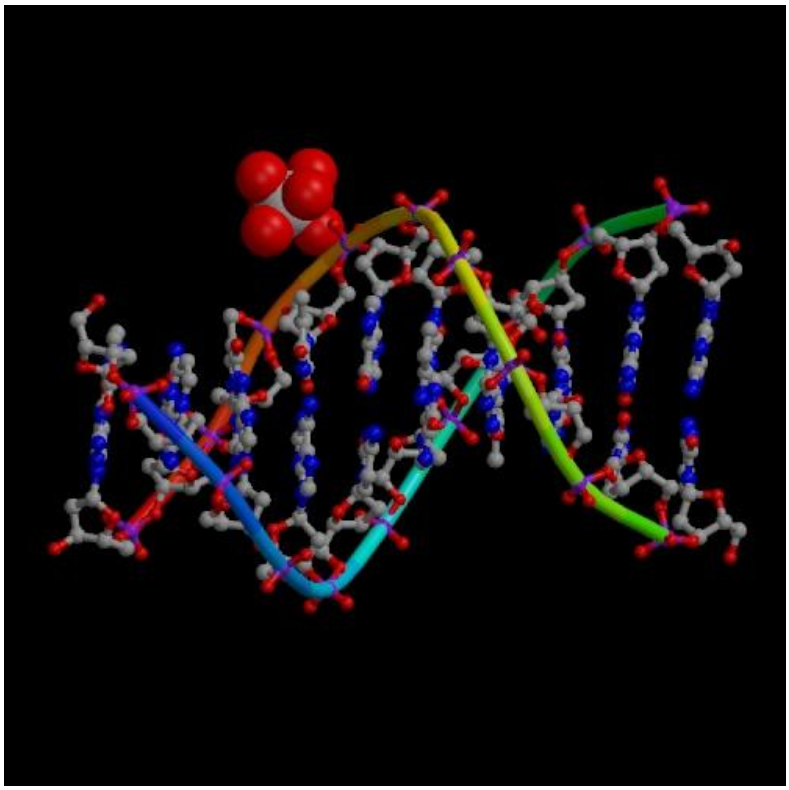
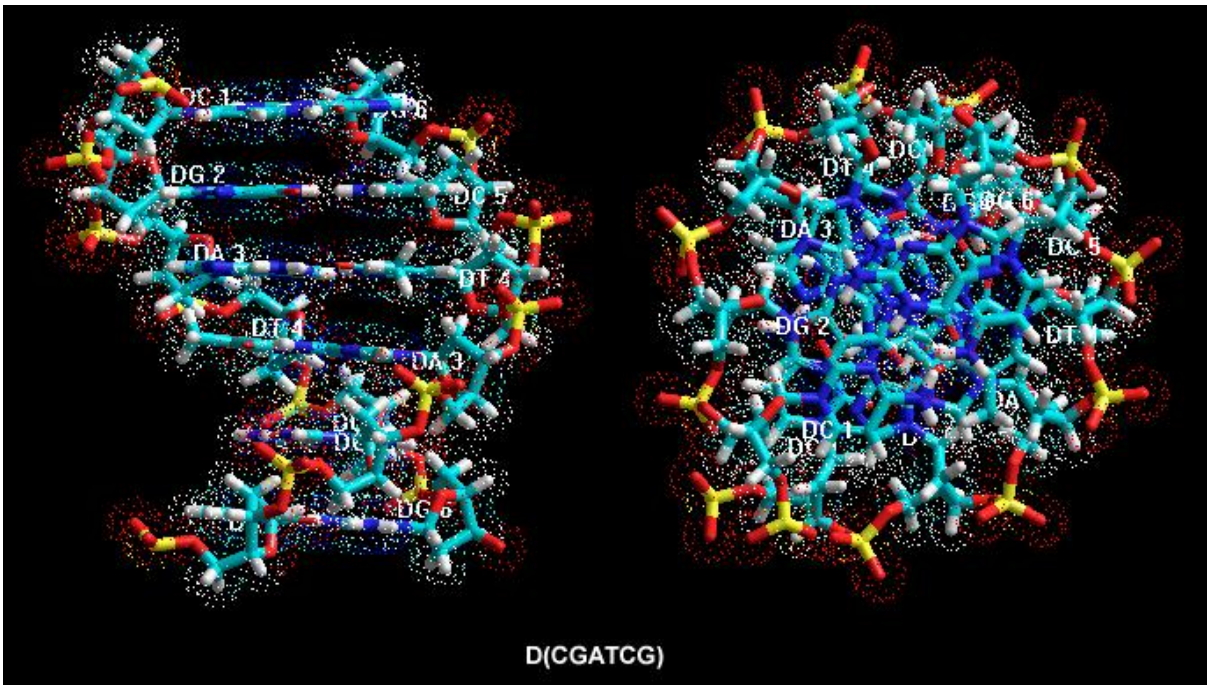
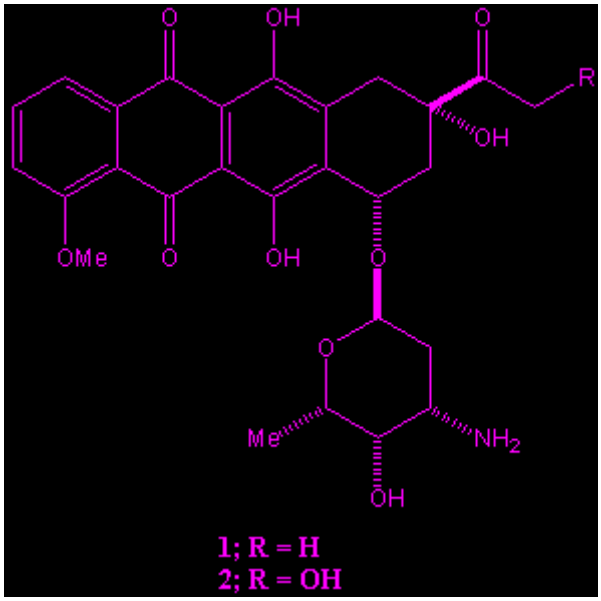
Intercalation between Anthracyclines and DNA

First of all, consider the 3-D structure of a DNA fragment (including a solvated magnesium ion), determined by X-ray crystallography:



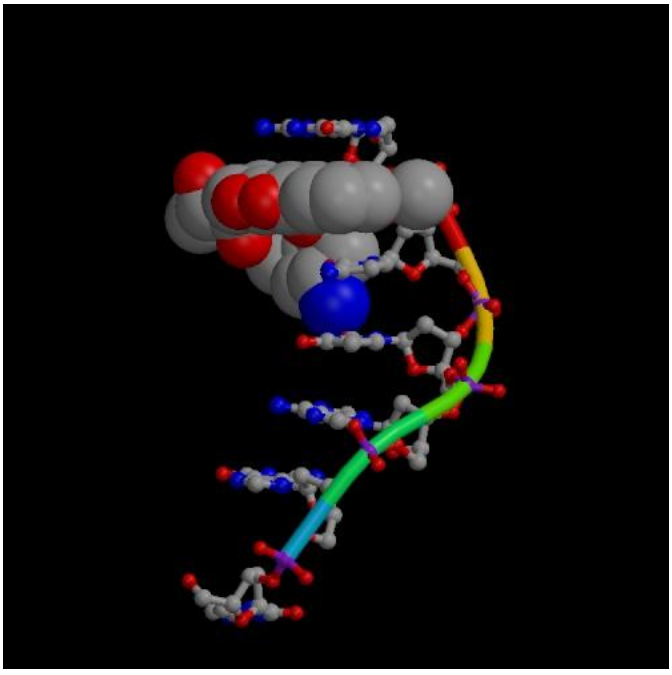
Alternative DNA Fragments: B-DNA fragment 1 (B-DNA-FRAGMENT.jpg), B-DNA fragment 1 view 2 (B-DNA-FRAGMENT2.jpg).





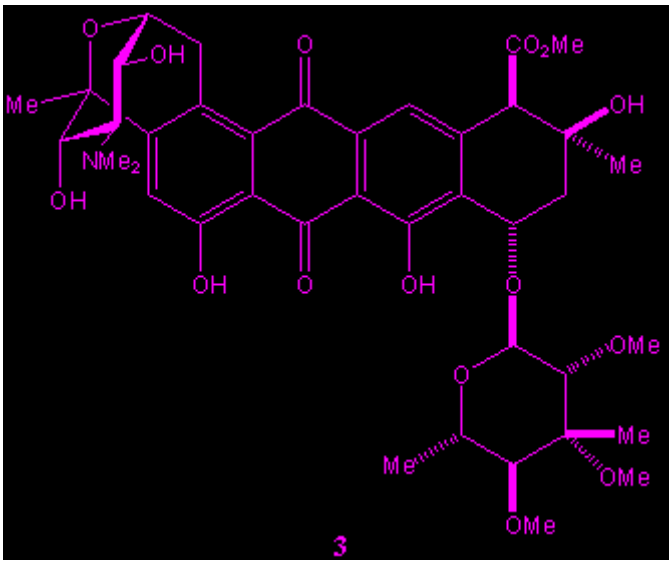
The primary mode of action of daunomycin (**1**) and Adriamycin (**2**) is believed to be their reversible binding to nucleolar DNA which causes inhibition of the replication process[1] and thence death. Numerous biochemical studies including evidence from NMR spectroscopic and X-ray crystallographic studies have shown that daunomycin and Adriamycin intercalate into the B-form of the DNA double stranded helix with guanine-cytosine d(CpG) site-specific interactions[2]. The base pairs above and below the drug 'buckle' in conformation to afford a distorted DNA helix thereby preventing association with the DNA helicase, DNA topoisomerase[3] and polymerase families of enzymes to initiate DNA replication for RNA synthesis, protein formation and thereby cell division.

i. DNA-Daunomycin Complex



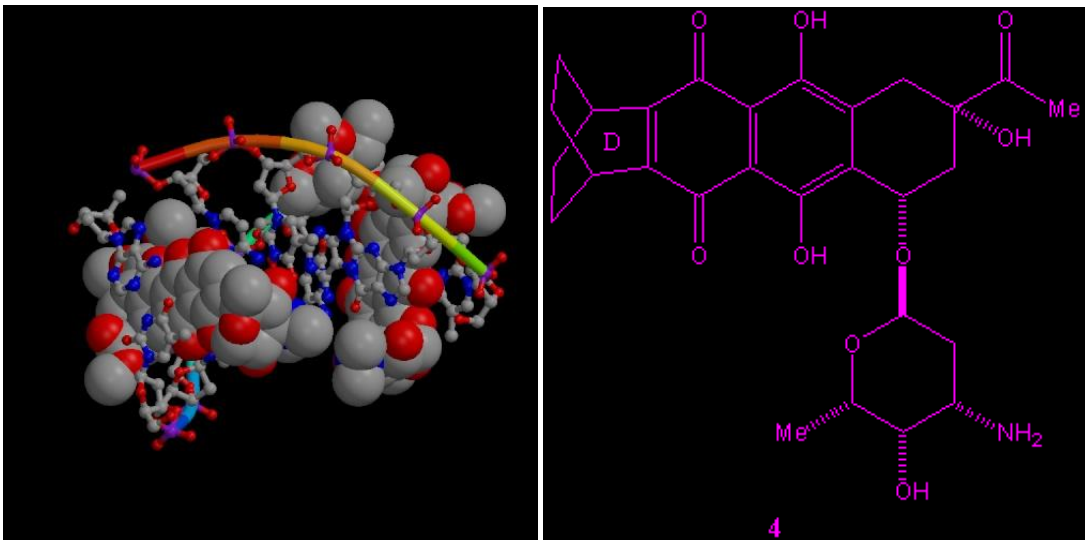
As a result of intercalation with daunomycin[4], the GC and CG base pairs 'buckle' by ca. 9^{o} and 15^{o} respectively to prevent excessive van der Waal's contacts. Also, the base pairs separate from a nominal distance of 3.4 Å to 6.8 Å when accommodating the drug and these distortions lead to a total DNA unwinding angle of ca. 8^{o} (5.2 measured from solution studies[6]) and a distortion of the tertiary structure of the helix, although it is still closer to the B-DNA conformation. Several factors play a role in the stabilisation of the drug-DNA complex. The anthracycline is stabilised by electrostatic hydrogen bond and stacking π-bond interactions between the electron-deficient quinone-based chromophore and the electron-rich purine-pyrimidine bases. Hydrogen bonds play an important part in the stabilisation of the complex assisted by way of several water molecules and a solvated sodium cation. Indeed, an anthracycline lacking the hydroxyl group at C-9 on the right side of the ring-A is devoid of anticancer activity. Also, the hydrogen atom of the charged amino group is hydrogen bonded to O-2 of the thiamine base (T10) and two water molecules. Replacing the C-13 hydrogen atom with the hydroxyl group as for Adriamycin (**2**), this created[7] additional hydrogen bonded interactions involving solvent media around the substituent. As this study[5] included the charged aliphatic-amino spermine molecules close to the intercalation site, an important change in the bonding interaction of spermine and the complex was observed between daunomycin and Adriamycin.

ii. *Unplanar chromphore-DNA complex*

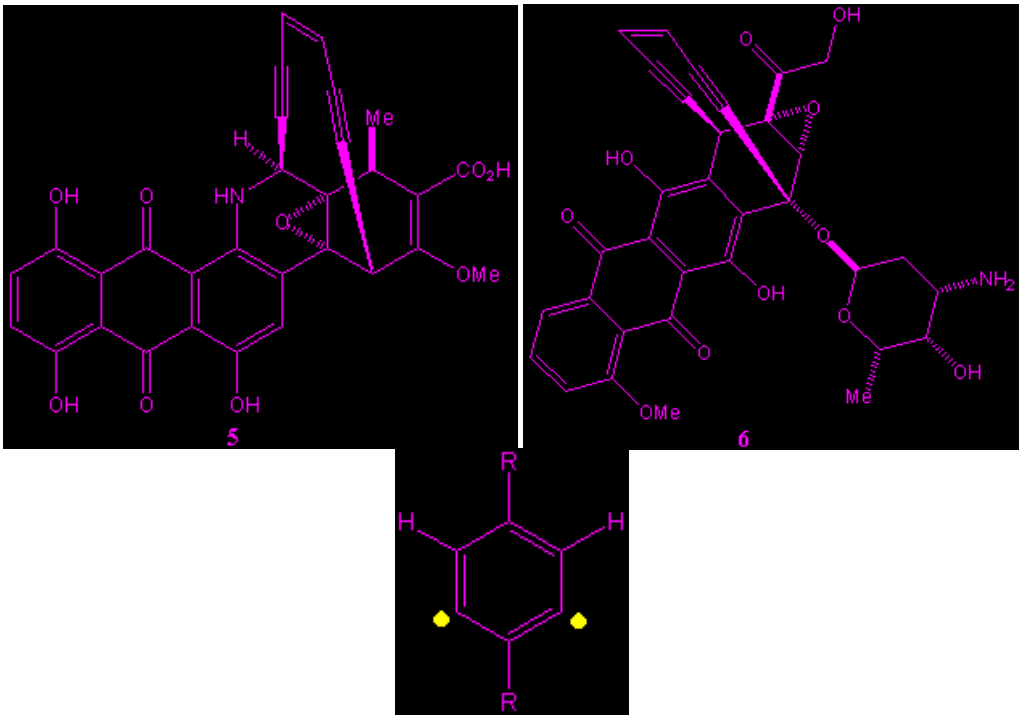


The dumbbell shaped anthracycline nogalamycin (**3**)[7] was found to form a stable intercalative complex with DNA as revealed by X-ray[7] and NMR spectroscopic[8] studies. To accommodate intercalation of the nogalamycin chromophore, the DNA helix must 'open up', by transiently melting to allow entry of the bulky bicyclic amino sugar attached to ring-D. The DNA helix then elongates, translocating the base pairs in the approximate direction of the helical axis[9]. In another study[10], a buckle of -25.4^{o} in the C11-G2 base pair was observed. This would shed some light on the possibility of the target ring-D modified anthracycline (**4**) (R=H) intercalating with DNA and thereby test anticancer activity and intercalation theory. However, anthracyclines are

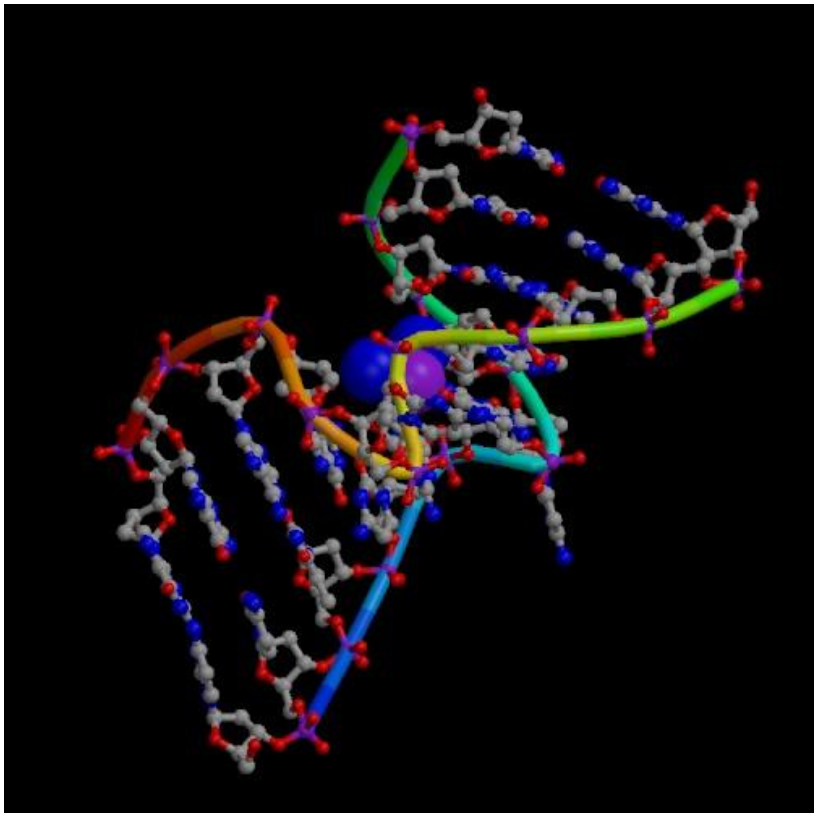
also known[11] to be enzymatically reduced to a radical species that form hydroxyl radicals (in the presence of molecular oxygen) to cause strand breaks in DNA and thereby cause inhibition of the replication process.



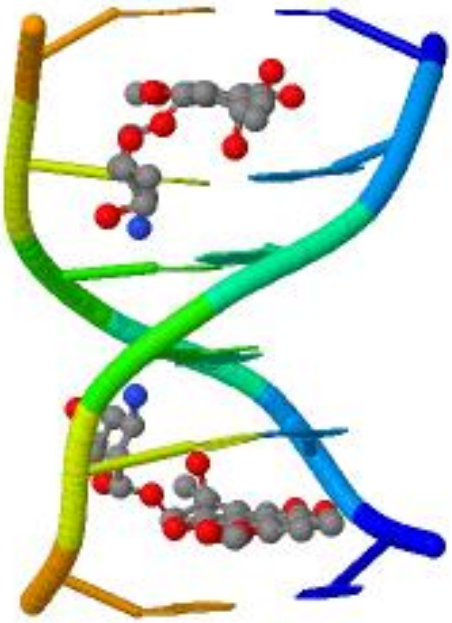
The antitumour ene-diyne antibiotics such as Dynemycin (**5**)[12] are known to inhibit cell replication by interfering with mitosis by causing single strand breaks in the DNA during spindle formation, by way of cyclisation of the ene-diyne bridge to a benzene biradical. On the basis of this, Adriamycin bearing the bridge on the A-ring could possess enhanced anticancer effectiveness by intercalating with DNA and causing single strand breaks by forming the benzene biradical, *in situ*. The benzene species is shown below; the radicals seen as yellow dots. The synthesis of such a compound would indeed be a highly challenging synthetic endeavour in the laboratory!



Other classes of anticancer drug-DNA interactions have been studied. For example, the image below represents the crystal structure of a double-stranded DNA decamer containing a cisplatin [$Pt(NH_3)_2$] interstrand cross-link adduct[13]. Advances in other small molecule DNA-intercalators (including anthracyclines) was recently reviewed[14].



A view of the idarubicin-D(CGATCG) complex[15] is shown below (via RCSB) and intercation is still being investigated[16].



References

1. S. Neidle, *Prog. Med. Chem.*, 1979, **16**, 151-221. F. Yang, S.S. Teves, C. J. Kemp and S. Henikoff, Doxorubicin, DNA torsion, and chromatin dynamics, *Biochim. Biophys. Acta*, 2014, **1845**, 84-89.
2. J. B. Chaires, J. E. Herrera and M. Waring, *Biochemistry*, 1990, **29**, 2538-2549.
3. G. Capanico and F. Zunino, "Molecular basis of Specificity in Nucleic Acid-Drug Interactions", eds B. Pullman and J. Jortner, Kluwer Academic Publishers, Netherlands, 1990, pp. 167-176; M. Dugnet, C. Lavenot, F. Harper, G. Mirambeau and A. -M. de Recondo, *Nucleic Acids Research*, 1983, **11**, 1059-1075. Henry Sobell's website discusses drug-DNA intercalation further.
4. A. H. -J. Wang, G. Ughetto, G. J. Quigley and A. Rich, *Biochemistry*, 1987, **26**, 1152-1163; Protein Data Bank Daunomycin-d(CGATCG) Fragment
5. C. A. Frederick, L. D. Williams, G. Ughetto, G. A. van der Marel. J. H. van Boom, A. Rich and A. H. -J. Wang, *Biochemistry*, 1990, **29**, 2538-2549.
6.A. Di Marco and F. Arcamone, *Arzneim-Forsch. (Drug Res.)*, 1975, **25**, 368-375.
7.C. K. Smith, G. J. Davies, E. J. Dodson and M. H. Moore, *Biochemistry*, 1995, **34**, 415-425.
8. M. S. Searle, J. G. Hall, W. A. Denny and L. P. Wakelin, *Biochemistry*, 1988, **27**, 4340-4349.
9. M. Egli, L. D. Williams, C. A Frederick and A. Rich. *Biochemistry*, 1991, **30**, 1364-1372.
10. Y. -C. Liaw, Y. -G. Gao, H. Robinson, G. A. van der Marel, J. H. van Boom and A. H. -J. Wang, *Biochemistry*, 1989, **28**, 9913-9918.
11. F. Arcamone, Doxorubicin (Medicinal chemistry, a series of monographs volume 17), Academic Press, London, 1981. ISBN 0-12-059280-0.
12. K. C. Nicolaou and W. -M. Dai, *Angew. Chem. Int. Ed. Engl.*, 1991, **30**, 1387-1416; R. L. Halcomb, S. H. Boyer and S. J. Danishefsky, *Angew. Chem. Int. Ed. Engl.*, 1992, **31**, 338-340.
13. F. Coste, J. M. Malinge, L. Serre, W. Shepard, M. Roth, M. Leng and C. Zelwer, "Crystal structure of a double-stranded DNA containing a cisplatin interstrand cross-link at 1.63 A resolution: hydration at the platinated site", *Nucleic Acids Res.*, 1999, **27**, 1837-1846.
14. A. Rescifina, C. Zagni, M.G. Varrica, V. Pistarà, A. Corsaro, Recent Advances in Small Organic Molecules as DNA Intercalating Agents: Synthesis, Activity, and Modeling, *Eur. J. Med. Chem.*, 2014, **74**, 95–115.
15. A. Dautant, B. Langlois d`Estaintot, B. Gallois, T. Brown, W. N. Hunter, *Nucleic Acids Res.* 1995, **23**, 1710-1716.
16. Idarubicin (4-demethoxydaunomycin) also forms an intercalation complex with DNA. S. Charak and R. Mehrotra, *Int. J. Biological Macromolecules*, 2013, **60**, 213-218.

What's New: A book chapter has recently been published (Recent Advances in Asymmetric Diels-Alder Reactions; author J.P. Miller) that may be of interest in organic chemistry (and includes routes or important synthetic steps towards molecules of antineoplastic activity) :free open access.

© Jonathan Miller

[source: http://dx.doi.org/10.7910/DVN/26948].