*MYC* promoter.[1057] The latter structure also forms a propeller-type parallel-stranded quadruplex in the presence of K^+ ions.[1058] A telomeric sequence containing three G-quartets forms an asymmetric sequence, which the authors claim is a novel folding topology.[1059] The solution structure of the K50 class homeodomain Pituitary homeobox protein 2 to its consensus DNA site (TAATCC) has also been reported.[1060]

A telomeric sequence has been reported that adopts different structures in solid and solution phase.[1061] The authors claim that biochemical data are inconsistent with the crystal structure. Quadruplex structures are derived from four nucleotides (usually G) forming quartet structures. It has been reported that an oligonucleotide containing the sequence TGGGGT forms a hexad structure resulting from an alignment of two GTG triads.[1062] The cation-binding forms of the quadruplex structure d($G_3T_4G_4$) have been examined where it was found that the structure could adopt mixed cation forms.[1063] Na^+ ions could be readily displaced by NH_4^+ ions, though NH_4^+ ions could not displace K^+. The effect of substituting dG for 8-methyl-dG into quadruplex structures has been examined. The presence of the analogue affected the tetrad in which it was involved by adopting a *syn* conformation, though it was found that it was sequence-dependent.[1064] Using a quadruplex structure from human c-*MYC*, the interaction of porphyrin within the quadruplex has been examined as a model for anti-cancer drug design.[1065]

There has been a number of nucleoside analogues incorporated into oligodeoxynucleotides. A triplex structure, in which the third strand is composed of alternating LNA (see **32**) and DNA binds in the major groove through Hoogsteen base pairing.[1066] As a result, the duplex conformation is altered into a structure intermediate between A and B form. Incorporation of the locked nucleoside (**128**), which is constrained into the C2′-*exo* conformation, was found to cause bending of 5° per substitution towards the major groove of the duplex.[1067] A carbocyclic abasic site has been used as a chemically stable analogue to study the impact of abasic sites in duplex DNA.[469] The incorporation of the 2′-azaquinolone nucleoside (**129**) into a duplex was found to cause disruption of the A–U pair as the quinolone intercalated into the duplex, stacking on the neighbouring G–C pair.[1068] An N^3-dT-ethyl-N^3dT interstrand crosslink in a DNA duplex has been reported, and the ethyl crosslink is shown to be accommodated between the minor and major grooves.[263] A stilbene endcap on a DNA duplex was used to determine the extent of π-stacking on the termini.[1069]



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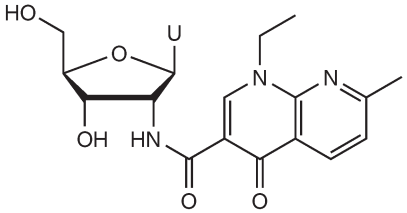

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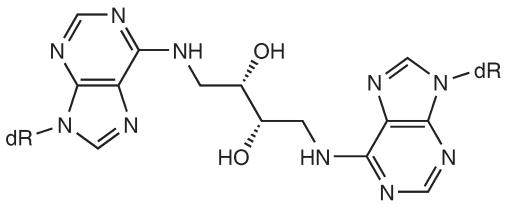
The structure of an oxaliplatin GG intrastrand crosslink has been solved, and the structure found to differ from those formed between AG.[1070] The GG intrastrand crosslink was found to exhibit much less distortion than AG crosslinks, and the duplex also exhibited a much narrower minor groove to accommodate the bend in the structure. A further crosslinked duplex structure (**130**) derived from butadiene diepoxide was found to reside in the major groove, with a break in Watson-Crick base pairing on the 5′-side of the crosslink, but with intact base pairing on the 3′-side.[1071] The platinum-acridine guanine adduct (**131**) arising from antitumor agents was found to bind in the major groove of the duplex with little perturbation of the neighbouring residues.[1072] However, the duplex structure adopted a structure intermediate between A and B forms. The butadiene oxide-derived guanine N7 adduct (**132**), however, adopted a high *syn* conformation within the duplex and no base pairing with the complementary base.[1073]



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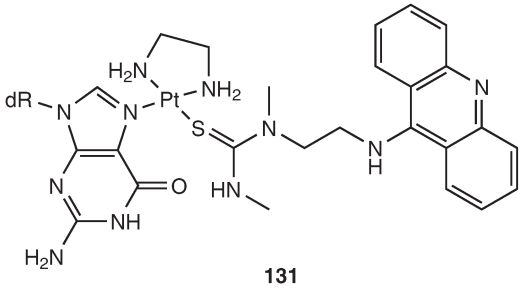

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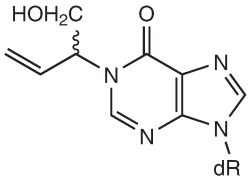

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The remaining structures all involve binding of aromatic species to a DNA duplex. The mechanism by which symmetrical cyanine dyes dimerise in the minor groove has been examined by NMR, where it was shown that a GC base pair is implicated in the dimerisation process.[1074] The quadruplex structure $d(TAGGGTTA)_4$, complexed with a quinobenzoxazine, revealed that the quinobenzoxazine is stacked onto the G-quartet.[1075] The structure of a threading intercalator based on a naphthalene diimide showed that the naphthalene diimide units intercalate into the duplex with the linkers alternating in the minor groove of the duplex.[1076]

RNA structures that have been examined are more diverse, and are frequently segments of larger RNA structures, such as ribozymes and tRNA. The stem-loop structures from the Varkud satellite (VS) ribozyme have been reported,[1077,1078] and structural work on the $tRNA^{Val}$ has been described.[1079] Various other structures have also been reported, including the stem-loop D RNA domain within entero-viruses and rhinoviruses,[1080] the U6 RNA stem-loop,[1081,1082] the HIV-1 frameshift inducing element,[1083] the GAAA tetraloop-receptor RNA complex,[1084] an RNA aptamer against mammalian initiation factor 4A[1085] and *E. coli* ribosomes.[1086]

A key difference between RNA and DNA structures is that RNA is able to form many other Watson-Crick base pairs. A solution structure of an internal loop contains three consecutive sheared GA pairs, which are pre-organised for ligand

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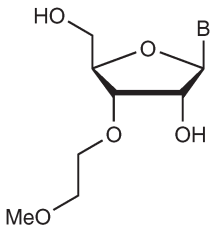
binding.[1087] The antisense RNA to antirepressor mRNA in bacteriophage P22 has a stable triplet of uracil–uracil base pairs in its stem-loop structure.[1088] There are many reports of Z-form DNA, but until recently there have been no examples in RNA. A structure for the duplex $(CGCGCG)_2$ in 6M $NaClO_4$ has been reported, which shows that the RNA adopts a left-handed helical structure.[1089] The structure shows no interstrand stacking, common in Z-DNA, and both major and minor grooves are well defined.

A solution structure of an RNA dodecamer in which all cytidines and uridines are substituted for their respective 3′-*O*-(2-methoxyethyl) (3′-MOE) (**133**) derivatives revealed that the oligomer could adopt both a hairpin and a duplex structure.[1090] The hairpin structure exhibited an unusually stable loop structure maintained by Watson-Crick base pairing. The solution structure of the ψ_{32}-modified anticodon stem-loop of *E. coli* $tRNA^{Phe}$ demonstrated that the pseudouridine maintains the integrity of the stem structure.[1091]



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The binding of a cyclic peptidomimetic of Tat protein to TAR RNA revealed that the cyclic peptide adopted a β-hairpin, but bound to TAR in the opposite orientation to that found for linear Tat peptides.[1092] Tat peptide binding to TAR has also been examined in the solid state using ^{31}P-^{19}F REDOR NMR.[1093] Structures have also been reported for the binding of polypyrimidine tract binding protein (PTB) to a CUCUCU oligonucleotide,[1094] and a trypanosome cytoplasmic RNA-binding protein (TcUBP1) to U-rich RNA.[1095]

Various groups have examined metal binding sites in RNA structures. Solution structures of two RNA hairpins have been examined to determine the position of the metal binding site.[1096] Using cobalt hexamine as a mimic for magnesium it was found that the metal binds in the major groove adjacent to a bulge loop. A study of the chemical perturbation revealed the position of binding of Mg(II) ions in the U6 RNA stem-loop,[1097] the L7/L12 stalk of the *E. coli* 50S subunit[1098] and a conserved RNA motif of picornavirus IRES element.[1099] The binding of Mg(II) ions at the pro-*R*p oxygen in a hammerhead ribozyme using phosphorothioate substitutions has also been reported.[1100]

4.3 Other structural methods

Oligonucleotide structures have primarily been studied by X-ray crystallography and NMR spectroscopy. However, recently new techniques have emerged or been adapted to study macromolecules. These techniques tend to reveal global structures of macromolecules rather than atomic structures, but have been used for a number of applications. Amongst the new developments in this field are the uses of surface plasmon resonance spectroscopy (SPR) and atomic force microscopy (AFM).

Surface plasmons are surface electromagnetic waves that propagate parallel along a metal/dielectric interface. For surface plasmons to exist, the complex dielectric constants of the two media must be of opposite sign. This condition is met in the IR-visible wavelength region for air/metal and water/metal interfaces. Typical metals that support surface plasmons are silver and gold. Surface plasmons have been used to enhance the surface sensitivity of several spectroscopic measurements including fluorescence and Raman scattering. SPR reflectivity measurements can be used to

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detect DNA or proteins by the changes in the local index of refraction upon adsorption of the target molecule to the metal surface.

Surface plasmon field-enhanced fluorescence spectroscopy (SPFS) was used for real-time *in situ* analysis of surface hybridisation of PCR products[1101] and primer extension reactions[1102] with sensitivities of 100 fmol and 500 fmol for PNA and DNA probes respectively. In primer extension reactions,[1102] binding and catalytic constants were also measured. The folding and unfolding rates of a human G-quadruplex telomeric sequence,[1103] and G-quadruplex conversion to duplex regulated by the human *c-myc* promoter[1104] were also measured using SPR. Drug kinetic interactions with DNA[1105] and RNA[1106,1107] have similarly been determined using SPR.

The atomic force microscope (AFM) (also known as scanning force microscope) is a high-resolution scanning probe microscope. It consists of a cantilever (probe) with a sharp tip, with a radius of curvature of the order of nanometers, which is used to scan the surface of the sample. When the tip is brought into proximity of a surface, the Van der Waals force between the tip and the sample leads to a deflection of the cantilever. The deflection is measured using a laser reflected from the top of the cantilever. AFM has several advantages over the scanning electron microscope (SEM). The AFM can produce images of materials down to 1 nm, whilst SEM is limited to around 100 nm; electron microscopy provides a two-dimensional image, whilst AFM provides a three-dimensional surface profile; samples do not require any special treatments that would alter or damage the sample with AFM; AFM can be used in air or a liquid environment, and thus it is possible to study biological macromolecules and living organisms.

After X-ray crystallography and NMR spectroscopy, AFM has been the next most widely used technique to study macromolecular systems. It has been used to visualise structures,[1108–1116] translocation,[1117] bending[1118,1119] and to measure binding constants.[1120–1126]

Electron microscopy is another method that has been used to examine macromolecular structures. It has been used to visualise single-molecule reconstructions of an archaeal clamp loader DNA complex at 12 Å resolution.[1127] Cryo-electron microscopy has been used to obtain structural data for a translation initiation complex from *E. coli*,[1128] viral internal ribosome entry site (IRES) bound to human ribosomes,[1129] the scaffold protein RACK1 on the 80S ribosome[1130] and an *E. coli* protein-conducting channel bound to a translating ribosome.[1131] Crystals of RuvA-DNA complexes have also been examined using tunnelling electron microscopy,[1132] and single nucleotide polymorphisms have been detected using scanning tunnelling microscopy.[666]

In addition to the above spectroscopic methods there are a number of other techniques that have been described. X-ray scattering has been used to examine how the ion atmosphere modulates interactions between duplexes in the absence of metal ion-binding sites.[1133] Neutron diffraction techniques have been applied to determine nucleic acid structures in solution.[1134,1135] X-ray photoelectron spectroscopy (XPS) has been used to determine the binding of metal ions on monolayers of ssDNA[1136] and the study of immobilisation of DNA to solid supports.[1137] UV photoelectron spectroscopy (PES) has been used to study multiply negatively charged DNA[1138] and the ionisation of guanine in oligonucleotides.[1139]

Using picosecond time-resolved infrared spectroscopy (ps-FTIR) the structural dynamics of UV-excited oligonucleotides in solution has been studied.[1140] Conformational changes within oligonucleotides can be studied using Raman spectroscopy. The B-to-A transition upon binding of protein of DNA,[1141] binding of Arc repressor to DNA[1142] and conformational changes on intercalation of ethidium into DNA[1143] have all been reported using Raman spectroscopy. Using UV thermal melting experiments, the global structure of oligonucleotides may be determined from its thermal difference spectrum.[1144] Finally, near-field microwave imaging has been used as a label-free method for detection of low surface coverage of DNA on solid surfaces.[1145]

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