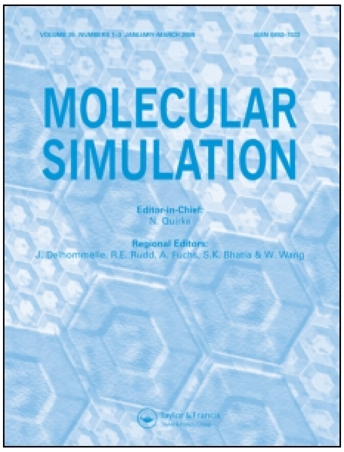

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Modified Proximity Criteria for the Analysis of the Solvation of a Polyfunctional Solute

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MODIFIED PROXIMITY CRITERIA FOR THE ANALYSIS OF THE SOLVATION OF A POLYFUNCTIONAL SOLUTE

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The proximity criterion of Mehrotra and Beveridge, that divides the region around a solute into the Voronoi polyhedra defined by the solute atoms, has been modified to use the radical planes based on the solute atom Van der Waals spheres, as suggested by Gellatly and Finney, or on the interaction strength of the atom with the solvent. A comparison of these promiximity criteria is given using the aqueous hydration of trans N-methyl acetamide.

KEY WORDS: Proximity criterion, hydration, Voronoi polyhedra.

I. INTRODUCTION AND BACKGROUND

The proximity criterion, introduced by Mehrotra and Beveridge [1] provides a unique assignment of solvent molecules to solute atoms around a polyfunctional solute molecule by assigning it to the nearest solute atom. Based on this assignment, the statistical state of the system can be described in terms of various distribution functions defined for a solute atom or a functional group [2,3]. In geometrical terms, this assignment is equivalent to partitioning the space around the solute molecule into the Voronoi polyhedra defined by the bisector planes between the solute atoms.

The Voronoi polyhedra of the solute atoms and solvent molecule centers have been used by David and David [4] as a tool to analyse solvent structures around a solute. The use of the Voronoi polyhedra for the partitioning of the space in a protein molecule has also been discussed by Gellatly and Finney [5]. They pointed out that the approach has the drawback that the differences among the sizes of the atoms are neglected and proposed instead the partitioning of the space by the radical planes (see next section) corresponding to the Van der Waals spheres of the atoms. Baranyai and Ruff [6] used the same approach to partiton the space in a molten salt. Unlike the proximity criterion, References 4 and 6 provide partitions of the space around the solute that depend on the solvent coordinates.

In this note it will be shown that a minimal modification of the proximity criterion leads to the partitioning of the space by the radical planes of spheres drawn around the solute atoms. The difference between the two approaches will be explored through a numerical example, using sphere radii based on both energetic and geometric properties of the solute atoms.

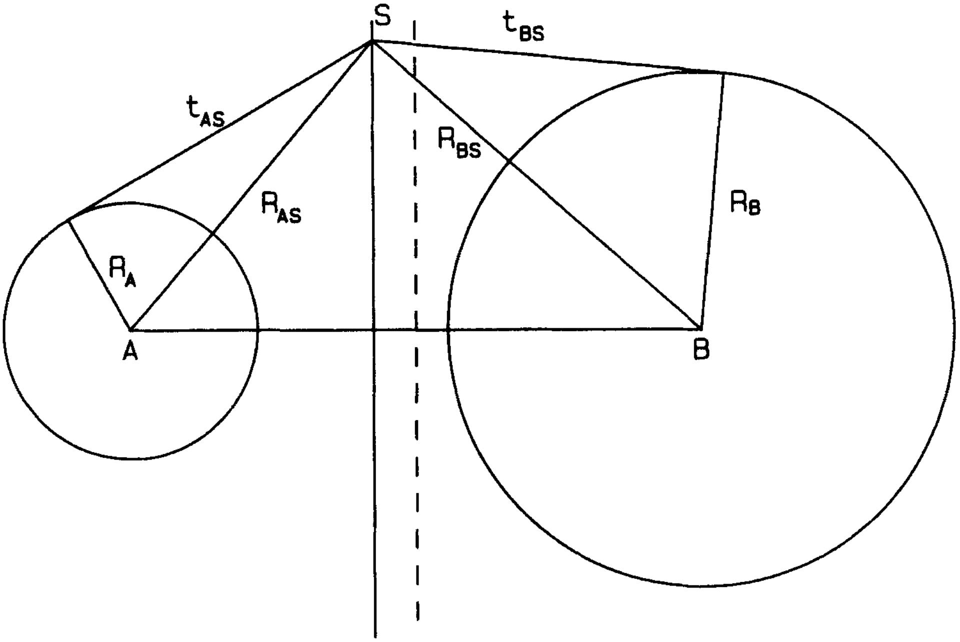

Figure 1 The division of space around two solute atoms based on the bisector and on the radical plane. Heavy line: radical plane, broken line: bisector plane.

II. THEORY

Figure 1 shows in 2 dimensions the partition between two atoms of different radii using both the bisector and the radical plane. The radical plane of two spheres is the locus of points from which the length of the tangent to the two spheres are equal. It is perpendicular to the line connecting the center of the two spheres but is displaced from the bisector towards the smaller sphere by $[R_A^2 - R_B^2]/(2D)$ where R_A and R_B are the radii of the spheres A and B, respectively, and D is the distance between their centers. For spheres of equal radii the radical plane coincides with the bisector of the sphere centers. Clearly, the radical plane partitioning assigns more space to the larger atom than does the bisector partitioning.

At any point S the length square of the tangents are given as

$$t_{AS}^2 = R_{AS}^2 - R_A^2 \tag{1}$$

$$t_{BS}^2 = R_{BS}^2 - B_B^2 \tag{2}$$

where R_{AS} and R_{BS} are the distances of the point S from the solute atoms A and B, respectively. Whereas the original proximity criterion finds the side of the dividing plane a solute atom is in by comparing R_{AS} and R_{BS} (or R_{AS}^2 and R_{BS}^2), the modified proximity criterion proposed here makes the same decision by comparing t_{AS}^2 and t_{BS}^2, leading to the radical plane division.

The use of the modified proximity criterion may go beyond the original geometric definition of the radical plane. For overlapping spheres the radical plane is the plane in which the circle of intersection lies and it is not possible to draw tangents to the spheres from the points of the radical plane that lie inside the spheres. However,

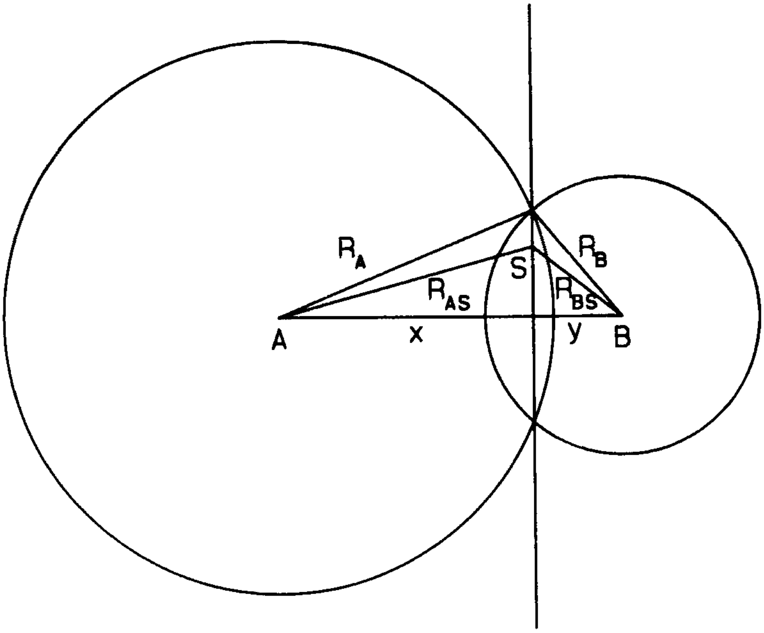

Figure 2 Radical plane of two intersecting spheres.

the modified proximity criterion will still give the correct partition, as can be seen from Fig. 2. By Pythagoras' theorem we have

$$R_A^2 - X^2 = R_B^2 - Y^2 \tag{3}$$

and

$$R_{AS}^2 - X^2 = R_{BS}^2 - Y^2. \tag{4}$$

Subtraction of Equation 3 from Equation 4 and use of Equations 1 and 2 gives

$$t_{AS}^2 = R_{AS}^2 - R_A^2 = R_{BS}^2 - R_B^2 = t_{BS}^2 \tag{5}$$

for any point s in the extension of the radical plane inside the spheres.

Care must be taken, however, for very large spheres. It is possible that the radical plane does not fall between the two sphere centers (Figure 3a) or – in case on sphere encloses the other – it falls outside both spheres but not between them (Figure 3b)! This would lead to the unacceptable partition where all points near the smaller sphere belong to the atom with the larger sphere and the region assigned to the atom with the smaller sphere starts far away from it.

It should be pointed out that nowhere in the discussion above was it assumed that the spheres are actually the Van der Waals spheres. Therefore, the R_A, R_B, ... values can be chosen based on other atomic parameters, such as the strength of the contribution of the atom to the solute-solvent interaction and this possibility will be explored in the present paper. To maintain an acceptable partition it is advisable to make sure that the case depicted on Figure 3b (caused by the large difference between the radii of two neighbouring atoms) does not occur.

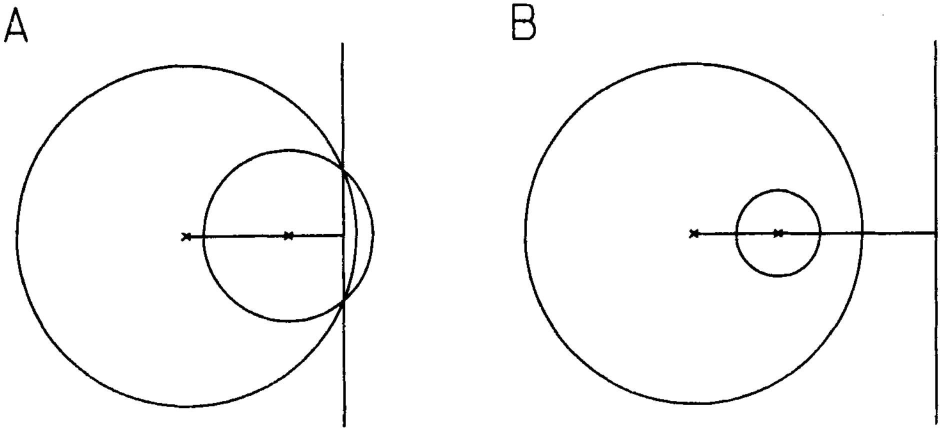

Figure 3 Examples of radical planes that do not lie between the centers of the two spheres.

III. CALCULATIONS

Recently, Monte Carlo calculations were perfomed [7] on the trans N-methyl acetamide (NMA) based on the OPLS functions developed by Jorgensen and coworkers for the solute-water interactions [8,9] and the TIP4P water-water potential [10,11]. Details of the calculations can be found in reference 7.

The following structural indices were calculated: (a) radial distribution functions for solvent molecules assigned to a given solute atom (called primary radial distribution function [1]) with the first peak height $g_{\max}$ and the corresponding distance $R_{\max}$; (b) first-shell coordination numbers $\bar{K}_s$ the average number of solvent molecules within a preassigned first shell radius R_c; (c) first-shell solvent density ϱ_{FS} and (d) total coordination number $\bar{K}_T$, giving the average number of solvent molecules in the total area assigned to a solute atom. R_c is usually defined by the first minimum in the primary solute–solvent radial distribution function for each atom. The computed energetic indices hydration shell water $\bar{v}_{FS}$; (b) the solute–solvent pair energy in the first shell $\bar{\varepsilon}_{FS} = \bar{v}_{FS}/\bar{K}_s$ and (c) solute–solvent binding energy from all water in the proximity region $\bar{v}_s$. In addition, The volume of the first hydration shell V_{FS} is defined as the volume of the proximity area (in either approach) that lies within the preassigned cutoff distance R_c. The solvent–structure is characterized by the averaged near-neighbour pair energy for water in the different proximity regions, $\bar{\varepsilon}_W$.

IV. RESULTS AND DISCUSSION

Table 1 collects the results of the proximity analysis on each of the solute atoms using both the original bisector partitioning (Voronoi polyhedra) and the partitionings by radical planes, based on the (a) Van der Waals radii of the atoms, (b) atomic charge parameter using

$$R_A = 1.5\,[q_A]/q_{\max} \tag{6}$$

where q_A is the charge parameter on solute atom A and $q_{\max}$ is the largest charge

Table 1 Comparative proximity analysis of trans-NMA R_c: First hydration shell radius; V_{FS}: First hydration shell volume; $\bar{K}_S$: Coordination number; ϱ_{FS}: First hydration shell density; g_{max}: First maximum of the primary radial distribution function; R_{max}: Location of the first maximum; ν_{FS}: First hydration shell solute binding energy; ε_{FS}: First hydration shell solute pair energy; $\bar{K}_T$: Total coordination number; ν_T: Total solute binding energy; ε_W: Solvent–solvent pair energy; *BS*: bisector plane divisions; *RP*1: radical plane division using Van der Waals radii; and *RP*2: radical plane division using charge magnitudes. Distances are in Å and energies are in *Kcal/mol.*

		R_c	V_{FS}	$\bar{K}_S$	ϱ_{FS}	g_{max}	R_{max}	$\bar{\nu}_{FS}$	$\bar{\varepsilon}_{FS}$	$\bar{K}_T$	$\bar{\nu}_s$	$\bar{\varepsilon}_W$
N	BS	4.0	16	0.2	0.40	2.6	3.6	−0.2	−1.14	1.3	−0.4	−3.36
N	PR1	4.0	10	0.1	0.41	2.5	3.7	−0.2	−1.33	0.8	−0.3	−3.38
N	PR2	4.0	50	0.6	0.35	2.0	3.7	−0.6	−1.03	3.9	−1.1	−3.39
H(N)	BS	2.3	29	0.6	0.57	1.4	2.0	−2.4	−4.40	44.3	−7.2	−3.32
H(N)	RP1	2.3	19	0.6	0.87	2.1	2.0	−2.4	−4.40	38.5	−6.2	−3.31
H(N)	RP2	2.3	21	0.6	0.80	1.6	2.0	−2.4	−4.40	45.0	−7.0	−3.32
Me(N)	BS	5.3	286	8.1	0.85	2.0	3.5	−2.6	−0.32	55.0	−3.6	−3.46
Me(N)	RP1	5.3	336	9.5	0.84	2.0	3.6	−3.5	−0.37	61.3	−4.6	−3.45
Me(N)	RP2	5.3	252	7.4	0.89	2.0	3.6	−2.2	−0.30	51.7	−3.1	−3.46
C(CO)	BS	4.3	20	0.4	0.56	3.0	3.7	−0.4	−0.98	1.5	−0.5	−3.34
C(CO)	RP1	4.3	18	0.3	0.53	2.7	3.6	−0.3	−0.97	1.2	−0.4	−3.32
C(CO)	RP2	4.3	28	0.5	0.60	3.0	3.7	−0.5	−0.92	2.1	−0.7	−3.34
O	BS	4.2	146	4.6	0.95	3.0	2.8	−10.8	−2.33	54.8	−12.3	−3.35
O	RP1	4.2	123	4.1	0.99	3.6	2.8	−10.5	−2.50	50.0	−11.5	−3.35
O	RP2	4.2	157	4.9	0.94	2.7	2.8	−11.0	−2.10	58.1	−12.7	−3.36
Me(C)	BS	5.3	288	8.5	0.88	2.2	3.7	−2.5	−0.29	58.1	−3.3	−3.35
Me(C)	RP1	5.3	334	9.7	0.87	2.1	3.7	−3.4	−0.35	64.1	−4.4	−3.35
Me(C)	RP2	5.3	254	7.6	0.88	2.1	3.7	−1.9	−0.26	54.2	−2.7	−3.35

(irrespective of sign) found in the solute molecule, giving R_A values between 0 and 1.5 Å.

An examination of the computed first-shell volumes show that, compared with the bisector partitioning (BS) the Van der Waals partition (RP1) will increase the primary regions of the methyl groups at the expense of the polar groups and increase the primary region of the oxygen at the expense of the hydrogen. The charge partition (RP2), again compared with the BS partitioning, will increase the primary regions of the polar groups at the expense of the methyl groups. Notice that this also means a significant increase in the primary regions of the atoms "inside" the molecule.

The computed first shell densities show that the change in coordination numbers can be explained very well by the change in the first shell volumes for the methyl groups but less well for the carbonyl oxygen, while the amino hydrogen's coordination number is insensitive to the volume change – a fact noted earlier [7].

The location of the first peak of the radial distribution function showed very little change while the height of the first peak was anticorrelated with the available first shell volume. The change in the height was significant for the hydrophylic atoms but small for the central carbon and nitrogen as well as for the methyl groups.

An interesting consequence of the change in the coordination number of the methyl groups is a disproprotionate change in the binding energies as reflected in the solute–solvent pair energies. This is a result of the reassignment of water between the methyl groups and the neighbouring polar groups, and shows that water around the boundaries examined is rather strongly bound. This tends to support the use of charge partitioning. On the other hand, no significant change was found in the water–water pair energies.

In summary, the results generally show little difference among the proximity criteria examined – trends are well preserved. Apart from the expected change in the volumes of the proximity areas and the concomittant change in the coordination numbers, larger than expected changes were observed only in the peak height of the solute–solvent radial distribution functions and in the first shell binding energies. The former affected most the hydrophilic atoms *N* and *H* while the latter affected the hydrophobic methyl groups. Based on the results on the solute–solvent energetics, it is concluded that the charge-based radical plane partitioning conforms the best to chemical intuition.

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