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Hydration Shell Model and a Correction for Three Intersecting Spheres

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ABSTRACT: The hydration shell model, which allows for the incorporation of solvent about atoms and functional groups, is examined. The volume available for solvent is proportional to the free energy of hydration. Because the traditional procedures only consider the intersection of a hydration shell with one atom (two intersecting spheres, 2IS), a simple approximation accurate to about ±2% is introduced to correct for the intersection of two atoms with the hydration sphere in the case of three intersecting spheres, 3IS. Results for the intercalation of 9-aminoacridine, proflavine, and ethidium with DNA show that the trends in binding remain unaltered for the case of no solvent, 2IS, or 3IS, but that the correction for 3IS must be included.

Introduction

Hydration effects have been approximated by shell models.[1] An approach[2-6] has evolved in which the change in free energy associated with a hydration shell for a solute molecule in a given conformation is a sum over hydration energies

$$F_i = \Delta f[n - v_i/(V_\mathrm{s} + V_\mathrm{f})] \qquad v_i < n(V_\mathrm{s} + V_\mathrm{f}) \tag{1}$$

$$F_i = 0 \qquad v_i \geq n(V_\mathrm{s} + V_\mathrm{f}) \tag{1'}$$

for each atom (or group) i. v_i is the excluded volume of all atoms in contact with solvated atom i. V_f is the free volume (unoccupied), and V_s is the volume occupied by the solvent. The effective volume occupied by the hydration shell of radius $R_{\mathrm{v}i}$ about atom i in the absence of other atoms or groups is $n(V_\mathrm{s} + V_\mathrm{f})$. The excluded volume in the ith hydration sphere due to atom j, represented by the shaded area in Figure 1, is denoted by v_{ij}. The volume of atom i includes the hydration shell, whereas the volume of atom j is calculated with the van der Waals radius ρ_j. Three cases have been considered.[4] If $r_{ij} \geq R_{\mathrm{v}i} + \rho_j$, then atom j does not intersect the hydration sphere about atom i and $v_{ij} = 0$. If $r_{ij} \leq R_{\mathrm{v}i} - \rho_j$, then atom j is contained within the hydration sphere and $v_{ij} = (4\pi/3)\rho_j^3$. Shown is the special case where $R_{\mathrm{v}i} - \rho_j \leq r_{ij} < R_{\mathrm{v}i} + \rho_j$. The excluded volume is calculated by

$$v_{ij} = \pi\int_{r_{ij}-\rho_j}^{w}[\rho_j^2 - (t - r_{ij})^2]\,\mathrm{d}t + \pi\int_{w}^{R_{\mathrm{v}i}}[R_{\mathrm{v}i}^2 - t^2]\,\mathrm{d}t \tag{2}$$

$$= \tfrac{2}{3}\pi[R_{\mathrm{v}i}^3 + \rho_j^3 + \tfrac{1}{2}r_{ij}^3] - \pi r_{ij}[w^2 + \rho_j^2] \tag{2'}$$

The intersection of the two spheres along the x axis is calculated with the law of cosines, $w = (R_{\mathrm{v}i}^2 + r_{ij}^2 - \rho_j^2)/2r_{ij}$. This formula is a simplification of that presented by Hopfinger.[4] Previous investigations approximated the excluded volume with the formula by using only two intersecting spheres (2IS)

$$(v_i)_{2\mathrm{IS}} = \sum_j v_{ij} \tag{3}$$

However, this equation overestimates the exclusion of solvent surrounding atom i when the excluded volume of two bonded atoms lies within the hydration sphere. This is illustrated in Figure 2. The hydration sphere about atom i encompasses several atoms bonded in a sequence, *iklnp*, where $j = k$, l, n, and p. As one proceeds along the sequence from atom i, the following occurs for a change in molecular conformation: Atom k is entirely within the hydration sphere. The excluded volume due to atom l does not change for rotations about bond *ik*. However, the excluded volume due to atom n changes for rotations about bond *kl*. In addition, the excluded volume within the volume common to atoms l and n changes for rotations about bond *kl*. This results in the intersection of three spheres, namely, the hydration sphere about atom i with the van der Waals spheres of two atoms l and n in sequence and removed from atom i by at least one atom.

A correction for this overestimation of v_i can be made by an approximation in which the volume of two intersecting atoms l and n is replaced by a sphere of equal volume centered at the midpoint m of the line connecting centers l and n. This volume, v_{ln}, is calculated with eq 2 by using ρ_l and ρ_n in place of $R_{\mathrm{v}i}$ and ρ_j. Then the radius $\rho_m = [(3/4\pi)v_{ln}]^{1/3}$. In Figure 2a, the shaded region represents the volume common to two atoms l and n, which is subsequently approximated by the sphere of radius ρ_m as shown in Figure 2b. This sphere intersects the solvation sphere and either eq 2 can be used to evaluate this excluded volume or, more efficiently, the following approximation. The radius of sphere i is at least 2–3 times that of atoms k, l, n, and p or of the sphere of radius ρ_m. If the surface of sphere i intersecting sphere m is assumed to be a plane, then the volume of a spherical segment of sphere m is given[7] by

$$V_\mathrm{h} = (\pi h^2/3)(3\rho_m - h) \qquad h < 2\rho_m \tag{4}$$

$$= (4\pi/3)\rho_m^3 \qquad h \geq 2\rho_m \tag{4'}$$

$$h = R_{\mathrm{v}i} - r_{im} + \rho_m \tag{4''}$$

The excluded volume corrected for three intersection spheres (3IS) becomes

$$(v_i)_{3\mathrm{IS}} = \sum_j v_{ij} - \sum_{\substack{j,j' \\ (j \neq j')}} v_{jj'}^{\,i} \tag{5}$$

where the correction $v_{jj'}^{\,i}$ is the volume of hydration sphere i common to atoms j and j'. The second term in eq 5 corrects eq 3 for the overestimation of the excluded volume.

The volume V_h was compared to the actual volume common to three intersecting spheres. The space was partitioned into a three-dimensional grid. Cubes which lie within the common volume were added together to obtain a numerical result. In examples for the binding of molecules to DNA, volume elements for each correction, $v_{jj'}^{\,i}$, were calculated with the approximation V_h and for the time-consuming numerical calculation of the actual volume of three intersecting spheres. The error reaches ±10% for the very small individual volume elements, but in most cases it is about ±2%. The overall error is approximately ±2%. The reduction in computation costs justifies the use

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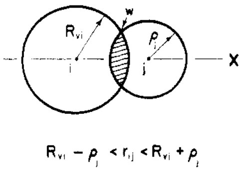


Figure 1. Intersection of the solvation shell of radius R_{vi} with an atom of van der Waals radius ρ_j to give the excluded volume v_{ij} (shaded region). The two-dimensional projection is cylindrically symmetrical about the x axis.

Table I
Total Energy Change, ΔE_{DNA}, Required To Open a Dimer Duplex of B-DNA to Intercalation Site (I, −0.4)[a]

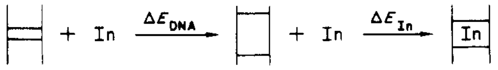
sequence	NS	2IS	3IS
$\uparrow\begin{matrix}A\cdot T\\T\cdot A\end{matrix}\downarrow$	19.1	20.7	23.5
$\uparrow\begin{matrix}A\cdot T\\C\cdot G\end{matrix}\downarrow$	20.0	22.0	26.5
$\uparrow\begin{matrix}G\cdot C\\C\cdot G\end{matrix}\downarrow$	20.5	23.0	28.6
$\uparrow\begin{matrix}A\cdot T\\G\cdot C\end{matrix}\downarrow$	23.8	26.2	30.5
$\uparrow\begin{matrix}G\cdot C\\G\cdot C\end{matrix}\downarrow$	24.7	27.2	31.3
$\uparrow\begin{matrix}A\cdot T\\A\cdot T\end{matrix}\downarrow$	25.3	26.9	33.1
$\uparrow\begin{matrix}T\cdot A\\C\cdot G\end{matrix}\downarrow$	26.2	28.5	34.0
$\uparrow\begin{matrix}T\cdot A\\A\cdot T\end{matrix}\downarrow$	29.1	30.9	36.0
$\uparrow\begin{matrix}T\cdot A\\G\cdot C\end{matrix}\downarrow$	29.6	32.2	38.0
$\uparrow\begin{matrix}C\cdot G\\G\cdot C\end{matrix}\downarrow$	30.7	33.7	39.4

[a] The conformation of intercalation site (I, −0.4) is given in ref 14. Energies are reported for no solvent (NS) and solvent with the approximation of two (2IS) and three (3IS) intersecting spheres.

of eq 4 and 4′ to correct for the double counting for three intersecting spheres.

Hydration Energy Calculations

The energy for the intercalation process



(6)

previously has been represented by two steps.[8-10] The first entails opening of the DNA to one of the intercalation sites, and the second entails binding of an intercalant (In) to DNA. The energy consists of two-body interactions. They are Coulomb (Q), van der Waals attractive and repulsive terms (U in a 6–14 potential), and a torsional potential (T).[8-10] Hydration effects are included as a sum over terms in eq 3 and 5.[11] Subscripts are used to denote the DNA or intercalant, In. Inclusion of the solvent in the total energy does not permit a partitioning of the solvation energy into independent contributions because the hydration energy in ΔE_{DNA} depends on the position of In, etc. In the case without solvation each term in the energy of an intercalation complex

$$\Delta\epsilon_{In} = \Delta E_{DNA} + \Delta E_{In} \quad (7)$$

can be calculated independently. The hydration energy can be partitioned into

$$S = S_{BP} + S_{P} + S_{In} \quad (8)$$

$$= \sum_i (v_i)_{nIS} \qquad (n = 2 \text{ or } 3) \quad (8')$$

where BP, P and In refer to solvation of the base pairs, the ribophosphate backbone, and the intercalant. However, the value of each term S_{BP}, S_P, and S_{In} depends on the positions of BP, P, and In, and each is calculated for the DNA, In, and the complete intercalation complex. One purpose of partitioning S is to examine the solvation energy under the approximation of two intersecting spheres (2IS) and the importance of a correction for three intersecting spheres (3IS). This common volume that intersects the solvation sphere is included twice in the calculations of the excluded solvent from the solvation sphere in eq 2 with the 2IS approximation, namely, when $j = l$ and $j = n$ as seen in Figure 2. The second purpose is to evaluate the

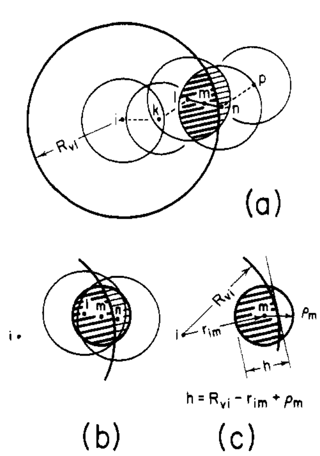


Figure 2. Approximation to the van der Waals volume of two intersecting atoms common to the hydration sphere. (a) Projection of an atom sequence showing the intersection of the hydration sphere about atom i of radius R_{vi} with atoms k, l, n, and p which have van der Waals radii ρ_k, ρ_l, ρ_n, and ρ_p. Shaded portion denotes the region common to atoms l and n, of which the heavily shaded portion lies within the hydration sphere about atom i. (b) A sphere of radius ρ_m about the midpoint m of l and n and the same volume as the shaded region. (c) Volume of a spherical segment in which the surface of the hydration sphere is replaced by a plane to approximate the heavily shaded region.

Table II
Comparison of Energies of Intercalation Complexes Calculated with the Approximation of Two Intersecting Spheres (2IS) and with the Correction Made for Three Intersecting Spheres (3IS)[a]

		NS	2IS				3IS			
In	ν	$\delta\epsilon_{In}$	$\delta\epsilon_{In}$	S_{In}	S_{BP}	S_P	$\delta\epsilon_{In}$	S_{In}	S_{BP}	S_P
9AAC	F			0.1				2.2		
	I	0.0	0.0	0.0	1.0	0.9	0.0	0.7	11.7	5.8
	I	0.4	0.9	0.0	1.5	0.9	0.5	0.8	11.9	5.8
PRFL	F			1.0				3.9	.	
	I	0.0	0.0	0.0	1.2	0.8	0.0	0.4	11.3	5.6
	I	7.6	8.7	0.0	1.9	0.9	9.1	0.8	12.3	5.8
ETHM	F			1.0				2.8		
	I	0.0	0.0	0.0	0.7	0.9	0.0	0.4	9.6	5.7
	II	10.7	11.7	0.0	0.9	1.1	11.9	0.5	10.0	5.8
	III	12.3	12.1	0.0	1.0	0.9	9.7	0.4	10.2	3.7

[a] $\delta\epsilon$ is defined by eq 9. Conformations for intercalation sites ν = I, II, and III are given in ref 9 and 14. F denotes the free molecule.

solvation effect on the intercalation process.

In Table I, the energies required to open B-DNA to intercalation site I are reported for the case of no solvent (NS) and with the approximations of two intersecting spheres (2IS) of eq 3, and with a correction for three intersecting spheres (3IS) of eq 5. The energies are reported in kcal/mol for a dimer duplex mole. The net change in energy is 1.5–3.0 kcal for 2IS and 4.4–8.7 kcal for 3IS relative to NS. Experimental evidence[12] for the stability of pyrimidine (p)–purine sequences and theoretical calculations[9,13] performed previously remain unchanged when solvent is included. Correction for the 3IS case over the 2IS case changes the values of ΔE_{DNA} for each base pair by approximately 5 kcal per dimer duplex unit. The dependence of the energy on the base sequence remains unchanged.

In Table II, the energies of intercalation complexes of 9-aminoacridine (9AAC), proflavine (PRFL), and ethidium (ETHM) with a dimer duplex $\uparrow^{C\cdot G}_{G\cdot C}\downarrow$ are given. The energy

$$\delta\epsilon_{In} = \Delta\epsilon_{In} - (\Delta\epsilon_{In})_{min} \qquad (9)$$

is reported relative to the global minimum of each intercalation complex. Calculations are performed for the intercalation sites ν = I, II, and III. These receptor sites occur for unwinding of B-DNA by small (8°), intermediate (16°), and large (30°) unwinding angles.[9,14]

The trends in the relative complex energy $\delta\epsilon_{In}$ remain unchanged in the three cases: NS, 2IS, and 3IS. The correction for 3IS is about 1 kcal for In, 10 kcal for base pairs (BP), and 5 kcal for the phosphate backbone (P). The importance of the solvent in the hydration model in the intercalation process is diminished by the observation that all energy terms in the thermodynamic process of eq 6 change uniformly. However, the results suggest that hydration effects provide a substantial contribution and may have to be considered in cases where dramatic conformational changes occur.

The problem of overcounting the excluded volume in the 2IS approximation has been recognized previously. To avoid this problem Hodes et al.[3] allow the volume of the hydration shell to decrease conformationally in a manner dependent on the overlap of the affected groups. Although this avoids the costly numerical calculation of the common overlapping volume as well as the overcounting of the excluded volume, strict adherence to the parameterization is not maintained.

Forsythe and Hopfinger[15] have replaced the discrete hydration shell with a radial density function, f, approximately the free energy of the solvent. The change in solvation free energy is assumed to be a function of the overlap of f_j and f_k for interacting groups j and k. The present study of the effect of three overlapping spheres suggests that their model should be modified to correct for the overlap of the distributions f_i, f_j, and f_k for three groups. The calculation requires two- and three-center integrals for two and three interacting groups. It is easily generalized to n-center integrals for n interacting groups.

In another approach, Huron and Claverie[16] have transformed the volume integral to an integral over the surface containing the van der Waals volume. All two-body interactions between solute and all solvent molecules must be calculated. This requires a numerical evaluation for each molecular conformation.

The approach to the calculation of hydration energies by an excluded volume requires a correction for overcounting due to three intersecting spheres (and perhaps even for four intersecting spheres). The value of our simple approximation is apparent by noting that the time required to calculate the sum over three interacting groups increases by N^3, where N is the number of interacting atoms. The importance of the 3IS correction is seen by the results for intercalation in which the solvation energies change by factors of 0.1–10. The simplicity of the approximation of eq 4 drastically reduces the computational time over numerical integration.

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