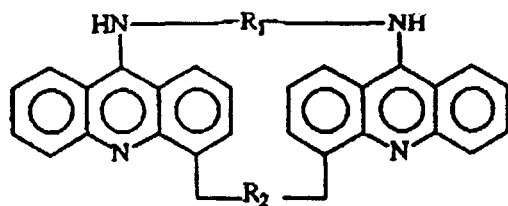


Polyfunctional intercalation has the potential of providing a mechanism for high-affinity binding to DNA. Such compounds could have interesting antitumor and antiviral properties. A topologically novel bifunctional DNA intercalator, **2**, has been synthesized and its DNA binding studied in comparison with the binding of 9-aminoacridine, **1**, and spermine diacridine, **3**. Compound **2** shows a high affinity for calf thymus DNA as indicated by large increases in the helix-coil transition temperature. Viscometric analysis of helix extension using sonicated calf thymus DNA gave results characteristic of a double intercalator. Metachromic shifts in the absorption spectra of **2** were observed upon addition of DNA. Macrocycle, **2** reverses the supercoils in a closed circular supercoiled plasmid (pOP1Δ6). These data, and other experiments, support the conclusion that **2** binds to DNA as a bifunctional intercalator. DNA binding and molecular modeling studies of these polyfunctional DNA intercalators will be discussed.

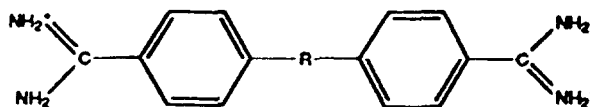


- 1 $R_1 = H, R_2 = H$
- 2 $R_1 = (CH_2)_3NH(CH_2)_4NH(CH_2)_3, R_2 = CH_2S(CH_2)_2NHCO(CH_2)_2CONH(CH_2)_2SCH_2$
- 3 $R_1 = (CH_2)_3NH(CH_2)_4NH(CH_2)_3, R_2 = H$

Structure and Molecular Modeling of the Anti-infective Drug Pentamidine

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Pentamidine (1a) is valuable for the treatment of *Pneumocystis carinii* infections in AIDS patients as well as trypanosomiasis. The molecule is terminated by the same aromatic amidine moieties as the DNA-binding drug berenil (1b), but the central chain is longer.



a: $R = -O-(CH_2)_5-O-$
b: $R = -NH-N=N-$

The crystal structure of berenil has been determined,¹ and its interaction with A-T rich regions of DNA has been investigated by graphic modeling and molecular

mechanics.¹ The present study comprises a determination of the crystal structure of (1a) as the hydrated isethionate salt and an investigation of the conformational preferences and electronic properties of three important structural features of the pentamidine molecule, namely the junction between amidinium groups and benzene rings, the ether linkages and the central chain.

The crystals have unit cell dimensions $a = 25.959$, $b = 14.105$, $c = 8.781$ Å, $\beta = 102.44^\circ$ and exhibit symmetry consistent with space group C2/c. The structure has been refined to $R = 0.06$, with typical standard deviations of 0.006 Å and 0.5° for nonhydrogen bond distances and angles. As in (1b), molecules of (1a) adopt a flat extended conformation and have twofold symmetry imposed by a crystallographic axis through the central methylene C atom. The planes of the amidinium groups and benzene rings intersect at 27° in (1a) but only 8° in (1b). However, the latter angle increased upon refinement using molecular mechanics of (1b) with DNA.¹ Our *ab initio* STO-3G calculations for the phenyl-amidinium cation show that the energy is relatively insensitive to twists up to ca. 35° , with a minimum at 27° .

The C-O-C angle is 117.9° with no significant twist about either bond. This corresponds with one of the two energy minima found by STO-3G calculations for anisole.²

Superposition of the middle three atoms of (1a) onto the central chain of (1b) places the aromatic rings in similar regions of space with their inner edges in (1a) aligned with their outer edges in (1b). Thus, the vector from end to end of the central chain is 5.20 Å longer in (1a) than in (1b). For a polymer to have an isohelical fit with the minor groove of a DNA helix at a distance of 5.0 Å from the helix axis, a chain length of 4.61 Å between contacts with successive bases is required.³ The bending and twisting needed to enable (1a) to conform to a helical template should reduce the length of the chain vector to around this value, thus enabling it to span one more base-pair than (1b).

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Accurate Redox Potentials from Theoretical Calculations

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