

A SYNTHETIC APPROACH TO THE MECHANISM OF DNA-CLEAVAGE
BY BLEOMYCIN-Fe(II)-O₂ COMPLEX

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The base-sequence specific DNA-cleavage by an antitumor antibiotic bleomycin (BLM) is considered to be due to (i) selective DNA-binding by the bithiazole-terminal amine portion and (ii) metal-chelation and oxygen-activation by the pyrimidine moiety. In the present study, the molecular mechanism of the DNA-cleavage by BLM was investigated using synthetic homologues and it was demonstrated that (i) molecular oxygen was activated by the ferrous complex of PYML, a model corresponding to the controversial metal binding site, (ii) certain substrates were oxygenated by the PYML-iron complex in the presence of relevant oxygen donor, and (iii) DNA was cleaved by a combination of PYML and a DNA-interacting site consisting of 1-methylpyrrole systems. Based on these results, the role of each functional group of BLM is to be discussed in relation to effective oxygen activation leading to DNA-cleavage.

