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A Theoretical Study of the Nonintercalative Binding of Berenil and Stilbamidine to Double-Stranded $(dA\text{-}dT)_n$ Oligomers

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SUMMARY

The nonintercalative binding of two diarylamidines, berenil and stilbamidine, to the minor groove of double-stranded $(dA\text{-}dT)_n$ oligomers in the B-DNA conformation was investigated by performing theoretical computations of their intermolecular interaction energies with the groove. The method consists of an additive procedure developed previously in this laboratory using empirical formulae based on *ab initio* computations. The objective was to assess the extent to which the particular structure of each diarylamidine bears on its binding mode and affinity to the minor groove. The results show that the intrinsically preferred configurations of the two compounds are markedly different. Owing to its slightly curved shape, berenil interacts with the groove predominantly through its concave side, the binding occurring principally with sites (O_2, $O_{1'}$) belonging to two thymidines on the opposite strands. The binding of stilbamidine involves a more limited number of hydrogen-bonding interactions, although an appreciably large number of interatomic distances between its hydrogens and sites on the groove (O_2, N_3, $O_{1'}$) falls in the range 2.7–3.1 Å. Each side of stilbamidine with respect to its long axis faces a distinct strand of DNA. The importance of the electrostatic contribution of the binding energy of the two diarylamidines is underlined. Preferential binding of berenil rather than of stilbamidine occurs only at the level of a complete helical turn of phosphates in $(dA\text{-}dT)_n$. The energy difference increases significantly upon further buildup of phosphates. These results can be interpreted in terms of the molecular electrostatic potential in the grooves.

INTRODUCTION

Berenil and stilbamidine are two diarylamidines shown to bind nonintercalatively to DNA (1). These molecules are endowed with a wide spectrum of antiparasitic and antimicrobial properties (2, 3) and have been demonstrated recently to inhibit oncornaviral DNA polymerase (4). Preferential binding to A-T rich sequences in DNA was initially evidenced in refs. 5 and 6. Subsequent measurement of C_{50} values, defined (1) as the micromolar drug concentration required to halve the observed fluorescence due to DNA-bound ethidium, indicated a distinct preference of both compounds for poly(dA-dT) over poly(dG-dC), the affinity of berenil for the respective polynucleotides being altogether slightly larger than that of stilbamidine (1).

The objective of the present study was to elucidate the effect of the particular molecular structure of each diarylamidine on its affinity for DNA and its intrinsically preferred binding configuration in the minor groove. For that purpose we performed computations of the theoretical intermolecular interaction energies of each diarylamidine with double-stranded $(dA\text{-}dT)_n$ sequences, in the framework of a computational procedure previously developed in this laboratory (7). The structural formulae of berenil and stilbamidine are shown in Fig. 1a and b, together with the atom numbering. The two molecules differ by the presence of a diazoamino moiety in the central region of berenil and an ethylene moiety in the central region of stilbamidine. Figure 1a and b, drawn with the help of the coordinates of the two molecules in their planar conformations, further shows that the overall shape of berenil is distinctly curved, in contrast to that of stilbamidine (such a difference in curvature persists if the molecules are distorted from the planar conformation).

The hydrogen bond donating group NH present in the diazoamino bridge of berenil is replaced in stilbamidine by the two CH bonds of the ethylene bridge, which may *a priori* be presumed to be devoid of H-bonding capabilities.

We have tried to assess the bearing on the affinity of the drugs for DNA of the two distinct factors, i.e., different curvatures of the two compounds, and the presence of different groups in the bridge region. The preferential affinity *of this type of compound* for the minor groove of A-T sequences of DNA (with respect to the minor groove

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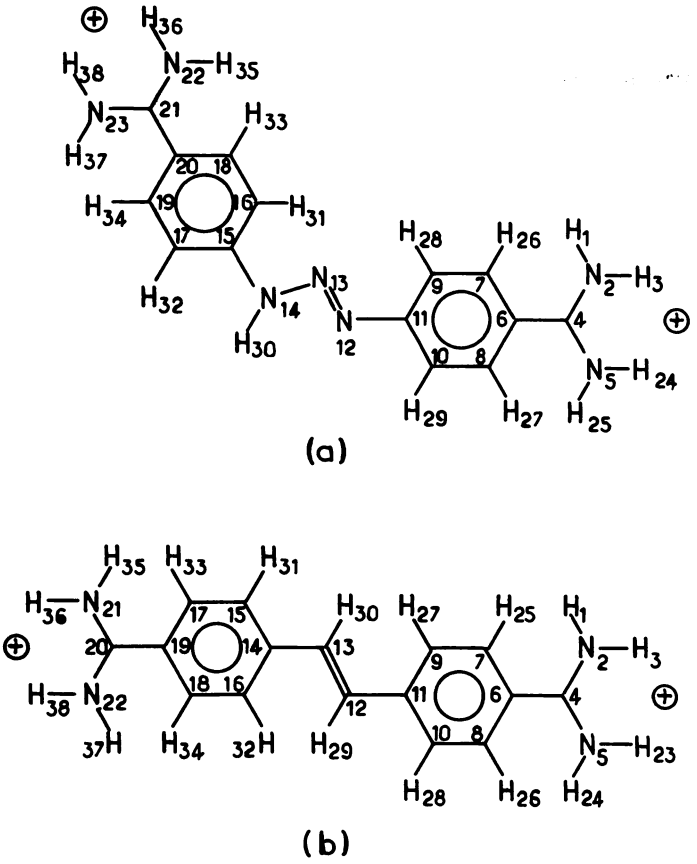

FIG. 1. *Structural formulae and atom numbering*
a, Berenil; b, stilbamidine.

of G-C sequences or the major groove of the two types of sequences) having previously been demonstrated in our laboratory on the related examples of netropsin and SN 18071 (8), we investigate here only the relative affinities of berenil and stilbamidine for the minor groove of A-T sequences. For this reason we consider their interaction with a complete helical turn of a B-DNA double helix built of an undecanucleoside decaphosphate A-T sequence (see Fig. 2), and with this complete helical turn flanked by another complete helical turn of phosphates on both strands and both 3′ and 5′ ends of the undecamer (denoted as the "triple phosphate turn" below). The choice of the latter representation follows the conclusions reached in a preceding study in the framework of the present computational procedure, in which the affinities of an aliphatic and an aromatic bisguanylhydrazone to the minor groove of double-stranded $(dA\text{-}dT)_n$ were compared (9). This study showed that, whereas an energy balance for complexation favored the aliphatic bisguanylhydrazone when short (up to heptameric) oligohelices were considered, the corresponding energy difference decreased when the chain was lengthened. At the triple phosphate turn, more representative of the situation prevailing in a polymer as contrasted to an oligomer, the energy balance was distinctly in favor of the aromatic bisguanylhydrazone. The conclusions reached could be interpreted in terms of the molecular electrostatic potential generated in the core of the grooves and its evolution as a function of chain lengthening.

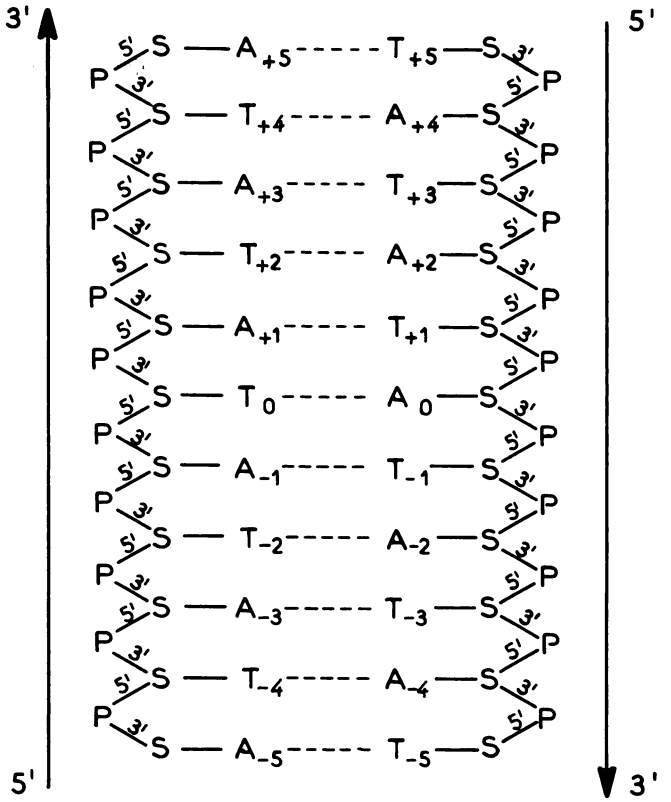

FIG. 2. *$(dA\text{-}dT)_n$ at the undecanucleoside decaphosphate level*
Atom numbering.

The calculations were carried out first for naked DNAs in order to compare their intrinsic affinities for the two diarylamidines. The effect of countercation binding to the phosphates was also investigated, by linking a monovalent cation to each phosphate, in a configuration bridging the two anionic oxygens (10), in the same manner as in our preceding works (8, 9).

COMPUTATIONAL DETAILS

The intermolecular interaction energies were computed by means of an additive procedure, developed in our laboratory (7), and applied to a number of problems related to binding specificities (9, 11–14). It was shown to reproduce satisfactorily the results of *ab initio* SCF supermolecule computations in representative cases (7, 11, 15) or experimental results when available (12, 16).

The interaction energy of ΔE was computed as a sum of four components:

$$\Delta E = E_{MTP} + E_{pol} + E_{rep} + E_{dl}$$

E_{MTP} is the electrostatic interaction energy, computed as a sum of multipole-multipole interactions between the involved molecules. For each molecule considered, the overlap multipole expansion of its charge distribution locates monopoles (that is, point charges), dipoles, and quadrupoles on all atoms and the centers of all pairs of atoms, whether or not chemically linked. The use of such an expansion was shown to be necessary for a correct representation of the molecular electrostatic potential generated by a molecule, and of the electrostatic contribution of the binding energy (17). E_{pol} is the polarization contribution, computed accordingly by using a multipolar expansion of the electrostatic field, generated by every interacting molecule in the supersystem considered, and using experimental bond polarizabilities, partitioned consistently into pure atomic and pure bond contributions. E_{dl} is a dispersion-*like* term, which contains the charge-transfer contribution when

present, and calibrated in ref. 7. E_{rep} is the repulsion contribution, computed as a sum of bond-bond interactions. This formulation of E_{rep} was adopted on the basis of the existing dependence of the repulsion on the square of the overlap integrals of the involved bond orbitals (7).

The multicenter multipolar expansions (up to quadrupoles) of the charge distributions of the diarylamidines, required to compute the electrostatic and polarization contributions to the binding energy (7), were derived from *ab initio* SCF computations using the Melius-Topiol pseudopotentials (18, 19); the minimal orbital basis set utilized is the one described in ref. 20, with a *dzeta* exponent of 1.2 on the C-H hydrogens and 1.5 on the N-H hydrogens.

The input data for the two diarylamidines are standard bond lengths and angles (21). For the nucleotide oligomer, we have retained throughout this study the standard B-DNA conformation, as given by the refined coordinates published by Arnott *et al.* in 1980 (22). This choice was adopted because of the results of recent theoretical computations of the proton shifts of the bases in a model dodecamer (23), which indicate the relevance of these coordinates to situations in solution.

The nucleic acid oligomers were constructed from their constituent fragments in the same fashion as that adopted for the computation of the molecular electrostatic potential or field of large macromolecules (24). The constituent fragments are the two bases, deoxyribose and monomethyl phosphate; their *ab initio* SCF wave functions were computed using our usual basis set (10).

The multicenter multipole expansions of the electron densities of the constituent subunits of DNA and of the diarylamidines were simplified according to a procedure recently developed in this laboratory (25) in which every dipole and quadrupole located on the center of a nonbonded pair of atoms is split between the two centers closest to it, either atom or bond barycenter.

The search for the optimal binding configurations of the diarylamidines was performed by means of an energy-minimization procedure (26). The interaction energy is minimized as a function of the six variables defining the binding configuration of the diarylamidines within the groove, *and* the dihedral angles defining the conformation of the diarylamidine proper (four angles for stilbamidine, five angles for berenil). Large numbers of such energy minimizations were performed for each diarylamidine, by selecting different starting points for the minimization procedure. This was rendered necessary because of the large number of variables involved, so as to ensure that configurations of interest energywise would not be overlooked. We present here the results pertaining to the so-derived global energy minima for each diarylamidine. Several configurations closely related to the respective minima, both energetically and geometrically, were also derived.[1]

RESULTS AND DISCUSSION

Isolated diarylamidines. The distributions of the Mulliken net charges in the two diarylamidines are represented in Fig. 3a and b, and are seen to be closely similar on all corresponding atoms. Thus, the replacement of diazoamino linkage of berenil by the ethylene linkage of stilbamidine does not influence the charge distribution on the terminal cationic groups. The distributions in the distorted conformation are very similar.[1]

Interaction with the oligomers. The values of the interaction energies are reported in Table 1, together with their different components. The optimal fitting of berenil in the groove is assisted by slight tiltings of the amidinium groups with respect to the aryl moieties, of +10° and −10° along bonds C_4—C_6 and C_{20}—C_{21}, respectively, and by changes in the conformation of the diazoamino moiety of −40° and −20° along the bonds C_{11}—N_{12} and N_{14}—C_{15}, no change occurring along bond N_{13}—N_{14}. In

[1] N. Gresh and B. Pullman, unpublished data.

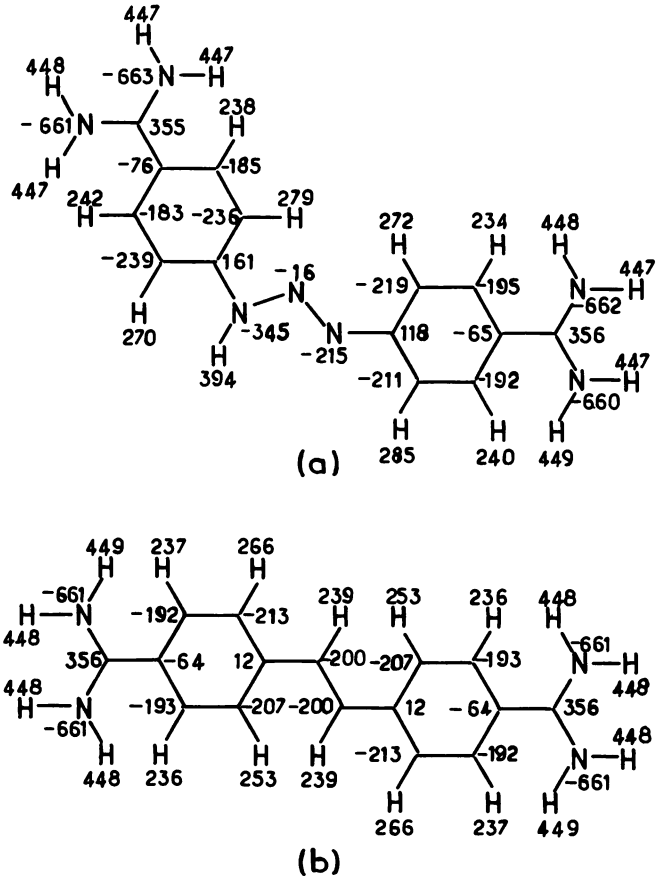

FIG. 3. *Distribution of the Mulliken net charges on berenil (a) and stilbamidine (b)*

a very similar fashion, the optimal fitting of stilbamidine in the groove is assisted by the tilting of the amidinium moieties by 20° and 30° with respect to the aryl rings along the C_4—C_6 and C_{19}—C_{20} bonds, respectively, and by a rotation of −20° and 30° of the aryl rings, along the C_{11}—C_{12} and C_{13}—C_{14} bonds, respectively, with respect to a coplanar conformation with the C=C central bond. It may be noted that these last values are close to the ones defining the intrinsically preferred conformation of stilbene (27, 28).

The complexes of berenil and stilbamidine with $(dA\text{-}dT)_n$ are represented in Fig. 4a and b, obtained with the help of the FIGATOM program (29) for drawing stereoscopic views with a graphic plotter. For reasons of clarity, only the fragment of the oligomer with three base pairs on both sides of the central base pair is represented.

The binding of the two molecules corresponds to two markedly distinct configurations. Thus, the binding of berenil occurs principally with two successive thymidines on the opposite strands, namely sites O_2 of T_0 on the 3′,5′ strand and sites O_2 of T_{+1} on the 5′,3′ strand. It involves in a predominant fashion hydrogen atoms of berenil situated on its *concave* side, namely H_1 and H_{35} of the amidinium moieties, and also hydrogen atoms H_{26} and H_{33} belonging to CH bonds of the aryl fragments. The most relevant interatomic distances have the values (in Ångström units): H_1—O_2 (T_0) = 1.79 and H_{26}—O_2 (T_0) = 2.01 on the 3′,5′ strand and H_{33}—O_2 (T_{+1}) = 1.98

TABLE 1

Values of the optimized intermolecular interaction energies of berenil and stilbamidine with double-stranded $(dA\text{-}dT)_n$

	Undecanucleoside decaphosphate	Triple phosphate turn	Undecanucleoside screened by M^+	Triple phosphate turn screened by M^+	Heptanucleoside hexaphosphate
			kcal/mole		
Berenil					
ΔE	−1196.7	−2012.1	−278.5	−294.5	−842.9
E_{MTP}	−1121.0	−1935.6	−203.3	−218.9	−773.8
E_{pol}	−37.4	−38.1	−36.8	−37.3	−33.3
E_{rep}	+39.3	+39.3	+39.3	+39.3	+39.1
E_{dl}	−77.6	−77.6	−77.7	−77.7	−74.9
Stilbamidine					
ΔE	−1193.0	−2000.9	−267.0	−281.9	−856.7
E_{MTP}	−1115.2	−1922.3	−189.4	−203.8	−782.5
E_{pol}	−38.5	−39.3	−38.3	−38.8	−35.6
E_{rep}	+47.3	+47.3	+47.3	+47.3	+47.3
E_{dl}	−86.5	−86.5	−86.6	−86.6	−85.9

and H_{35}—$O_{1'} = 2.65$ on the 5′,3′ strand. It is noteworthy that the NH group of the diazoamino bridge, which is on its convex side, is not involved in a direct interaction with the groove. On the other hand, H_{25} of the amidinium group and H_{27} of an aryl CH bond on this side are involved in an elongated contact with $O_{1'}$ of S_{-2} of the 5′,3′ strand, the corresponding interatomic distances being (in Ångström units): H_{25}—$O_{1'}S_{-2} = 2.24$ and H_{27}—$O_{1'}S_{-2} = 2.57$.

The binding of stilbamidine encompasses a number of sites in the minor groove ($O_{1'}$, N_3 and O_2) larger than that of berenil, the interatomic equilibrium distances being, however, altogether larger than with berenil. In fact, only two elongated contacts are found, with the sugar oxygens, namely (in Ångström units): H_3—$O_{1'}$ of $S_{-3} = 2.24$ and H_{25}—$O_{1'}$ of $S_{-2} = 2.25$ on the 5′,3′ strand. A certain number of interatomic distances between the hydrogens of stilbamidine and different sites of DNA (ranging from $O_{1'}$ of S_0 to $O_{1'}$ of S_{+2} on the 3′,5′ strand and from N_3 of A_{-2} to $O_{1'}$ of S_0 on the 5′,3′ strand) falls within the still longer range of 2.7–3.1 Å. Each side of the stilbamidine molecule, with respect to its long axis, faces a distinct strand of the double helix, in marked contrast to the optimal configuration derived from berenil, the concave side of which interacts with both strands simultaneously.

Let us now compare the intermolecular interaction energies of the two diarylamidines and their components.

Unscreened $(dA\text{-}dT)_n$. The intermolecular interaction energy computed at the undecamer level is slightly larger for berenil than for stilbamidine. This global energy difference stems essentially from the difference of the electrostatic contributions to the binding (E_{MTP}), which is more favorable for berenil than for stilbamidine. For both diarylamidines, E_{MTP} provides by far the dominant contribution to the binding energy. Its magnitude is a reflection of the strong attractive values of the molecular electrostatic potential computed in the minor groove of A-T sequences of B-DNA (30, 31). This effect ensures the binding of cationic drugs in this groove even when no hydrogen bonding possibilities exist, as in the case of stilbamidine, provided that an adequate fit in the groove is obtainable. This conclusion is in line with the one derived in a previous study of the binding of SN 18071 to DNA (8), which also underlined the role of the electrostatic factor in the interaction. In the present case, we may further point out that at the unscreened undecamer level, the sole monopole-monopole component of E_{MTP} is even *larger* with stilbamidine than with berenil (−1125.5 kcal/mole as opposed to −1122 kcal/mole).

The value of the repulsion component, E_{rep}, to the binding energy is larger (by 8 kcal/mole) for stilbamidine than for berenil, owing to the larger number of sites encompassed by the former. This larger value of E_{rep} is compensated for by more attractive values of the dispersion-like contribution, E_{dl}, and, to a lesser extent, of the polarization contribution, E_{pol}, in stilbamidine than in berenil. In fact, the summed values of these three contributions favor, albeit slightly, stilbamidine over berenil.

The intermolecular interaction energies of the two diarylamidines increase considerably upon passing from the undecamer level to the "triple phosphate turn" level. This increase results from the accumulation of the phosphate charges of the backbone (that are now equal to 60), which increases the electrostatic contribution to the binding. The energy difference favoring berenil increases upon passing from the undecamer level to the triple phosphate turn, this increase being paralleled by the increase in the corresponding value of the difference between the respective electrostatic contributions to the binding. Owing to its more curved shape, berenil is buried more deeply in the core of the minor groove than is stilbamidine, and is thus more sensitive to the increase in the molecular electrostatic potential in that zone.

In this connection, it is interesting to observe here that the interaction energies of berenil and stilbamidine, with a *shorter* oligohelix, namely a double helix built of a heptanucleoside hexaphosphate, *are in favor of stilbamidine* (see last column of Table 1). Hence a minimal length of the helix, approximately a complete helical turn, is necessary for a reversal of the relative affinities in favor of berenil. A related effect of the oligomer chain length was previously noted in ref. 9, comparing the affinities of two bisguanylhydrazones for $(dA\text{-}dT)_n$: it was shown there that an intrinsic preference displayed at the heptamer level in favor of the shorter, aliphatic

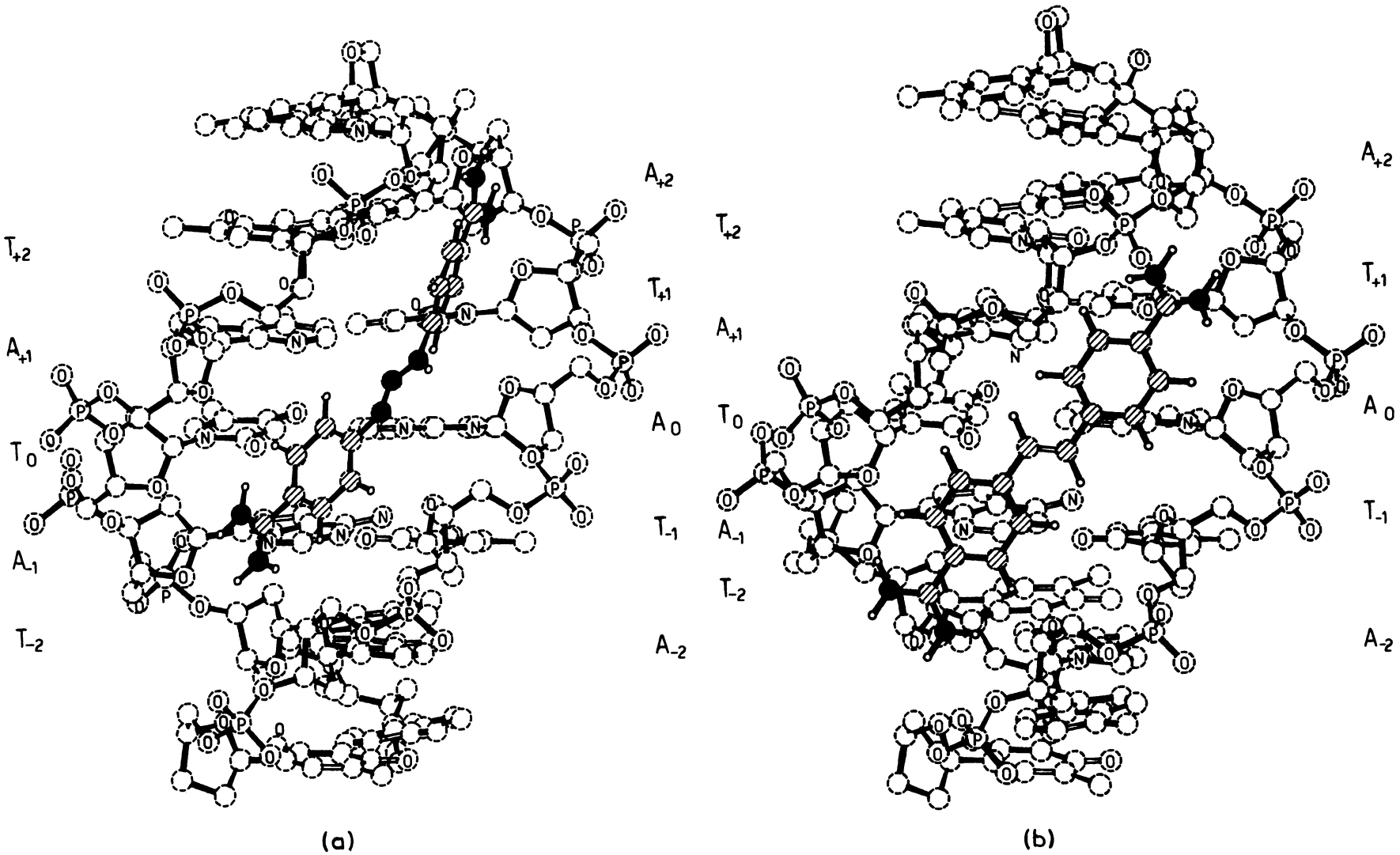

FIG. 4. *Representation of the intrinsically preferred configurations of binding of berenil (a) and stilbamidine (b) to (dA-dT)$_n$*

bisguanylhydrazone, with respect to a longer aromatic bisguanylhydrazone, decreased considerably when the oligomer chain was lengthened. In the present situation, the two diarylamidines have comparable lengths, and the lengthening of the oligomer chain favors berenil because this compound can be buried more deeply in the core of the groove. We may thus estimate that the deeper the cationic ends of a nonintercalating molecule are located within the minor groove, the more will the buildup of anionic charges and the resulting increase in the molecular electrostatic potential enhance its affinity for this groove.

The interaction energy differences between the two diarylamidines are seen to represent only a fraction of the total interaction energy, especially at the unscreened undecamer level. Nevertheless, the trend observed upon gradual buildup of phosphates, which increasingly favors berenil over stilbamidine, is clear-cut.

Screened (dA-dT)$_n$. As a result of countercation binding to the phosphates, the value of ΔE and of E_{MTP} are reduced 5- to 6-fold with respect to their values with unscreened phosphates, the other contributions being rather insensitive to this effect. The value of the energy difference between the two diarylamidines, favoring berenil over stilbamidine, is slightly larger with screened DNAs, both at the undecamer and at the triple phosphate turn levels.

CONCLUSIONS

The principal conclusions of the present study are that the two related diarylamidines, berenil and stilbamidine, can bind to the minor groove of DNA in two distinct types of configurations and that their compared affinities for the groove may be enhanced differently as a function of the chain length of the oligonucleotide. The binding of berenil occurs essentially with one thymidine on each strand and involves predominantly its concave side. The molecule is deeply buried in the groove, deeper than is stilbamidine. These results underline the role of an adequate curvature of the drug for attaining an optimal fitting within the groove and may be of importance in the design of minor groove binders.

In the intrinsically preferred binding configuration of stilbamidine, each side of the molecule, with respect to its long axis, faces a different strand of the oligonucleotide. Only two relatively elongated molecular contacts are found, involving two hydrogens of an amidinium group and $O_{1'}$ of two successive deoxyriboses on the 5′,3′ strand.

The interaction energy of the two molecules with the minor groove is dominated by the electrostatic contribution, E_{MTP}, and reflects the existence of the strong attractive values of the molecular electrostatic potential in the minor groove of A-T sequences for cationic molecules. The dominant effect of E_{MTP} exerts itself even when only a limited number of H-bonding interactions takes place beween DNA and the substrate.

The affinity of berenil for (dA-dT)$_n$ is computed to be slightly larger than that of stilbamidine, at the undecamer level. The interaction energy difference increases significantly from the undecamer level to the triple phosphate turn level, the latter level being more representative of the situation prevailing in a polymer as contrasted to an oligomer. Such a result can be interpreted in terms of the molecular electrostatic potential in the groove, the increase of which favors configurations locating the cationic ends of the diarylamidine more deeply in the core, at the expense of more peripheral configurations. By contrast, with a shorter oligomer (that is, at the heptamer level), the energy difference favors stilbamidine.

As previously emphasized (8, 9), the absolute values of the gas-phase interaction energies derived in this study must not be correlated quantitatively with experimental values of the complexation of the diarylamidines by the oligonucleotide in solution (unavailable at present). Such a correlation would require a more exhaustive inclusion of the solution environment of the complex (for discussion of a similar case and suggestion for a formal treatment see, e.g., ref. 32).

However, it is unlikely that such an inclusion would modify the conclusions reached on the basis of our intermolecular approach.

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