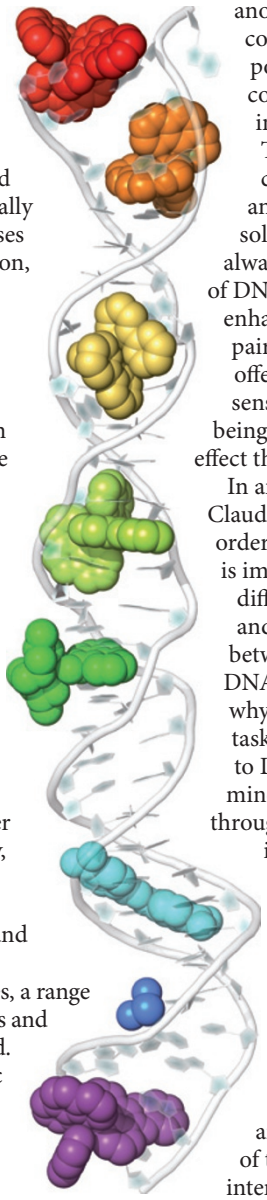
Double-helix disruption

Structure by structure, more information is steadily being gathered on how small molecules bind to DNA. A better understanding of the interactions involved in such processes will be crucial for the successful design of compounds for specific diagnostic and therapeutic purposes.



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The order in which four relatively similar (and simple) heterocycles are appended along the backbone of a polymer chain has incredibly profound consequences for every one of us. The sequence and structure of our DNA is intrinsically linked to many biological processes — those required for us to function, as well as others that are not so welcome. Certain diseases, for example, are associated with specific base sequences, or base-pair mismatches that sometimes occur during DNA replication. In particular, DNA mismatches have emerged as promising targets for biomedical diagnostics and therapeutics — with carefully designed small molecules as the active agents.

Perhaps the best-known molecule that binds to DNA is *cis*-diammine-dichloro-platinum(II), a simple square-planar complex that gained international recognition under the name cisplatin. It is worth noting that whereas the *cis* isomer has significant anticancer activity, its *trans* counterpart does not — offering a glimpse into just how specific interactions with DNA, and effects on its biological role, are.

Over the past couple of decades, a range of DNA binders with varying sizes and characteristics have been prepared. Oligonucleotides[1], peptide nucleic acids[2] and pyrrole–imidazole polyamides[3], for example, interact with base pairs in a specific manner — sometimes by forming triple helices — and can thus recognize particular sequences. Other oligomers[4] have been prepared that feature naphthalene diimide derivatives, which slide between base pairs at various positions and anchor them to the DNA.

As is clear from cisplatin, however, molecules that bind to DNA do not necessarily need similar shapes or composition. This is highlighted by another class of metal-containing compounds — 'light-switch' polyazaaromatic ruthenium complexes — which bind to DNA in a very noticeable manner. The luminescence of these complexes is DNA dependent and their emission in aqueous solutions is often (albeit not always) switched on in the presence of DNA. Conveniently, it can even be enhanced if the DNA contains base-pair mismatches. This characteristic offers a very practical route to sensing, and holds the promise of being able to switch on a therapeutic effect through irradiation.

In an Interview[5] in this issue, Claudia Turro explains why, in order to realize these prospects, it is important to identify the subtly different binding modes that exist and determine which one occurs between a given compound and DNA sequence. She also points out why these investigations are no easy task. A small molecule can bind to DNA in either the major or the minor groove of the double helix, through covalent or non-covalent interactions, and may disrupt the π-stacked base pairs in a number of ways. Will it simply move two base pairs apart and slide between those? Will it do that, but only partially, leading to kinking? Another possibility is that it could force an entire base pair outside of the central π-stack and take its place altogether. All of these binding modes — called intercalation, semi-intercalation and insertion, respectively — lead to significantly different effects on the properties of the resulting DNA–ruthenium-compound adduct, and thus affect cellular processes differently.

Understanding such binding in a more general manner inevitably involves elucidating the details of how different compounds interact with DNA. In this issue, two Articles — from teams led by Jacqueline Barton[6] and Christine Cardin[7] — contribute further insight by describing the crystal structures of two enantiomers of a 'light switch' ruthenium complex with different oligonucleotide duplexes. In an accompanying News and Views piece, crystallographer Stephen Neidle discusses[8] a feature that may at first seem surprising: in all three crystal structures that are reported, the ruthenium complexes are bound to the oligonucleotides through their minor grooves. This finding may seem counter-intuitive because the major groove is more accessible.

In fact, both minor-[9] and major-groove[10] binding for a related DNA–ruthenium-compound adduct have been proposed on the basis of solution studies, whereas major-groove intercalation has been observed for a rhodium complex through both solid-state and solution characterization[11]. Yet, taking into account a number of features of the crystal structures, Neidle presents a rational explanation for the minor-groove preference for those three adducts in the solid state.

Although seemingly conflicting, these conclusions are not contradictory. Rather, the experimental data gleaned in different environments and with different complexes will all add to our overall understanding of how these small metal complexes interact with DNA. It may well be that the major- and minor-groove bindings are energetically very close, and that both interactions do occur in solution. These investigations offer an excellent illustration of how science progresses. One structure at a time, the ability to understand, design and ultimately use these complexes for biomedical purposes, is getting closer. ❐

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