# 1,10-Phenanthroline: A Versatile Ligand

**Peter G. Sammes and Gokhan Yahioglu**
*Molecular Probes Unit, Department of Chemistry, Brunel University, Uxbridge, Middlesex UB8 3PH, U.K.*

## 1 Introduction

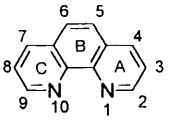
1,10-Phenanthroline (1) is the parent of an important class of chelating agents. Compared to the more common 2,2'-dipyridyl system (2), 1,10-phenanthroline has several distinct properties: the rigid structure imposed by the central ring B means that the two nitrogen atoms are always held in juxtaposition, whereas, in (2), free rotation about the linking bond allows the two nitrogens to separate (2a ⇌ 2b), in particular under basic or strongly acidic conditions. This entropic advantage for 1,10-phenanthroline means that complexes with metal ions can form more rapidly, a property of importance, for example, in the formation of cooperative complexes with lanthanide ions.[1] Another consequence of the planar nature of 1,10-phenanthroline is its ability to participate as either an intercalating or groove-binding species with DNA and RNA. One other important property of the phenanthroline nucleus is its ability to act as a triplet-state photosensitizer, especially in complexes with lanthanides such as europium.

The metal chelating properties of 1,10-phenanthroline have been utilized in a range of analytical reagents and probes as well as herbicides. Since the seminal review of Summers[2] in 1978, several natural products incorporating this heterocyclic nucleus have now been isolated, several of which possess interesting anticancer properties.[3] In the last decade the phenanthroline group has also been exploited by workers interested in molecular recognition and self-assembling systems.[4]

This review covers some of the recent chemistry of 1,10-phenanthroline and its derivatives and their use as chelating agents for the development of bioorganic reagents and probes.

## 2 Synthetic Studies

The enormous interest in molecular recognition processes and the increased use of 1,10-phenanthrolines in this area has renewed interest in the synthetic manipulation of these systems. 2,9-Dimethyl-1,10-phenanthroline (3) ('neocuproine') has been converted into a range of oxidized derivatives (Scheme 1). Selenium dioxide affords the dialdehyde (4), that can either be oxidized to the diacid (5) or reduced to the diol (6). Formation of the bisoxime from the dialdehyde and dehydration affords the dinitrile and, by reduction, the diamine (7). The diol (6) can be converted into its dibromide with HBr and this has been aminated to give a range of chelating agents.




(1)


(2a) (2b)

A useful alternative route to the diacid (5) is available by initial perchlorination of neocuproine with *N*-chlorosuccinimide, followed by acid hydrolysis.[5]

Methyl groups at positions 2, 4, 7, and 9 on 1,10-phenanthrolines can be lithiated with lithium diisopropylamide and then alkylated;[6] the 3,8-dimethyl groups are resistant to such lithiation.

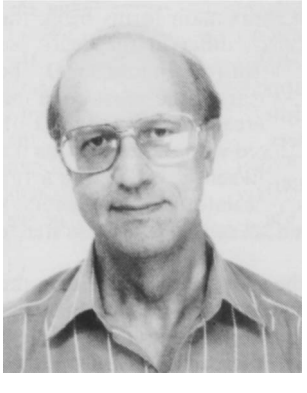
1,10-Phenanthroline (1) can be oxidized to the mono-*N*-oxide (8), steric constraints precluding formation of the bis-*N*-oxide. The *N*-oxide reacts with benzoyl chloride and potassium cyanide to give the nitrile and, by hydrolysis, the monocarboxylic acid (9).[3] The nitrile hydrolysis is strongly assisted by metal ions such as $Cu^{2+}$ and $Ni^{2+}$, possibly by initial chelation and intramolecular delivery of hydroxide ions from the metal.[7]

In 1,10-phenanthroline, the 5,6-double bond is most susceptible to electrophilic attack and even epoxides can be formed from it.[8] Nitration of either the parent (1) or neocuproine (3) leads to the 5-nitro-derivatives, *e.g.* (10) generally accompanied by some of the 5,6-dione (11), and the ratio of the two products can be partly controlled by careful choice of conditions.[2] Reduction of the nitro-group to the amine is best achieved by a catalytic transfer hydrogenation.

The recent reaction to convert $\alpha\beta$-unsaturated nitro-compounds into pyrroles can be applied to the nitro-phenanthrolines to give products of the type (12).[9]

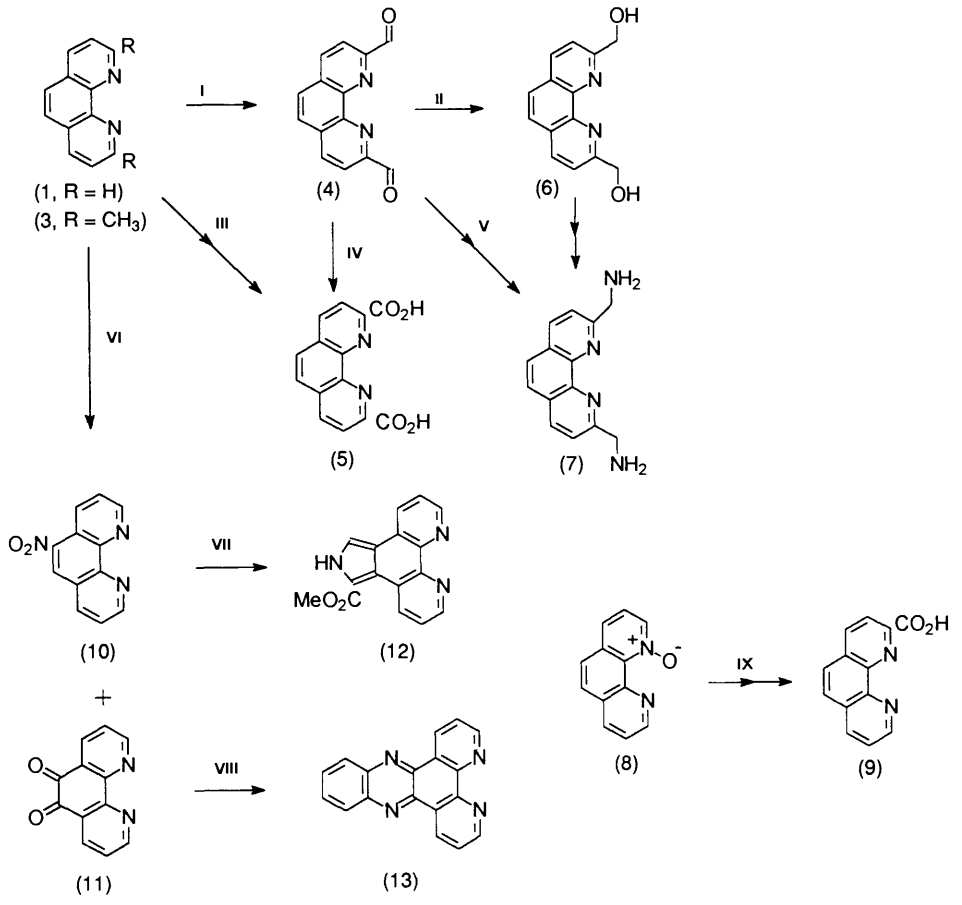
The dione is also of importance since condensation with 1,2-diamines produce the pyrazines, *e.g.* 1,2-diaminobenzene produces the chelating compound (13) (DPPZ), which acts as a solvent-sensitive ligand when chelated to ruthenium (see below).[10]

The introduction of aryl groups into positions 2 and 9 may be achieved by adding lithium aryls. Thus Sauvage treated phe-



*Peter Sammes was trained at Imperial College. He held chairs in Organic Chemistry at City University, London and the University of Leeds before joining Brunel University in 1989. He spent several years in industry, first with Glaxo as a Junior Laboratory Assistant before he entered academia and, more recently, as a research Vice President at SmithKline and French. His current research work is focused on a variety of molecular probes. He has published over 200 research papers.*

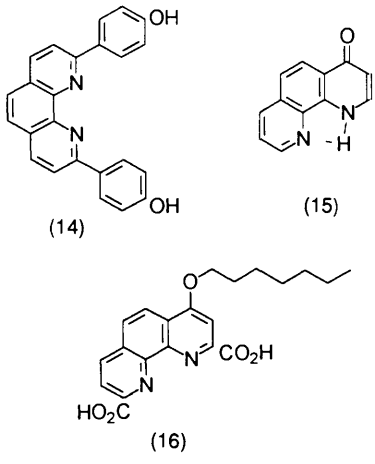
*Gokhan Yahioglu was born in Cyprus, grew up in Turkey, and moved to London in 1972. He obtained his B.Sc. from Brunel University, and after a period in industry, he returned to Brunel University to study for a Ph.D. on new DNA assays with Professor P.G. Sammes. He is currently a post-doctoral fellow at Brunel working on discotic liquid crystals with Dr L.R. Milgrom.*



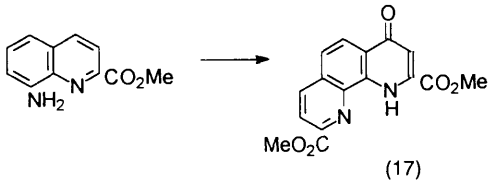
Scheme 1

nanthroline with lithiated 4-bromoanisole, followed by $MnO_2$ oxidation of the intermediate to give the diarylated phenanthroline [11] Removal of the methyl protecting groups, by heating the product with pyridinium hydrochloride at 200 °C gave the phenol (14) in high yield

Placement of functional groups at other positions on the phenanthroline skeleton is best achieved by ring synthesis, most approaches using the Skraup reaction starting with an 8-aminoquinoline Thus a Conrad–Limpach reaction of ethyl acetoacetate with 8-aminoquinoline leads to the 4-hydroxyphenanthroline, existing mainly as its pyridone tautomer (15),



although O-alkylation may be readily effected Chandler and colleagues have used this method to generate the potentiometric sensors such as (16),[12] oxidation of the methyl groups was effected by use of selenium dioxide followed by sodium chlorite oxidation to the acid, using isobutene as a chlorine scavenger In some of our studies, the diester (17) was produced by heating 8-amino-2-methoxycarbonylquinoline with dimethyl acetylenedicarboxylate followed by thermolysis in diphenyl ether



## 3 Intercalating Properties of 1,10-Phenanthroline Derivatives

Intercalation of planar heteroaromatics between stacked duplex bases in DNA and RNA was first recognized by Lerman in 1961 The phenomenon of intercalation depends on the type of double stranded DNA (ds-DNA) under examination ds-DNA commonly adopts several motifs, the three main forms being the right-handed A- and B-forms, which differ in the degree of hydration, and the left-handed Z-form (see Figure 1) Of the right-handed forms the B-motif appears to be most common under normal saline conditions Intercalation can occur with either A- or B-DNA but is not observed with the Z-form, as the base pairs are not aligned in a sufficiently ordered stacked manner to allow the insertion of intercalators without a distortion of the chain, intercalators often act on Z-DNA to isomerize it into the B-form [13]

Binding of agents into one of the grooves running down the ds-DNA helices can often compete with intercalation, many heteroaromatic compounds can form tight complexes, particularly in the minor grooves, without intercalating, whilst others can either intercalate or groove bind as two *competing* processes

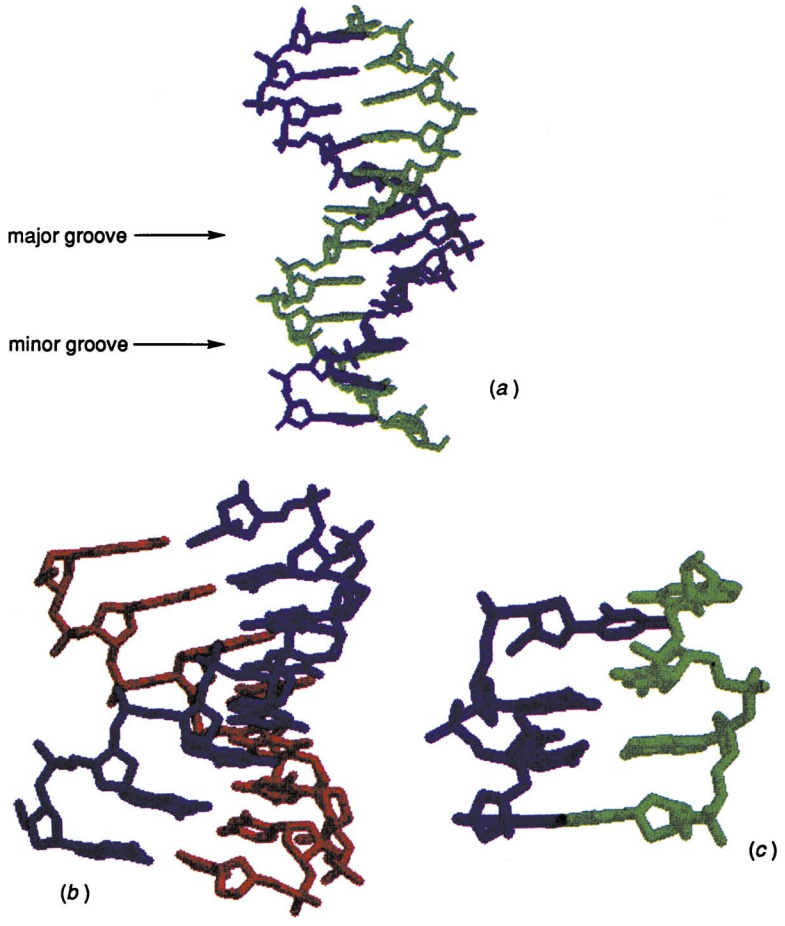
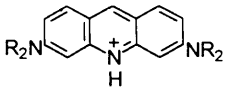
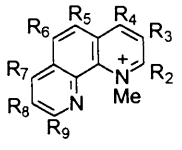



**Figure 1** (a) A-DNA; (b) B-DNA; (c) Z-DNA (left-handed). Note the relative order and vertical alignment of the base pairs in the right-handed A and B forms as compared to that in Z-DNA.

Intercalation leads to unwinding of the DNA helix and tests have been developed to distinguish between intercalation and groove-binding. Substituents on the heteroaromatic framework can either enhance or hinder intercalation. Thus proflavine (18) is a strong intercalator whereas its tetramethyl derivative (19) is not,[12] acting as only a groove binder. Positively charged species also bind more strongly by electrostatic interactions with the bridging phosphate groups.




(18, R = H)
(19, R = Me)




(20)

A detailed study has been made on a series of substituted *N*-methyl-1,10-phenanthrolinium salts (20), which showed that although methyl substituents did not totally prevent intercalation into the right-handed B-form of DNA, some modifications in the selectivity for the ten identified intercalating sites was observed (Figure 2). Steric interference between A–T pairs favours binding between G–C sequences.[14] The tetramethyl derivative (20; $R_2 = R_5 = R_6 = R_9 = Me$) was the most strongly bound and gave the greatest increase in viscosity (unwinding) of the helix, attributed to intercalating. In contrast the diphenyl derivative (20; $R_4 = R_7 = Ph$) showed only a relatively weak binding, a result in contrast to that of the corresponding metal chelates (see below).

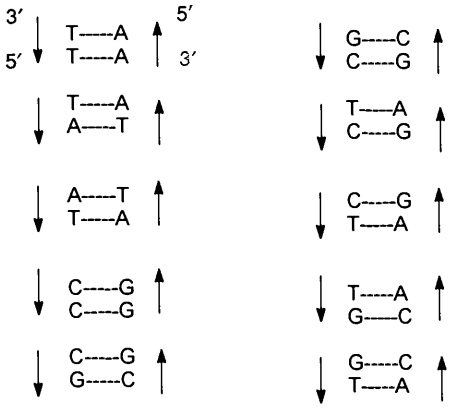



**Figure 2** Possible intercalation sites.

Replacement of the *N*-methyl group by a coordinated metal ion can also produce intercalators and a range of metals have been utilized including ruthenium, rhodium, cobalt, and copper. The trisphenanthroline complexes of $Ru^{II}$, for example (21), are coordinatively saturated, stable complexes inert to substitution but, because of their positive charge, they are generally soluble in water. They possess a very rigid structure, existing as racemates which may be resolved into the right handed $\Delta$- and left-handed $\Lambda$-isomers (see Figure 3), which allow enantioselective studies on DNA. The complexes are luminescent, showing a strong metal-to-ligand charge-transfer excited state, which is perturbed by changes in the local environment. Intercalation usually leads to an enhancement in luminescence and an increased lifetime (from

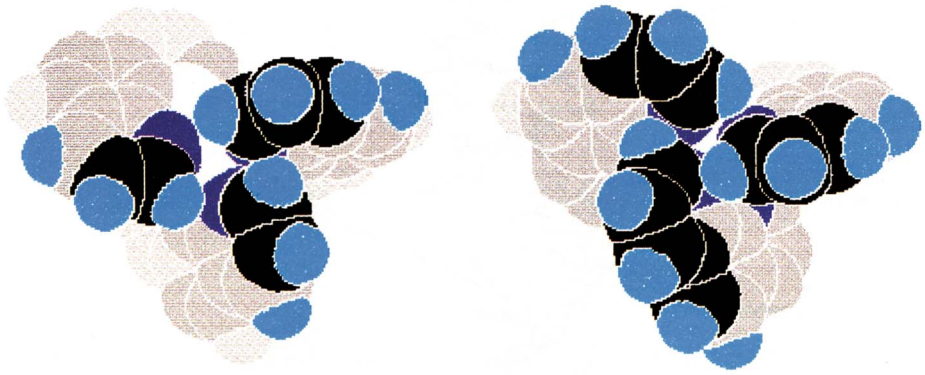
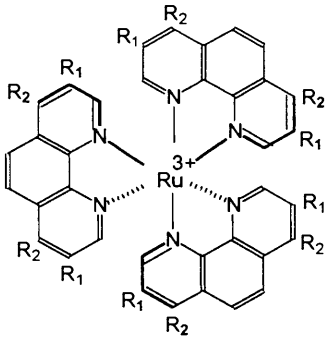
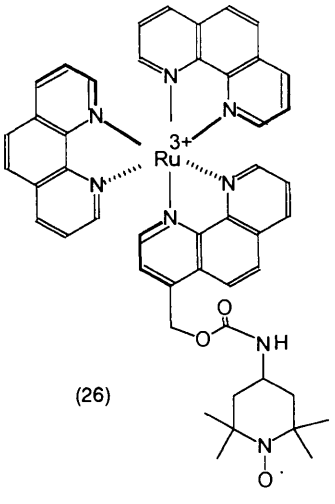



**Figure 3** Representation of the twisted forms of tris-phenanthroline metal complexes. (a) the right-handed $\Delta$ form; (b) the left-handed $\Lambda$ form



(21) $R_1 = R_2 = H$ [Ru(phe)$_3$]
(22) $R_1 = R_2 = Me$
(23) $R_1 = R_2 = Ph$ [Ru(dip)$_3$]
(24) As 23 but Co III complex
(25) As 23 but Rh III complex

0.6$\mu$s to > 5$\mu$s). At least two modes of non-covalent binding to DNA have been shown to exist[15] – external binding (such as groove binding) and intercalation, modes that have been confirmed by using nitroxide labelled probes of the type (26) employing ESR spectroscopic studies.[16] Binding is enantioselective; intercalation into B-DNA (right-handed duplex) is favoured by the $\Delta$-isomer from the major groove. Models

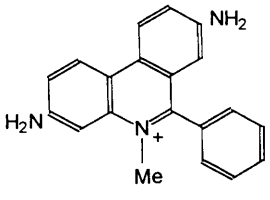


(26)

indicate that this binding is consistent with the complementary shapes of the helix and the complex. External binding occurs with the $\Lambda$-isomer and NMR studies indicate that this occurs in the minor groove.[14] The discrimination is high enough to enable the use of B-DNA as a resolving agent for the enantiomers!

By using variants on (21), these 'shape-selective' binding studies have been extended to other forms of DNA. Thus the $\Lambda$-isomer of the methylated derivative (22) binds more tightly than the $\Delta$-enantiomer to A-form nucleic acid duplexes; in this case binding is in the major groove with the left-handed form being *against* the right-handed DNA helix and does *not* involve intercalation.[17]

The diphenyl derivative (23), [RuDip$_3$], behaves in a similar fashion to (21) towards B-DNA, showing an even greater discrimination ('shape selectivity') between isomers, the $\Delta$-isomer showing some intercalation involving the pendant phenyl groups whereas steric buttressing of the phenyl groups of the $\Lambda$-enantiomer prevents any binding. In contrast to the Ru (phe)$_3$ isomers, the Ru (Dip)$_3$ isomers both bind equally to the left-handed Z-DNA but the $\Lambda$-isomer shows hypochromicity on binding, suggesting a test for the Z-conformation.[18] Model studies on poly-dGC duplexes were informative since this duplex can be made to exist either in the B-conformation or the Z-form by changing the buffer conditions. Whereas ethidium (27) acts mainly as an intercalator, preferably from the minor groove, and, upon interaction with the DNA, changes the conformation of the Z- to the B-form, none of the isomers of (21) and (23) cause this interconversion; for the B-form the $\Delta$-enantiomers bind more strongly whereas for the Z-form both isomers bind. The difference in behaviour with these complexes compared to ethidium was explained by assuming shape-selective binding into the major groove of these isomeric helices is the strongest interaction.[19]



(27)

A detailed study using the analogous $\Lambda$-isomer of the Co$^{III}$ complex (24), which can act as a DNA nicking agent on binding (see below), was used as a study on the Z-binding regions of two plasmids. An analysis of the regions that were specifically nicked

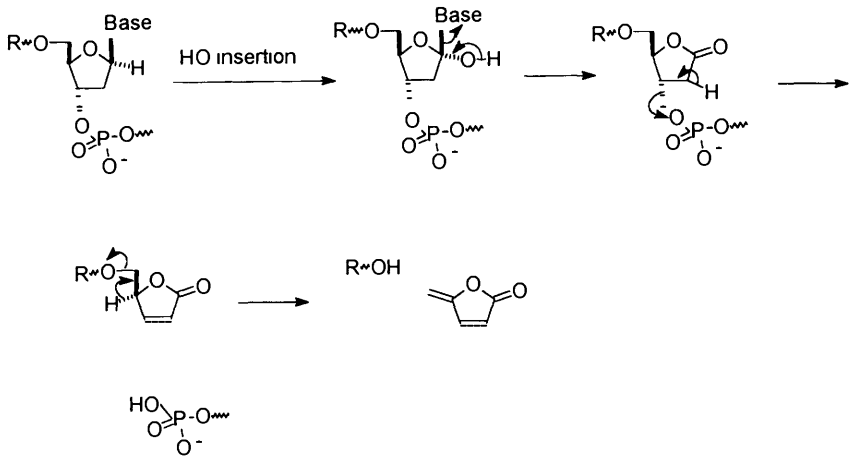
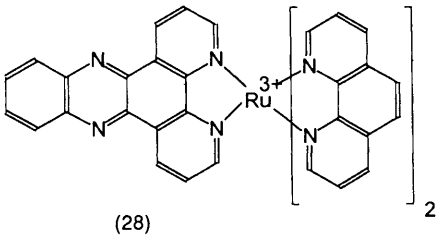



**Figure 4** OH insertion mechanism for DNA nicking process

by this reagent led to the suggestion that the Z-regions served as a genetic punctuation mark, used to describe the ends of transcription regions of genes[120] Shape-selective interactions with these phenanthroline complexes have also been used to study the nature of the folds in t-RNA$^{phe}$ [21]




(28)

The phenanthroline derivative (28) shows interesting photophysical properties [22] In aqueous solution the ruthenium complex shows no emission upon irradiation, whereas in non-aqueous systems it shows intense luminescence properties This change is explained by the formation of a metal-to-ligand charge-transfer system in the excited state, the increased electron density in the dipyridophenazine system has the effect of turning the excited-state pyrazine nitrogens into strongly basic groups that, in water, abstract a proton from the solvent to form the protonated, ground-state species, relaxing to the starting material in the process In aprotic solvents this protonation pathway is precluded and the charge-transfer state is in equilibrium with the excited metal species that then collapses to the ground state with emission of a photon

This enviromental sensitivity has been elegantly exploited in studying intercalation Under intercalation conditions the dipyridophenazine system is effectively in a local aprotic region, no protonation can occur and any excited states exhibit luminescence A careful examination of the decay of luminescence against time indicates a biexponential process, suggesting the presence of two species, these were assigned as two different intercalated forms, rather than one intercalated form and one groove-bound form, since experiments to try to quench the luminescence with anions such as ferricyanide ion failed although this is known to quench the luminescence of groove-bound forms of such reagents [23] The luminescent enhancement on binding to DNA is $\geq 10^4$, by comparison the enhancement observed when ethidium intercalates to DNA is $\geq 20$ Thus intercalation can literally be seen as a 'switching on' of the luminescence This phenomenon has been exploited in specific probes for DNA The ruthenium ligand is first attached to a probe piece of DNA of known sequence, using a fairly flexible link When this probe meets a complementary piece of target DNA under hybridizing conditions, a local segment of duplex DNA is formed The ligand can then fold back and intercalate with this local duplex DNA, an event marked by the appearance of luminescence A minor problem with this approach is the inability to distinguish between a hit with the desired duplex piece of DNA and any adventitious binding of the dipyridophenazine chelate with other duplex DNA material that may be present in the assay mixture [24]

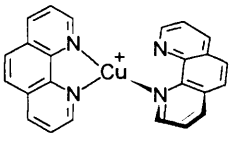
## 4 DNA Nicking Reagents involving Phenanthrolines

The herbicidal activity of many phenanthroline derivatives has been explained by the incorporation of copper, the ligand helping to transport this into the plant cells where the copper exerts its toxic behaviour

The generation of free-radical species, such as hydroxyl groups, in the vicinity of DNA chains can lead to nicking of the links and cleavage of the chain Metal complexes of reducible species, such as the EDTA complexes of iron and copper, are particularly active By building these chelates into DNA probes the technique of DNA footprinting has been developed, whereby the point of attachment of the probe can be determined Since 1,10-phenanthrolines act as good ligands for such metal ions it is not surprising to find that several recent studies have used these complexes to help probe the structure of DNA

Sequence-specific scission of DNA has been achieved using the 2 1 complex of 1,10-phenanthroline with cuprous ions [see (29)] with hydrogen peroxide as co-oxidant [25] Use was made of 5-substituted DNA derivatives (30) to prove that a similar degradation occurred with both the complementary DNA or RNA sequences, after hybridization, to cleave sites on the substrate at base positions up to ± 3 nucleotides from the point of attachment of the ligand Related nicking agents, such as bleomycin, are found to be less active on RNA than DNA A mechanism involving attack at the site of base attachment to the sugar was indicated (see Figure 4) [26] A similar approach has been adopted by Helene and his team [27]

As mentioned above, the cobalt and rhodium complexes (24) and (25) can also catalyse the formation of free-radical species Cleavage of RNA occurs by irradiating the ruthenium complexes in the presence of oxygen which forms local concentrations of singlet oxygen leading to nicking of the RNA chains

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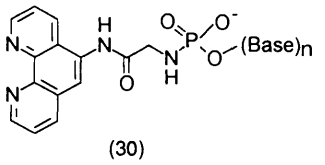
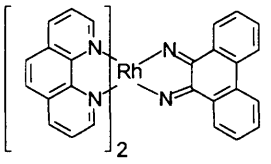



(30)

After examining several of the reagents described, which show a variety of different nicking patterns, it was found that the rhodium(III) complexes (25) and (31) show very selective nicking patterns at sites adjacent to and at the triple helix region at cruciform sites. It was argued that intercalation is possible at these centres since, at these, the helical structure is more open than in normal duplex regions. The observed breaking of the sugar–base bond, rather than at sugar–phosphate bonds, is evidence for the intimate association of the reagent with the RNA.[28]



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## 5 Phenanthrolines and Europium

Europium(III) ions and related lanthanide species have attracted much rapidly increasing attention over the last decade as robust luminescent species in a variety of diagnostic probes and assays. The main features of $Eu^{3+}$ photochemistry are:

(i) the ground-state ion has only a very weak absorption coefficient, since the main excitation transitions are formally forbidden.

(ii) Triplet sensitizers may be used to help populate the excited state, but these sensitizers need to be in close proximity with the ion, as in metal chelates, to observe efficient energy transfer.

(iii) The excited state involves excitation of an inner *f*-shell electron and the transitions are shielded by the residual valence-shell electrons. Observed emissions occur as a series of sharp emission bands.

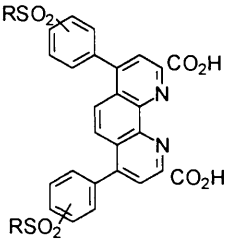
(iv) The energy emitted is generally at a much longer wavelength than the energy absorbed by the sensitizer, leading to a large Stoke's shift. Hence concentration-dependent self-quenching of the luminescent state is not observed.

(v) Since the emission process is also formally spin-forbidden it is a relatively slow process (lifetimes in the microsecond to millisecond range), allowing the use of time-resolved measurements. This feature allows one to remove interferences arising from background fluorescence, autofluorescence, and scattering phenomena.

(vi) Solvated water molecules can quench the luminescence by a vibronic-coupled deactivation of the excited state. The degree of quenching is dependent on the number of water molecules in the solvent shell; the lanthanide ions can form solvates with up to nine molecules of water. In order to observe efficient luminescence the majority of these water molecules have to be removed by using ligands that shield the ions from water.

Two main ways for utilizing europium ions in probes have been developed. In the DELFIA system, developed by Soini, Lovgren, and colleagues,[29] europium is chelated to species like ethylenediamine tetraacetic acid conjugates of biological substrates, in a straight replacement of a corresponding radioactive tag. These compounds are themselves non-luminescent. After separation of the labelled reagent–substrate complex (such as an antigen–antibody complex), the europium is removed by sequestration at low pH with a large excess of an aromatic β-diketone reagent, which can also act as a sensitizer. In order to increase the europium luminescence a mixture of further reagents, such as surfactants and trioctylphosphine oxide, is added (an 'enhancer' solution) in order to form hydrophobic micelles and thus eliminate water quenching. The DELFIA system can only be used in heterogeneous assays (those in which a separation of the excess of reagent from the substrate–reagent complex has to be carried out).

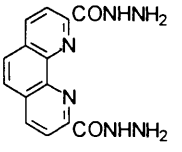
Rather than use an inert chelating agent, Diamandis *et al.*[30] utilized derivatives of phenanthroline-2,9-dicarboxylic acid (5). This is a powerful sensitizing ligand for europium ions and avoids the need for a separate sensitizing ligand such as the β-diketones used in the DELFIA approach. The main reagent used in these assays (*e.g.* the CyberFluor assay) is the bathophenanthroline derivative (32). A detailed study of the binding of $Eu^{3+}$ with the diacid (5) showed that at neutral and acid pH a 1:1 complex forms ($K^1_{ass}$ $2 \times 10^8$ $M^{-1}$) but that at higher ligand concentrations a 2:1 complex can also form ($K^2_{ass}$ $2 \times 10^6$ $M^{-1}$).



(32)

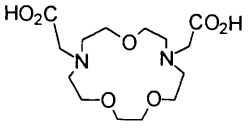
The 2:1 complex produces high luminescence and shows only one molecule of water in its coordination shell (mean lifetime 0.72 ms). Luminescence of the 1:1 complex can be enhanced by drying. At pH values > 7, the complex collapses with formation of europium hydroxides and the 2:1 complex.[31]

Enzyme-linked assays have been reported which involve oxidation of phenanthroline-2,9-dicarbohydrazide (33), which is oxidized to the dicarboxylic acid (5) and then assayed with europium.



(33)

The DELFIA and CyberFluor systems are not readily applicable to homogeneous assays. In an approach to overcome this we have been investigating the use of a cooperative signalling system, one that is only turned on when two components meet.[1] We have shown that, under defined conditions, europium can form discrete, *mixed* 1:1:1 chelates. One ligand is used as a shielding agent, to protect the ion from water molecules, the other as a sensitizer. Reagents such as the diazatrioxa-[15]-crown (34) can be used as the shielding agent. This has a high binding constant to $Eu^{3+}$ ions ($K^1_{ass} > 10^{12}$ $M^{-1}$) but does not coordinately saturate the metal. A molecule of the diacid (5) can also approach the ion in the pH range 6.5 to 8.0 to form a 1:1:1 complex ($K^2_{ass}$ *ca.* $10^6$). Because this is now highly shielded from water the system shows efficient luminescence ($\tau$ 0.72 ms), the phenanthroline acting as the sensitizer. A variety of shielding ligands may be used in place of the crown (34), including EDTA and its derivatives. The cooperative effect is concentration-dependent and, at concentrations below $10^{-6}$ M, the phenanthroline dicarboxylic acid starts to dissociate from the 1:1:1 complex and luminescence disappears.



(34)

The cooperative approach has been developed for use as a homogeneous assay for DNA. This is outlined in Figure 5. In this, use is made of the organization created by formation of a segment of duplex DNA when a probe DNA strand meets its

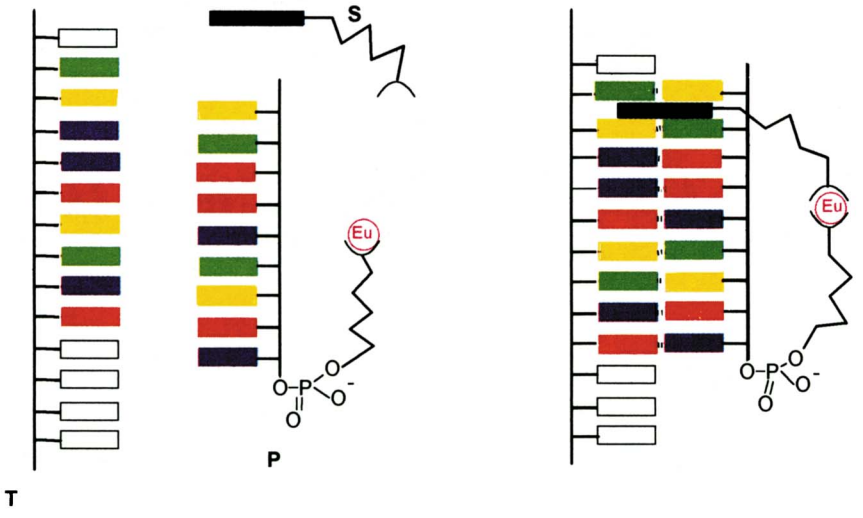
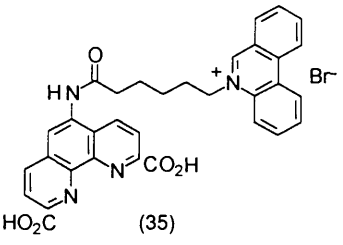



**Figure 5** A homogeneous DNA assay. Only when the target and the probe DNA strands meet and hybridize can intercalation occur and the sensitization of the $Eu^{3+}$ ions be observed. **T**, target; **P**, probe; **S**, sensitizer; **Eu**, europium ion.




(35)

5'
O.A.A.G.A.T.G.A.T.A.T.T.T.T.C.T.T.T.A.A.T.G.G.TG
P-O(CH2)6NHCO.CH2NCH2CH2N(CH2CO2H)2
CH2CO2H

(36)

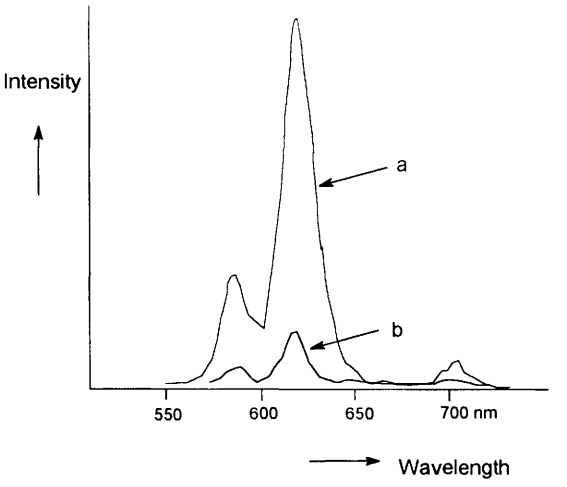



**Figure 6** Curve a, reagents (35) and (36) with target (37); curve b; without target (37). Concentrations: (35) and (36), $2 \times 10^{-8}$ M; (37), $5 \times 10^{-9}$ M.

3' 5'
C.C.T.T.T.G.T.G.GT.**T.T.C.T.A.C.T.A.**T.**A.A.A.A.G.A.A.A.T.T.A.C.C.A.C.** G.G.T.C.C.G.T.A.T.T.A.

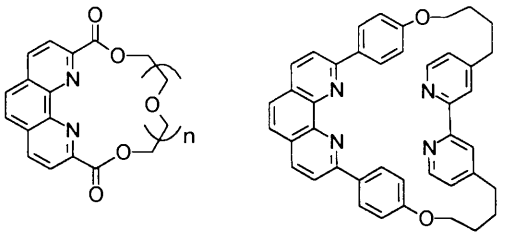
(37)

complementary sequence at a target and when the pair hybridize. In our assay system the probe DNA is linked at one end to a short handle bearing a molecule of EDTA to which is chelated europium. The EDTA complex of $Eu^{3+}$ is very tightly bound ($K^1_{ass} > 10^{17}\ M^{-1}$). At this stage the labelled duplex DNA shows no luminescence. However, duplex DNA can accommodate either groove-binding agents or intercalators, whereas the single-stranded target DNA alone cannot. This property is utilized to help increase the local concentration of the sensitizer molecule. We use the phenanthroline dicarboxylic acid derivative (35), in which the linked phenanthridinium group can act as an intercalator. Since intercalation has a binding constant of *ca.* $10^5$, the effective binding constant of the sensitizer in the region of duplex is increased to *ca.* $10^{11}$, *i.e.* an enhancement of luminescence is observed. Figure 6 shows the output from a typical test with the probe (36) against the target DNA strand (37) as against the background signal observed (due to adventitious approach of the europium-labelled probe DNA to sensitizer molecules at the $10^{-8}$ M concentrations used) when using a non-matching strand of DNA. The advantage of this approach is that it allows a direct test for a specific DNA sequence under homogeneous conditions.[1] *In situ* assays of DNA from biological specimens are currently being developed.

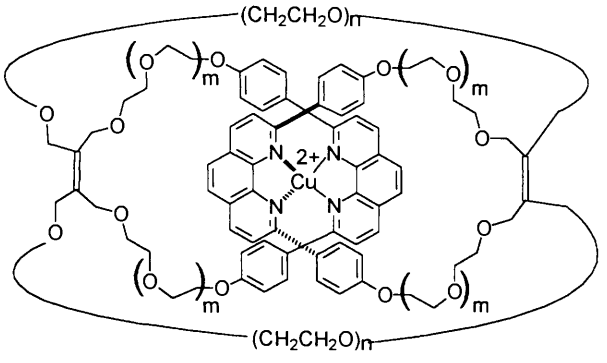
## 6 Supramolecular Reagents utilizing Phenanthrolines

A large number of studies on supramolecularity[4] involving 1,10-phenanthroline derivatives have been made over the last decade and space limitations allow for the mention of just a few of these. Chandler and colleagues have studied a range of aza-crown derivatives of the diacid (5), such as the cyclic lactones (38)[12] whilst Sauvage *et al.*[11] have studied related macrocyclic systems by making extensive use of the diphenol (14). The rigid structure of this molecule, in conjunction with the large separation of the phenolic groups from the chelating nitrogens, have made it particularly useful in macrocyclic and topological studies. Inclusion of other metal chelating heterocyclic systems into the ring, such as in compound (38), provides a means for using metal chelation to control the formation of various new topological systems such as the catenanes. Recent successes in this area include the description of the molecular knot (39).[32]

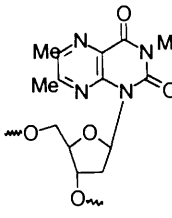
In an alternative approach to that used by Barton's group, Bannwarth has used 4,7-diphenylphenanthroline complexes of ruthenium(II) as general labels for nucleic acid strands to which they are attached by a covalent linker.[33] The ruthenium luminescence may be stimulated by a through-pace, fluorescence



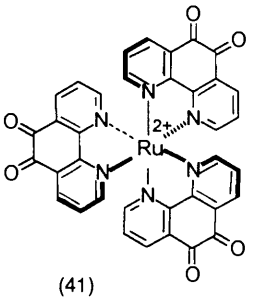
(38)



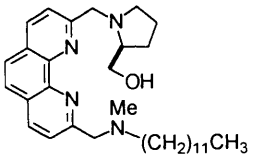
(39)



(40)



(41)



(42)

energy transfer (FRET) from an excited energy donor, such as the lumazine (40) Since the efficiency of energy transfer is related to its distance from the acceptor the system can be used as a molecular ruler

Phenanthroline derivatives have also been used as enzyme mimics The redox properties of the tris(1,10-phenanthroline-5,6-dione) ruthenium(II) complex (41) and related compounds have been used as efficient mediators for the $NAD^+$-promoted oxidation of alcohols The mediators oxidize NADH to $NAD^+$ and are themselves reoxidized by either aerobic or anodic oxidation [34] Phenanthroline analogues of flavins have also been reported [35] Chiral phenanthroline complexes, such as the pyrrolidinemethanol derivative (42), in conjunction with metal ions such as zinc or cobalt, act as catalysts exhibiting enantioselectivity towards various peptide ester substrates [36]

The above examples attest to the wide range of chemical applications made of the 1,10-phenanthroline system other than its historical use as a chelating indicator We would expect further exciting revelations in the near future

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