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An Analysis of van der Waals Attractive Forces in DNA-Minor Groove Binding

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Abstract: Force field methodology (AMBER) has been used in conjunction with X-ray crystallographic data to evaluate the importance of attractive van der Waals forces in complexes of d(CGCGAATTCGCG)$_2$, d(CGCAAATTTGCG)$_2$, and d(CGCGTTAACGCG)$_2$ with a variety of ligands. Large negative energies were obtained (-128 to -246 kJ/mol) which, with exception of netropsin, were insensitive to base-pair sequence.

Recent discussions of the molecular basis for minor groove binding of DNA-drug binding molecules have stressed the importance of various factors, for example, hydrogen bonding, electrostatic forces, and van der Waals interactions as major contributors.[1] A full understanding of these forces is essential to the future development of new ligands with DNA recognition specificity. In view of the results of a recent comprehensive experimental study[2] that provided evidence for the relative importance of van der Waals forces for benzimidazole:DNA complexes, we initiated a theoretical evaluation of the role of van der Waals binding forces in DNA complexes. Our objectives were to provide a basis for quantitative comparisons of these attractive[3] forces in a variety of complexes, and to seek correlations of ligand structure with van der Waals energy.

Empirical force field methodology provides a straightforward approach to this problem.[3-6] A comparison of van der Waals components of the steric energy of the DNA complex with the analogous sum for the duplex+ligand provides an estimate of the magnitude and direction of this aspect of the energetics of binding. It is recognized that these energy differences will be somewhat dependent on the force field because of differences in parameterization, but we have shown in a survey of several systems that the differences are minor.[3]

Methodology: Cartesian coordinates and connectivity data for the complexes were obtained from the Brookhaven National Laboratory Protein Data Bank as *.pdb files. These files were edited to remove water and extraneous ions, and visualized by MacroModel v.4.0.[7] Prior to calculation of the steric energies, the representations of the ligands were modified to include double bonds, charges, and certain hydrogen atoms, (e.g. NH, OH) to convert them into the appropriate format for single point energy computations by the united-atom version of AMBER.[7,8] The total steric energy of the complex was calculated; next, the ligand was excised and the total energy of the duplex was calulated. Similarly, the total steric energy of the ligand could be obtained. The van der Waals contributions to the total steric energies resulting from these single point calculations are listed in the Tables.[9,10,11]

Results and Discussion. In each case (**Tables 1, 2,** and **3**), the sum of the calculated single point van der Waals energies of the components (*i.e.* ligand + duplex) is substantially *greater* than the van der Waals energy of the corresponding complex. These differences reflect the relative importance of steric attractive forces

between the ligand and the duplex and are independent on the presence or absence of solvent. Since the calculated van der Waals attractive energies range from -128 kJ/mol to -246 kJ/mol and the experimentally determined enthalpies are in the range of 35-50 kJ/mol[12] it is clear that there are counteractive forces at work.[13]

Table 1 van der Waals Energies (kJ/mole) of Complex Formation with $d(CGCGAATTCGCG)_2$

Ligand	pdb No.	Complex	Duplex	Ligand	Difference
4'-6-diamidine-2-phenylindole	1d30	-800.2	-678.0	30.4	-152.6
1,3-bis(4'-amidinophenyl)triazene	2bde	-1273.0	-1159.6	39.8	-153.2
netropsin	1d86	-881.2	-801.6	48.3	-127.9
1,3-bis(4-amidophenoxy)propane	1prp	-1072.6	-953.8	45.9	-164.7
ethyl-bis-benzamide (Hoechst 33342)	129d	-875.3	-688.8	47.6	-234.1
1,5-di(4-amidinophenoxy)-3-oxapentane	166d	-1092.0	-938.8	29.8	-183.0
pentamidine	1d64	-891.3	-853.2	104.2	-142.3
bis-benzimide (Hoechst 33258)	1dnh	-737.6	-599.6	61.8	-199.8
bis-benzimide (Hoechst 33258)	1d44	-1097.8	-970.8	80.4	-207.4
imidazolinyl-hydroxyphenylbenzimidazol	109d	-1211.4	-1021.9	28.1	-217.6

Table 2 van der Waals Energies (kJ/mole) of Complex Formation with $d(CGCAAATTTGCG)_2$

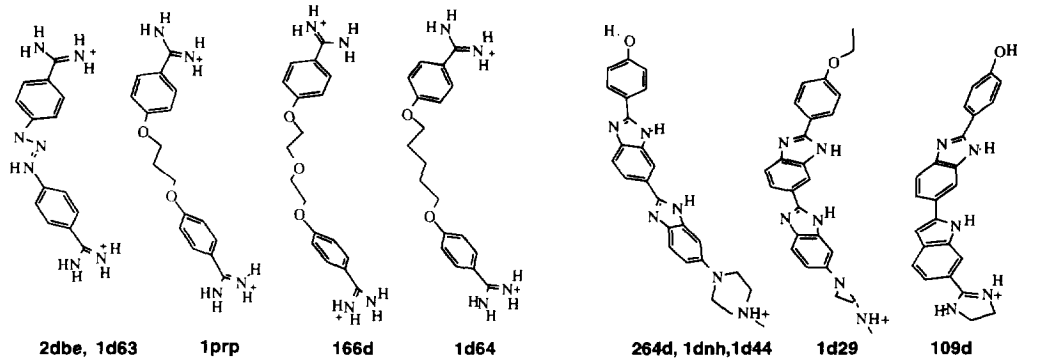
Ligand	pdb No.	Complex	Duplex	Ligand	Difference
1,3-bis(4'-amidinophenyl)triazene	1d63	-1220.8	-1093.9	37.1	-164.0
netropsin	121d	-1031.8	-828.4	1.6	-205.0
1,3-bis(4-amidophenoxy)propane	102d	-1071.8	-941.3	37.1	-167.6
bis-benzamide (Hoechst 33258)	264d	-1126.2	-937.1	46.8	-235.9
distamycin	2dnd	-490.7	-395.3	78.5	-173.9

Table 3 van der Waals Energies (kJ/mole) of Complex Formation with $d(CGCGTTAACGCG)_2$

Ligand	pdb No.	Complex	Duplex	Ligand	Difference
netropsin	195d	-1178.2	-933.9	2.0	-246.2

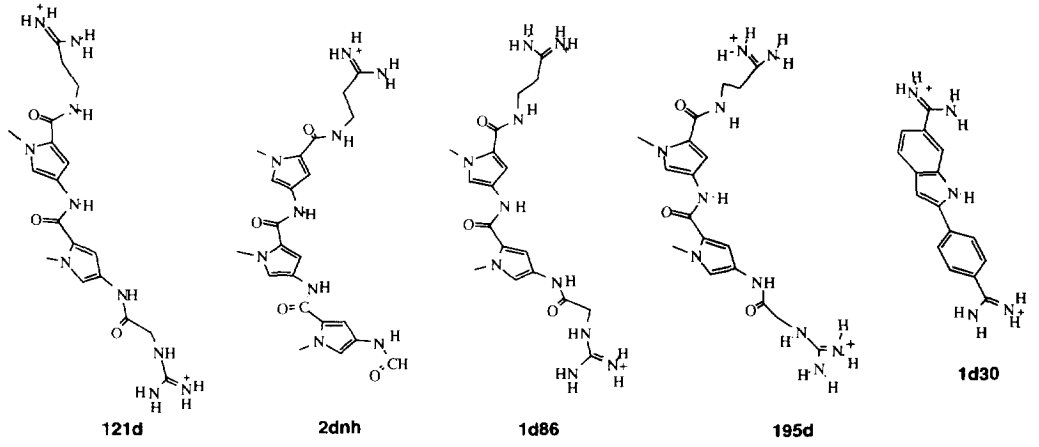
On the basis of these results, some generalizations can be made *vis-a-vis* structural effects. The magnitude of the van der Waal contribution is not very sensitive to of base-pair sequences[14] but depends more on the nature of the ligands. Those ligands with heteroatom linkers between aromatic end groups (Nos. 1prp, 166d, 1d64, 2bde, 1d63) each have relatively small van der Waals binding energies: 114-164 kJ/mol. On the other hand, ligands with several contiguous aromatic groups (Nos. 1dnh, 109d. 129d, 1d44) have relatively large van der Waals binding energies: 200-234 kJ/mol.[11] Representations of these molecules are shown in formulae that were generated directly from the Brookhaven *.pdb files (**Figure 1**). The low calculated van der Waals energy for complex No. 1d30 (**Figure 2**) is consistent with its position as a truncated member of the aromatic series.

Figure 1



A third class of ligands including (modified) netropsin and distamycin (**Figure 2**) combines both of these elements, having aliphatic chains interspersed with pyrrole rings. The calculated van der Waals energies for modified netropsin are more variable and highly sensitive to the base-pair sequence (cf. **Tables 1-3**). Atomic superposition of the three ligands shows large variations in the relative positions of the side chains. This may be a reflection of the proposal by Kopka, *et al.* that base sequence information is read out by virtue of non-bonding van der Waals packing contacts.[15]

Figure 2



Our results not only affirm the findings of Czarny, *et al.*[2] but we believe that this protocol provides a useful approach to the problem of understanding and optimizing this aspect of DNA-drug binding. For example, our modeling methodology can be used to monitor the energy changes associated with structurally modified ligands in bound complexes: an overall reduction in the van der Waals energy of the complex relative to that of the components signals the likelihood of a more stable complex. In this way, one might be able to customize ligands to fit the grooves more effectively . Future communications will deal with this concept and the energetics of duplex conformational changes associated with binding.[13]

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References and Notes:

1. For a recent review see, Geierstanger, B. H.; Wemmer, D. E. *Annu. Rev. Biophys. Biomol. Struct.* **1995**, *24*, 463.

2. Czarny, A.; Boykin, D. W.; Wood, A. A.; Nunn, C. M.; Neidle, S.; Zhao, M.; Wilson, W. D. *J. Amer. Chem. Soc.* **1995**, *117*, 4716.

3. (a) We have used the term "steric attraction" in a related context to emphasize the dispersive aspect of van der Waals forces; see, Sauers, R. R. *J. Chem. Ed.*, **1995**, in press. (b) Abstracts of the 209th Meeting of the American Chemical Society, Division of Computational Chemistry, Anaheim, CA, April 1995, Abstract. no. 084.

4. (a) For a recent review, see: Neidle, S.; Jenkins, T. C. in *Methods in Enzymology Vol. 203, Molecular Design and Modeling: Concepts and Applications, Part B*; Langone, J. J., Ed.; Academic: New York, 1991, p 433. (b) Jenkins, T. C.; Lane, A. N.; Neidle, S.; Brown, D. G. *Eur. J. Biochem.* **1993**, *213*, 1175.

5. Caldwell, J.; Kollman, P. *Biopolymers* **1986**, *25*, 249.

6. Gago, F.; Reynolds, C. A.; Richards, W. G. *Mol. Pharmacol.* **1989**, *35*, 232.

7. Mohamadi, F.; Richards, N. G. J.; Guida, W. C.; Liskamp, R.; Caufield, C.; Chang, G.; Hendrickson, T.; Still, W. C. *J. Comp. Chem.*, **1990**, *11*, 440.

8. Weiner, S. J.; Kollman, P. A.; Nguyen, D. T.; Case, D. A. *J. Comp. Chem.* **1986**, *7*, 230.

9. The absolute accuracy of the energies listed is unknown, but the relative values are reliable indicators of binding energies of the isolated molecules. Except for the electrostatic component of the total steric energy, the sums of the other steric energy terms (bond stretching, bending, and torsion) of the ligand plus duplex exactly equal that of the complex. We are exploring this approach to evaluate electrostatic effects, but because solvation plays a major role in overall binding, meeting this objective is more problematic.

10. The equation used for the van der Waals energy computations was a Lennard-Jones 6-12 potential with a "soft-cutoff." The latter refers to a damping of the interactions as interatomic distances approach 7Å.

11. Aromatic rings are not given special treatment in these calculations, *i.e.*, π-stacking effects are accounted for as a summation of atom-atom van der Waals interactions. For recent comments on π-stacking: Newcomb, L. F.; Gellman, S. H. *J. Amer. Chem. Soc.* **1994**, *116*, 4993.

12. Marky, L. A.; Breslauer, K. J. *Proc. Natl. Acad. Sci. USA* **1987**, *84*, 4359.

13. Entropic effects are likely to be small in the complexes examined.[12] Although it appears to be generally conceded that the duplex undergoes minor changes on binding,[1,2] the sum of a lot of small structural changes can result in a significant overall energy increase. See Spolar, R. S.; Record, M. T. Jr. *Science* **1994**, *263*, 777 for a discussion of the coupling of local folding to site-specific binding of proteins to DNA. In addition, since none of the bound forms of the ligands examined were in their lowest energy conformations overall energies of binding must take this factor into account.

14. We intend to test this idea more comprehensively with examples that contain a broader spectrum of base-pair sequences.

15. Kopka, M. L.; Yoon, C.; Goodsell, D.; Pjura, P.; Dickerson, R. E. *Proc. Natl. Acad. Sci. USA* **1985**, *82*, 1376.

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