Molecular Mechanics and Molecular Shape. Part 1. van der Waals Descriptors of Simple Molecules

Amatzya Y. Meyer *
Department of Chemistry, University of Glasgow, Glasgow G12 8QQ, Scotland

A computer program was written to calculate and display graphically the van der Waals volume (V_w) and surface area (S_w) of molecules. Using van der Waals radii of C, H, Cl, and Br, and geometries optimised by the force-field method, V_w and S_w were obtained for about a hundred simple molecules: alkanes, cycloalkanes, and chlorinated and brominated derivatives thereof. S_w is more sensitive than V_w to stereochemical and positional isomerism. It was found that V_w correlates with the molar refraction and with the constant b in the equation of state, and can be used to estimate the molar volume. For very similar species, S_w correlates with the free volume that encapsulates the molecule in the bulk, so that a combined usage of V_w and S_w leads to the difference in molar volume between conformers. Numbers obtained by the procedure bear upon the 'conformational rule' of organic stereochemistry, and suggest a novel interpretation of the torsional term in the molecular-mechanical force field.

'Molecular mechanics usually performs less satisfactorily in energy than in structural calculations'.[1] Calculated geometries have been said to compete in accuracy with actual measurements.[2] They have been used indeed in lieu of,[3,4] in anticipation of,[5] and to interpret structural determinations.[6] And yet, as a recent review[7] might reveal, publications in molecular mechanics concentrate on energies; calculated details of structure, apart, perhaps, from torsional angles, are touched at only fragmentarily. One possible explanation is that a report on bond lengths and bond angles is wont to assume the unpalatable format of long tables with short commentaries. Another is that there is no urge to dwell on the results, since they either mimic experiment or conform with qualitative expectation.

The present study was prompted by a wish to find uses for the castaway material.[8] Recent interest in the van der Waals volume and surface area of molecules[9–12] offered a suitable point of departure. As it turns out, the published material consists mainly of applications to crystallography, molecular biology, or drug design, virtually bypassing the more common topics of organic stereochemistry. We chose therefore to follow the prescribed lines of approach, but concentrate on basic structural aspects of simple molecules. At this stage, we limit ourselves to few structural categories: alkanes and cycloalkanes, unbranched and branched, unsubstituted and mono- and di-substituted by chlorine and bromine. This report is based on a scan of about a hundred structures, ranging from ethane to decalin and to the dibromocyclohexanes. Since the molecules are numerous but similar in feature, fine details stand out and link van der Waals volumes and surface areas with topics such as the conformational rule, molar volume, solvation energy, and molecular electrostatic potential. Light is also shed on the nature of the molecular-mechanical process itself. Some of the connections were expected; some were unexpected; all provided new outlets to computed geometries, energy differences, and charge distributions. We cite and discuss some of our observations.

The Calculated Quantities.—Discussions of molecular volume and surface area revert ultimately to two classical papers by Bondi.[13,14] In a molecular-mechanical context it is helpful to set down a systematics more rudimentary than his. Let a 'van der

Waals sphere', of radius r_a and volume V_a be centred about each atom in a molecule [equation (1; $r = r_a$, $V = V_a$)]. On the

$$r = (3V/4\pi)^{\frac{1}{3}} \tag{1}$$

grounds of crystallographic evidence, r_a can be assigned to common types of atom.[12] The assumptions as to sphericity and atom-centricity are not compelling: alternatives to the sphere can be envisaged[15] and, for certain ends, it is customary to shift the centre of the sphere along the covalent bond.[16] The 'van der Waals volume' of a molecule (V_w) is then the sum of atomic volumes, provided that overlapping regions be counted only once [equation (2)]. In equation (2), i counts the atoms, j counts

$$V_w = \Sigma(i)V_{a,i} - \Sigma(j)(\eta_j - 1)\text{overlap}_j \tag{2}$$

all regions, and η_j is the number of spheres that overlap at j. To illustrate, the shaded area in Figure 1 is a cut through V_w of a four-atom assembly; the arcs divide it into many regions j. On the basis of equation (2), V_w can be calculated analytically,[10] as can be the area of its surface (see Appendix). In practice, a point-by-point scan[11,12] saves the need to delimit regions and find η_j, and also anticipates an eventual adoption of more complex geometrical representations of the V_a. Since V_w is considered impenetrable at ordinary temperatures to other molecules,[14] it may be understood to lie within the 'inner molecular space'.[17] We construe this qualitative notion in the qualitative sense that the attraction of a chemical reagent to the molecule, and the reagent's route of approach, are determined before it touches the van der Waals surface.

It is convenient to define an 'equivalent sphere', equal in volume to V_w and centred at the centre of mass of the molecule. Its radius r_e is given by equation (1; $r = r_e$, $V = V_w$). Since the equivalent sphere encloses a volume equal to V_w, it cannot circumscribe V_w. A great circle of this sphere is plotted in Figure 1. Figure 2a shows the Br/Br-*anti* conformation of *threo*-2,3-dibromobutane, viewed perpendicular to a BrC(2)C(3) plane. The shaded area in Figure 2b is the corresponding cut through V_w. The innermost of the three concentric circles is a great circle of the equivalent sphere.

In a dense assembly, each molecule is constrained by its neighbours to a limited region in space, a 'cell'.[18a] For a liquid, the volume of the cell is the 'molecular volume', as obtained from the measured density [equation (3), where ρ is the density,
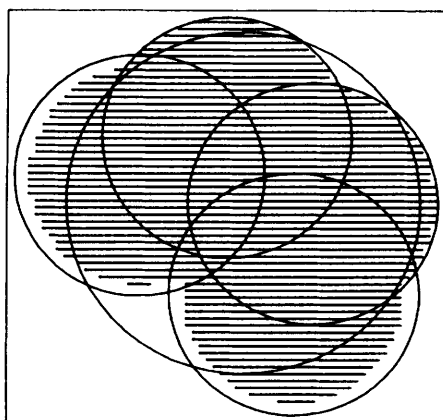
$$V_{in} = M/N_0\rho \tag{3}$$

Figure 1. A plane-projection of the carbon skeleton of *gauche*-butane. The shaded area is a cut through V_w in the plane bisecting C(1)C(2)C(3)C(4). The superposed circle is the corresponding cut through the equivalent sphere

M the molar mass, and N_0 Avogradro's constant]. For graphical reasons, we refer to it as the 'inner volume', V_{in}. The inner volume, unlike V_w, characterises the bulk compound. It is made up of V_w and a 'free volume', V_f, that may amount to 50% of the total.[13] Thus, $V_f = V_{in} - V_w$ and, using R to denote the ratio V_w/V_{in}, equation (4) follows. The volume V_{in} is required

$$V_f/V_{in} = 1 - R \qquad (4)$$

when calculating conformational equilibria in solution, whereat it is usually approximated as spherical.[19] For organic halogen compounds, this approximation proves to be numerically satisfying.[20] It is therefore convenient to define an 'inner sphere', of volume equal to V_{in}. V_{in} once estimated [by equation (3) or otherwise], the radius r_{in} of the inner sphere is known [equation (1; $r = r_{in}$, $V = V_{in}$)]. In Figure 2b, the second of the concentric circles represents the inner sphere, centred about the centre of mass. Alternative locations envisageable are the centres of molecular volume[19,21] and of charge.[22] In general, the inner sphere does not circumscribe V_w, even though $V_{in} > V_w$.

We use the term 'outer sphere' to label the smallest sphere that circumscribes V_w. Its radius r_{out} is the longest among the rays that connect the centre with the atoms, each ray being extended by the appropriate atomic radius r_a. Since the sphere is tangential to V_w, it may be considered as spanned in the 'outer molecular space',[17] but events on its surface can still be taken to be governed by properties of the molecule itself, not by surrounding agents. The outer sphere, then, is our substitute for the 'rolling-ball probe' of the molecular biologist,[23,24] or the 'molecular envelope' of the drug designer.[25] In particular, a mapping of the molecular electrostatic potential (MEP), as derived for this surface from information on the isolated molecule, is expected to be meaningful. Since the molecular-mechanical process provides nuclear co-ordinates and point charges,[26] such mapping is within its reach.[27] In plotting figures for this paper, we resorted to a crude approximation, stopping at the monopole contribution to the MEP.[28] The curves, therefore, cannot contend in quantitative detail with those resulting from refined quantum-chemical work,[29] but are made to stress those features that are of interest in applications, e.g. in drug design.[24,25,30,31] These features are the general shape, as required in comparing different molecules, and the position of potential wells.

In Figure 2b, the outermost circle is a cut through the outer sphere. The superposed plot is the electrostatic energy.
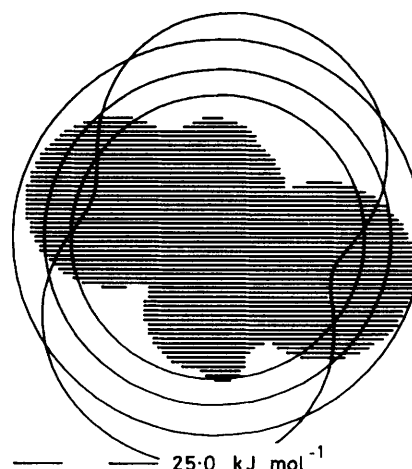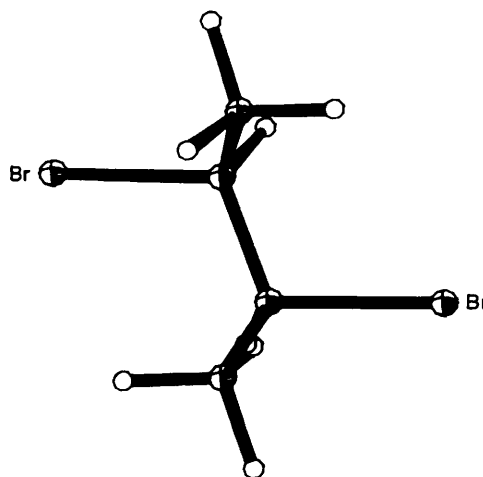
Figure 2. a, *threo*-2,3-Dibromobutane (Br/Br-*anti*), Br(rightmost)C(2)C(3) in plane. b, Graphical analysis of *threo*-2,3-dibromobutane, positioned as in Figure 2a

$W(\bar{r}) = \Sigma(i)q_i/\bar{r}_i$, as calculated for a positive unit of charge travelling along the arc of the outer circle. The outer circle serves as origin of a polar co-ordinate system: positive values of W are plotted outwith the circle, negative values are plotted within. The two arrowheads thus formed represent minima, and point at the preferred pathway of an approaching electrophile.

Another typical variant of the graphs is shown in Figure 3. It is the molecule of Figure 2, but this time viewed across the plane BrC(2)C(3). In the cut of Figure 3 the molecule is slimmer than in the cut of Figure 2, practically not protruding beyond r_{in}. The MEP does not contain sharp arrowheads, suggesting that this plane is but of minor chemical interest.

As to surface areas, S_w is best calculated at the stage of point-by-point scan. The spherical surfaces S_e, S_{in}, and S_{out} can be obtained from the corresponding volumes and radii through $S = 3V/r$. Since, by definition, S_e is spherical and encloses the same volume as S_w, $S_e < S_w$.

Computation.—Our program was written under the influence of an early suggestion by Allinger[32] and, in particular, of recent publications by Gavezzotti[12] and Marsili *et al.*[11] It runs on a Digital PDP11/40 computer, interfaced with a FPS 100
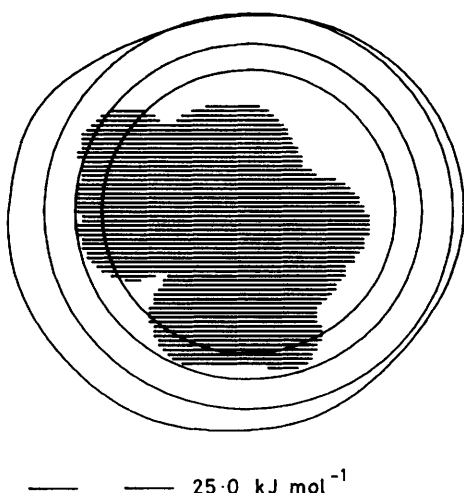
——— ——— 25·0 kJ mol^{-1}

Figure 3. Graphical analysis of *threo*-2,3-dibromobutane (Br/Br-*anti*), viewed across the plane BrC(2)C(3). Methyl silhouettes are below and at left. The bromines (perpendicular to plane of paper, right and top) are hardly sectioned by this cut

arithmetic processor, Megatek 7000 graphics display unit, and a Tektronix 4662 interactive digital plotter.

The first stage of computation can be conducted either in the arithmetic processor or by support of the MGS-7000 software package. The molecule is enclosed in a cuboid (shown in Figure 1 as a rectangle), leaving a space of length $\geqslant G$ between the outermost spheres and the sides. The cuboid is subdivided by a grid $g \leqslant G$. The scan is conducted point-by-point and atom-by-atom, checking (a) whether the point is within distance r_a of any of the nuclei, or, if not, (b) whether it is within distance $r_a + g$. In case (a), the point is taken to contribute an element g^3 to V_w; in case (b), it is taken to contribute an element g^2 to S_w. Clearly, the approximation for surface is coarser than for volume, and S_w converges much slower than V_w. To illustrate, for a solid made of two overlapping spheres ($r_1 = 0.175$, $r_2 = 0.117$, $d = 0.240$ nm), calculation at $g = 0.005$ nm yields $V = 0.02860$ nm^3 and $S = 0.5259$ nm^2; the analytical values are 0.02860 and 0.5114, respectively (see Appendix). It is only at $g = 0.002$ nm (and over 10^7 points) that S comes down to 0.5139 nm^2.

The second stage is conducted interactively, using the graphics display. A molecular projection in the form of overlapping spheres is inspected, and the plane of cut chosen (as in Figure 1); all the cuts shown in this paper contain the centre of mass. The program shades then the sectioned volume of the molecule (as in Figure 2b and 3). Using V_w, r_e is obtained and the equivalent circle drawn. V_w is also used to approximate the inner radius and the bulk density (see below); the error in density is of the order of 0.01 g cm^{-3}. Next, the outer radius is calculated and the outer circle drawn. Finally, the MEP along the outer circle is evaluated and plotted, the outer circle serving as origin in the polar co-ordinate system. In conformity with current practice,[17] the units are actually of energy: in Figure 2b and 3, the two dashed segments and the intersegment space each stand for 25 kJ mol^{-1} of electrostatic energy. Any combination of the displayed features can be hardcopied. The geometries of all molecules come from MM2 calculations.[16,33] Charge distributions are by the method of Del Re, including field effects in dihalides.[26] The van der Waals radii of atoms were taken from Gavezzotti.[12] Each molecule was run at least twice, once with $g = 0.01$ and once with $g = 0.0075$ nm. The changes (not necessarily improvements, since the numbers sometimes oscillate) are of the orders of 0.0002 nm^3 in V and 0.002 nm^2 in S.

Selected results that bear upon the first phase of the Discussion are cited in Table 1.

Volumes.—By its definition [equation (2)], V_w depends on structural features that affect ΣV_a, notably the number and type of atoms, and the occurrence of ring-systems. It is almost unaffected by conformation and configuration, and depends but slightly on positional isomerism. This is because 1,4-nonbonded distances are generally very close to the optimal contact distances;[34] when a stereochemical change creates a new 1,4-overlap, a previous 1,4-overlap simultaneously disappears, and both the former and the latter are small with respect to ΣV_a. To illustrate, when internal rotation converts *anti*-butane into *gauche*-butane, the major events are the disappearance of two skew-CH interactions (d 0.272, Σr_a 0.292 nm), and the appearance of one skew-CC (d 0.314, Σr_a 0.350, shown in Figure 1) and one skew-HH (d 0.252 > Σr_a 0.234 nm). From the formulae in the Appendix, two overlapping regions, of 0.000 04 nm^3 each, are replaced by a region of 0.000 34, and this out of a total molecular volume of *ca.* 0.079 nm^3. There is, of course, an accumulation of changes in 1,3-overlaps, due to delicate variations in bond lengths and bond angles, but these are very small and their sum contributes little. In eclipsed rotamers, 1,4-overlapping is somewhat higher than in stable conformers, but still small. In eclipsed butane, for example, the zone of C(1)C(4) overlap amounts only to 0.0009 nm^3 (d 0.291 nm), while the total volume of two carbon spheres is 0.0449 nm^3. This supports, incidentally, the observation that nonbonded repulsion cannot contribute much to barriers to internal rotation.[35,36] Branching increases the volume of overlapping regions, reducing V_w thereby, but the outcome is again small (in Table 1, compare pentane with 2-methylbutane, or 1-chloropropane with 2-chloropropane). This is why V_w is almost additive,[37a] though not strictly so. The additivity follows its definition [equation (2)], given that r_a is fairly constant for a particular type of atom,[14,37] and that ΣV_a is large with respect to Σ overlaps.

V_w is a topological index, in the sense that its numerical value is characteristic of a molecule and encodes information on the molecular formula.[38] In being insensitive (almost) to conformation and configuration, it resembles the indices of connectivity.[39] It is superior to them in having the notion of a heteroatom built into it in a natural way, and in being unique for a given molecule. It is inferior in not being sensitive enough to positional isomerism. Now, indices of connectivity have been made to correlate with various properties of molecules and bulk compounds, but at a price: relationships of predictive quality require multiple regression over five or more different indices, as well as assumptions concerning the representation of heteroatoms.[40] Also, the indices treated as an inseparable set respond in contrary ways to structural modification, *e.g.*, some increase and others decrease on chain-branching. By contrast, a molecule is endowed of one sole V_w, the evolution of V_w along a series of compounds can have at most one trend, and no mechanism is allowable for smoothing numbers out. Lower malleability implies less accurate predictions, but the relation between different physical quantities is expected to come out neater. For example, the heats of vaporisation of saturated hydrocarbons are linear in V_w,[11] a meaningful relation that is totally obscured in the seven-parameter topological representation.[39]

As an obvious check, consider the molar refraction R_M, a molecular property that has, like V_w, the dimension of volume. Data for 16 of our compounds, nine hydrocarbons and seven halides (starred in Table 1), are listed in a compilation.[39] When the hydrocarbons alone are examined, linear regression yields $R_M = 274.6V_w - 1.0607$ (V_w in nm^3 per molecule; R_M, as usual, in cm^3 mol^{-1}; $r = 0.9999$). The largest deviation is for 2,2-dimethylbutane (calculated 29.82, reported 29.94 cm^3 mol^{-1}).

Table 1. van der Waals volumes and surface areas

	Structure[a]	V_w^b	Density[c]	R^d	S_w^e	Δ^f
1	Ethane †	0.0451			0.706	
2	Propane †	0.0624			0.924	
3	Butane † (a)	0.0792			1.134	
4	Butane (g)	0.0792			1.130	
5	Cyclopentane	0.0855	0.7457	0.5475	1.154	0.06
6	2-Me-butane *·†	0.0959	0.6201	0.4964	1.342	0.07
7	Pentane *·†	0.0960	0.6262	0.5020	1.351	0.07
8	Cyclohexane	0.1015	0.7785	0.5653	1.339	0.06
9	Hexane *	0.1129	0.6594	0.5199	1.560	0.07
10	Hexane †·ᵍ (3,4-g)	0.1117			1.538	
11	2,2-Me₂-butane *	0.1125	0.6492	0.5102	1.517	0.07
12	2,3-Me₂-butane *	0.1127	0.6616	0.5209	1.528	0.07
13	Cycloheptane	0.1180	0.8098	0.5862	1.514	0.06
14	Heptane *·†	0.1297	0.6838	0.5330	1.776	0.06
15	3,3-Me₂-pentane *	0.1293	0.6933	0.5388	1.703	0.06
16	Octane *·†	0.1466	0.7025	0.5430	1.988	0.06
17	Nonane *	0.1634	0.7176	0.5507	2.196	0.06
18	1-Cl-propane *·† (g)	0.0771	0.8909	0.5266	1.106	0.06
19	2-Cl-propane	0.0770	0.8617	0.5086	1.106	0.07
20	1-Cl-butane * (a, a)	0.0939	0.8862	0.5416	1.326	0.06
21	1-Cl-2-Me-propane *	0.0936	0.8780	0.5354	1.297	0.06
22	1-Cl-3,3-Me₂-butane	0.1271	0.8670	0.5503	1.695	0.06
23	1-Cl-CH (eq)	0.1164 ⎱	1.000	0.591	1.518 ⎱	0.05
24	1-Cl-CH (ax)	0.1164 ⎰			1.511 ⎰	
25	1,2-Cl₂-ethane (a)	0.0748 ⎱	1.2462	0.568	1.057 ⎱	0.05
26	1,2-Cl₂-ethane (g)	0.0749 ⎰			1.054 ⎰	
27	2,3-Cl₂-butane (erythro, a)	0.1084	1.1134	0.5724	1.463	0.06
28	1,2-Cl₂-2-Me-propane	0.1083	1.093	0.561	1.460	0.06
29	cis-1,2-Cl₂-CH (eq, ax)	0.1310	1.2021	0.6195	1.671	0.05
30	trans-1,2-Cl₂-CH (ax, ax)	0.1310 ⎱	1.1839	0.610	1.669 ⎱	0.05
31	trans-1,2-Cl₂-CH (eq, eq)	0.1310 ⎰			1.674 ⎰	
32	1-Br-propane *	0.0838	1.3537	0.5557	1.155	0.06
33	2-Br-propane *	0.0837	1.3140	0.5385	1.155	0.06
34	1-Br-butane * (a, a)	0.1006	1.2758	0.5557	1.386	0.06
35	2-Br-2-Me-propane	0.1001	1.2209	0.5294	1.354	0.06
36	1-Br-2-Me-propane *	0.1010	1.2532	0.5483	1.376	0.06
37	1-Br-3,3-Me₂-butane	0.1344	1.1556	0.5664	1.776	0.06
38	1,2-Br₂-ethane (a)	0.0894 ⎱	2.1792	0.625	1.199 ⎱	0.05
39	1,2-Br₂-ethane (g)	0.0895 ⎰			1.197 ⎰	
40	2,3-Br₂-butane (threo, Br/Me-a)	0.1229 ⎱			1.593 ⎱	
41	2,3-Br₂-butane (threo, Br/H-a)	0.1230 ⎬	1.791[h]	0.614	1.590 ⎬	0.05
42	2,3-Br₂-butane (threo, Br/Br-a)	0.1230 ⎰			1.593 ⎰	
43	cis-1,4-Br₂-CH (eq, ax)	0.1453			1.798	0.04
44	trans-1,4-Br₂-CH (eq, eq)	0.1453 ⎱	1.7834	0.6448	1.821 ⎱	
45	trans-1,4-Br₂-CH (ax, ax)	0.1453 ⎰			1.774 ⎰	

[a] Abbreviations used: g—gauche, a—anti, Me—methyl, eq—equatorial, ax—axial, Cl—chloro, CH—cyclohexane, Br—bromo. Asterisks and daggers label, respectively, species included in the examination of molar refraction and of covolume. Straight-chain alkanes calculated in the all-anti conformation, except when marked otherwise. Calculations at a grid of 7.5×10^{-3} nm, except for the following 5×10^{-3} for straight-chain alkanes (ethane to nonane) and for the bromopropanes; 4×10^{-3} nm for the dihalogenoethanes. [b] Calculated van der Waals volumes in nm³ (1 nm³ $\equiv 1\,000$ Å³), considered reliable to within 10^{-4} nm³. [c] D_4^{20} in g cm⁻³, compiled from various sources, mainly through Beilstein's Handbuch der organischen Chemie. [d] $R = V_w/V_{in}$, with V_{in} calculated by equation (3) from the densities. [e] Calculated van der Waals surface areas in nm² (1 nm² $\equiv 100$ Å²), considered reliable to within 10^{-2} nm². [f] $\Delta = (V_{in} - V_w)/S_w$ in nm, with V_{in} calculated by equation (3) from the densities. [g] See discussion in ref. 43. [h] Estimated from densities at other than 20 °C.

When all 16 compounds are included, one gets $R_M = 255.4V_w + 1.6228$ ($r = 0.9942$); the largest deviation is for 1-bromo-2-methylpropane (27.42 versus 28.54 cm³ mol⁻¹). For a more diversified assembly of molecules, the accuracy, no doubt, would diminish further. But the advantage is that a connection between the two types of volume is clearly established, and can even be set roughly in quantitative terms: $R_M(\text{cm}^3\text{ mol}^{-1})$ ca. $250V_w(\text{nm}^3\text{ per molecule})$.

Another evident check concerns the covolume, that is the constant b in van der Waals equation of state.[41] A compilation[42] contains data on ten of the compounds (daggered in Table 1) and these verify $b' \equiv b/N_0 \sim 2.5V_w$. The largest deviations are for propane ($2.25V_w$) and for octane ($2.68V_w$). The factor 2.5 applies to molecules of other types[12] and should be considered meaningful, even if it is lower than van der Waals' estimate of $b'/V_w \sim 4$. The lowering cannot have to do with our choice of r_a values: to recover the factor of 4 these have to be reduced by ca. 25% (e.g., r_C from 0.175 to ca. 0.13 nm), which is untenable in view of the crystallographic evidence. Whatever the explanation, a staightforward relation between two types of volume is at hand. This also suggests that other manifestations of volume would inter-relate through the intermediacy of V_w. The topological pathway does not offer such a prospect.

Even the volume occupied by a molecule in the bulk (molecular volume V_{in}) is found to be related to V_w, albeit not in

a simple way. For reference, we start with straight-chain alkanes, and consider V_w, V_{in}, and the ratio $R = V_w/V_{in}$. In somewhat pictorial terms, R represents the fraction that is filled by mass out of the total volume that a molecule is allowed to occupy in the bulk. The numbers in Table 1 (pentane to nonane) are fit by power curves in the number N of carbon atoms (the

$$V_w = 2.2358 \times 10^{-2} N^{0.905} \qquad (5)$$

$$V_{in} = 5.7130 \times 10^{-2} N^{0.746}$$

$$R = 0.391 N^{0.157}$$

or, better, $\qquad R = 0.370 + 0.083 \ln N \qquad (6)$

coefficients of determination, in respective order, are 1.0000, 0.9995, 0.9957, and 0.9969). We now perceive, by equations (6) and (4), that the fraction of free volume decreases with chain length.

Ratios R, as evaluated for all compounds from calculated V_w and measured densities [equation (3), $\rho \equiv D_4^{20}$], are listed in the third column of Table 1. Their accuracy is variable, since densities were compiled from variegated sources and V_w was not averaged over conformers. The following remarks are not affected by this reserve.

It is essential to realise that equation (6) or any alternative connection between V_w and the molecular volume of linear alkanes does not apply to molecules of other types.[43] As one confronts R values in Table 1 with appropriate reference values (same N) for straight-chain alkanes, one notices that cyclisation is accompanied by a significant increase (0.04—0.05). Chain-branching brings about a small lowering. The ratio is raised by substitution (0.05—0.06 for chlorine, 0.08—0.09 for bromine). When several features intervene simultaneously, the cumulative effect is less than additive. In sum, halogens and cyclisation increase the contribution of V_w to the molecular volume, while alkyl-branching decreases it somewhat;[37b] the former act to pull neighbouring molecules closer, and the latter pushes them apart. Among the compounds on our list, the free volume is highest in liquid 2-methylbutane (ca. 50% of the total at 20 °C) and lowest in liquid dibromocyclohexanes (ca. 35%). Needless to add, these trends bear out quantitatively the qualitative anticipation that molecules more apt to pack do indeed pack better.

On the basis of these data, one can formulate an approximate incremental pathway to R, and hence to V_{in} and r_{in}. The formulation is not particularly elegant, in that it calls for the distinction of numerous constitutive descriptors (ring, halogen, ring and halogen, and so on); also, it furnishes at best an average over configurations and conformations. Yet, it provides the computer program with a link between V_w and V_{in} which is intuitively more satisfying than the usual incremental estimates of density.[44] It has again the pleasing nature of relating two types of volume to each other.

Up to this point, the effect of stereochemical change on the molecular volume has not been considered. The question is tractable and best approached through the examination of surface areas.

Surface Areas.—Edward and Farrell investigated the partial molar volumes of hydrocarbons and other organic substances in water.[45] In our notation, the relation they obtained is equation (7), from which (8) follows [cf. equation (4)]. The free volume is thus proportional, through a factor Δ, to a quantity

$$1/R = V_{in}/V_w = 1 + (\Delta/r_e) \qquad (7)$$

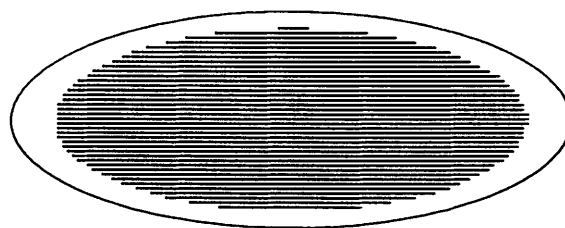$$V_f = V_{in} - V_w = V_w \Delta/r_e \qquad (8)$$

Figure 4. A representation of molecular volume: the van der Waals volume is encapsulated in a crust of free volume. Schematic (two ellipsoids), with proportions approximating those of all-*anti* octane.

that has the dimension of area. r_e is the 'molecular radius', as derived from V_w [equation (1); $V = V_w, r = r_e$)]. Using partial molar volumes (V_{in}) from measurement, and estimated van der Waals volumes, they plotted V_{in}/V_w against $1/r_e$ and obtained a value close to 0.053 nm for Δ. Assuming sphericality further, these authors also arrived at the relation $V_{in} = 4\pi(r_e + \Delta)^3/3$. It is as if a molecule wraps itself in an envelope of free volume, the envelope being endowed with a uniform thickness Δ. Thus, if two molecules of similar constitutive elements differ in surface area, the molecule with the more extensive surface would have a proportionately more voluminous envelope.

van der Waals surfaces are more sensitive to structural modification than the corresponding volumes (see Table 1 and the Appendix). Now that values for S_w are available from computation (Table 1), it is possible to forego the assumption on spheroidality, and examine numerically an unsimplified version of the model, as proposed schematically in Figure 4. One should bear in mind, though, that we will be comparing different neat liquids, not solutions of various substances in a common solvent: Δ is known to depend on environment.[45] Measured densities furnish V_{in} [equation (3)]; by substracting the calculated V_w, V_f is obtained. Does the free volume increase in proportion to S_w?

The least demanding testing-ground is stereoisomerism. As worded elsewhere,[46] this is because the forces acting in and between the molecules of one stereoisomer are similar to those in the other, and differences in properties are due to a minimum number of differences in the forces. The physical consequences of spatial modification are traditionally reviewed in the preambles to the so-called 'conformational rule'.[47,48] In brief, a *trans*-configuration usually requires a higher volume than *cis*, an equatorial conformer is more voluminous than the axial, and so is *anti* with respect to *gauche*. A classical example is 1,2-dimethylcyclohexane, where *cis* (axial, equatorial) has a smaller molecular volume than *trans* (diequatorial). Conformation is more decisive than the formal distinction between *cis* and *trans*: in 1,3-dimethylcyclohexane, *trans* (axial, equatorial) has a smaller molecular volume than *cis* (diequatorial).

We know from the calculations that these propensities do not reflect trends in V_w. By contrast, we now find that differences in density do correlate with S_w: the stereoisomer that requires the larger molar volume is the one endowed of the larger molecular surface. Table 2 delineates computation for five of the 'critical cases'.[46] Listed are V_{in}, V_w, V_f, and S_w, as well as the ratio $\Delta = V_f/S_w$, taken to represent the average thickness of the empty envelope. The isomers in each pair, of similar V_w but dissimilar S_w and shape, have close Δ values, and all cluster within a small range. As could be anticipated, values for some of the neat hydrocarbons are larger than the average Δ of hydrocarbons in water.[45]

The 'conformational rule' states that the stereoisomer of higher density (and higher b.p. and index of refraction) is the less stable. This was rationalised by observing that intramolecular repulsions are stronger when the molecular volume is smaller.[46]

Table 2. The conformational rule[a]

Structure	V_{in}	V_w	V_f^b	S_w	Δ
1 1,2-Me$_2$-CH					
cis (ax, eq)	0.2340	0.1350	0.0990	1.718	0.06
trans (eq, eq)	0.2401	0.1349	0.1052	1.734	0.06
2 1,3-Me$_2$-CH					
cis (eq, eq)	0.2432	0.1349	0.1083	1.757	0.06
trans (ax, eq)	0.2378	0.1350	0.1028	1.731	0.06
3 1,4-Me$_2$-CH					
cis (ax, eq)	0.2387	0.1339	0.1048	1.726	0.06
trans (eq, eq)	0.2443	0.1349	0.1094	1.751	0.06
4 Bicyclo[3.3.0]octane					
cis	0.2108[c]	0.1253	0.0855	1.595	0.05
trans	0.2123[c]	0.1253	0.0870	1.598	0.05
5 Decalin					
cis	0.2561	0.1573	0.0988	1.925	0.05
trans	0.2639	0.1571	0.1068	1.966	0.05

[a] Notation, abbreviations, and dimensions as in Table 1. [b] Free volume, $V_f = V_{in} - V_w$, in nm^3. [c] Estimated from densities at other than 20 °C.

Table 3. Straight-chain hydrocarbons

N^a	S_w/V_w^b	Δ^c
3a	14.822	
4a	14.546	
4g	14.317	
5a	14.179	0.070
6a	14.015	0.066
6g	13.192	
7a	13.823	0.063
8a	13.650	0.062
9a	13.582	0.061

[a] Number of carbon atoms and conformation: a—all-anti; g—gauche [C(3)C(4) in 6g]. [b] In nm^{-1}. [c] In nm.

Now that the molecular volume can be dissected into V_w and V_f, we know that V_w is affected by stereoisomerism only to a minor extent and in an erratic sense (Table 2); it is actually the packing, the empty envelope, that is too tight in the less stable species. Since the thickness of the capsule is, in turn, almost insensitive to stereoisomerism, one is led to recast the generalisation in terms of the surface-to-volume ratio: the more globular a stereoisomer is (*i.e.*, of a lower S_w/V_w), the less stable it is. Electrostatic interaction, of course, might upset this propensity. For example, the two conformers of 1,2-dichloroethane have the same surface-to-volume ratio (14.1 nm^{-1}), but the *gauche* is less stable.[49] The challenge to elucidate circumstances that cause the 'conformational rule' to fail[46] can perhaps be met on these grounds.

Quantum chemistry has ways to deal with stereochemical change [50] but not ready interpretations.[51] One may well ask where, in the molecular-mechanical force field, is the notion of globularity hidden. Part of it, of course, is contained in the term of nonbonded interaction, which is frequently more repulsive (or less attractive) for axial than for equatorial substituents and for *gauche* than for *anti* conformers. But another part, frequently more important, is absorbed into the so-called 'intrinsic torsion potentials'. These are periodic potentials of the form $V_{tor} = \Sigma(n)A_n(1 + S_n\cos n\omega)$, attributed to each of the dihedral angles ω in the molecule. In modern force fields, actually, one of the roles of the torsional term is to alleviate the burden thrust on the term of nonbonded interaction.[52] The term does not occur in spectroscopic force fields and the need for it was not recognised in early molecular-mechanical work.[53] Hendrickson put it in [54] with the apology that, although its origins were not even qualitatively understood, its neglect would probably introduce serious error. The torsional contribution to the total energy is now regarded as a corrective term,[55] inserted in the energy equation so as to take care of factors other than the readily interpretable strains. In fitting a force field to experimental energy differences, one is compelled to formulate this corrective term such that it increases on going from *anti* to *syn*, that is, as the molecule becomes more globular in shape. In a new calculation of butane, for example, 42% of the *gauche-anti* energy difference is relegated to the ω(C-C-C-C) torsional

correction: 1.53 out of ΔE 3.64 kJ mol^{-1}.[56] The most recent hydrocarbon force field sets the percentage at 45: 1.57 out of 3.47 kJ mol^{-1}.[57] The notion of destabilising globularity has, incidentally, an antecedent in the 'principle of minimum bending'.[58] Our tentative conclusion is that nonbonded interactions have to do with the van der Waals space, while torsional strain is a way to express constraints imposed by the disposition of the empty space.

Apparent average thicknesses Δ of the empty envelopes are listed in the last column of Table 1. As with R values, regularities are evident. As the chain grows longer, its envelope becomes thinner (from 0.07 in pentane to 0.06 nm in nonane); branching thickens it, while ring formation makes it slimmer (*cf.* 0.07 *versus* 0.06 nm for pentane and cyclopentane). Substitution by halogens leads always to shrinkage. As remarked above, in discussing R, these trends were to be expected.

A note is here in place on the surface-to-volume ratio in straight-chain alkanes. Contrary to intuitive expectation,[18b] S_w/V_w actually decreases as the chain-length increases. Calculated ratios are listed in Table 3. Two examples are given of *gauche* conformers, and these show that the diminution is not peculiar to all-*anti* species. Also, as the hydrocarbons grow longer, *gauche* forms become more highly populated, if only for statistical reasons; the averaged S_w/V_w ratio then becomes increasingly smaller than the number cited in Table 3 for the extended conformer of a given N. The fitted power curve $V_w(N)$ has been given [equation (5)]; by conjoining it with the corresponding curve for $S_w(N)$ [equation (9)], one obtains the analytical generalisation (10). The diminution carries over to Δ [equation (11)], reflecting the increase in density that accompanies chain lengthening.

$$S_w = 0.382N^{0.796} \qquad (9)$$

$$\frac{d}{dN}\left(\frac{S_w}{V_w}\right) = -0.187N^{-1.109} < 0 \qquad (10)$$

$$\Delta = 0.105N^{-0.256} \qquad (11)$$

This result poses a constraint upon the choice of group increments in additive procedures for obtaining van der Waals descriptors.[9,12,37a] Suppose one attributes increments S_2 and V_2 to a methylene group, and increments S_3 and V_3 to a methyl. For a straight-chain alkane of N carbons, the van der Waals surface area and volume become $S_w = 2S_3 + (N-2)S_2$ and $V_w = 2V_3 + (N-2)V_2$. Equation (12) follows, where the inequality is based on equation (10). The choice of group incre-

$$\frac{d}{dN}\left(\frac{S_w}{V_w}\right) = \frac{\text{positive}}{\text{function}} \times (S_2V_3 - V_2S_3) < 0 \qquad (12)$$

ments is then subject to the restrictions $(S_2/V_2) < (S_3/V_3)$ or $(S_2/S_3) < (V_2/V_3)$.

Volume Requirements and Conformational Change.—The discussion above leads to equation (13) (V_m is the molecular

$$V_m = V_w + S_w\Delta \qquad (13)$$

volume, previously denoted by V_{in}). There is a way to confront this equation with experiment, namely, by using it to calculate the difference of volume between the conformers of a molecule. The required data come from studies of pressure effects upon neat liquids and solutions.[59] The simplest case is of a neat liquid, where computation and measurement refer both to molar volumes (not partial molar). Taking butane as an example, and using $\Delta = 0.07$ nm (as in pentane), the data in Table 1 lead to $V_m(gauche)$ 0.1586, $V_m(anti)$ 0.1598, and ΔV_m 0.0012 nm^3 per molecule. The difference in molar volume is then 0.72 cm^3 mol^{-1}, within the accuracy bounds of the reported value,[60] 1 ± 0.3 cm^3 mol^{-1}.

A second type of cases concerns solutions, where the most one can do at present is compare the calculated ΔV_{molar} with the measured $\Delta \bar{V}_{molar}$. There are grounds to expect $\Delta V < \Delta \bar{V}$.[61] For a numerical examination, consider the two conformers, diequatorial (ee) and diaxial (aa), of 1,4-dibromocyclohexane. Judging by data for the *cis* isomer (ea), $\Delta \sim 0.044$ nm, so that the computed V_w and S_w lead to molecular volumes of 0.2263(ee) and 0.2243 nm^3 per molecule (aa) in the *trans*. The calculated molar volumes of the two species differ then by 1.3 cm^3 mol^{-1}. The experimental counterpart comes from a study of pressure effects on the i.r. spectrum of dissolved *trans*-1,4-dibromocyclo-hexane.[62] For a solution in CS$_2$, the difference in partial molar volumes (ee − aa) has been estimated as 3.8 ± 0.2 cm^3 mol^{-1}.

There are cases where equation (13) seriously underestimates the order of volume difference. Specifically, the Raman spectrum of pressurised solutions of 1,2-dichloroethane and 1,2-dibromoethane indicates that *gauche* occupies an appreciably lower volume than the *anti* conformer, $\Delta \bar{V}_m$ being *ca.* 4 cm^3 mol^{-1} in a nonpolar solvent.[63] Calculations at a fine grid (g 4×10^{-3} nm, see Table 1) characterise the *gauche* species as endowed with a slightly lower S_w than the *anti*, but a slightly higher V_w. By equation (13), one still gets $V_m(a) > V_m(g)$, but ΔV_m is vanishingly small. The source for the closeness of descriptors is of some interest. In *gauche*, unlike in *anti*, the two chlorine spheres overlap; but bond lengths and bond angles are larger in *gauche* than in *anti*. In the delicate balance of overlaps [equation (2)], the higher 1,4-overlapping in *gauche* is balanced by the higher 1,2- and 1,3-overlapping in the *anti*.

The domain of equation (13) and its accuracy have yet to be ascertained, but it is evident that a relation of this type is awaited in molecular mechanics. The radius of the inner sphere [equation (1; $r = r_{in}$, $V = V_m$)] occurs in the computation of solvation energies.[13] If the solvent is treated as a uniform, structureless medium, the energy of solvation comes out as a sum of terms, in the charge distribution within the solute molecule and in a parameter 'a', the radius of the cavity that the solute molecule occupies in the condensed phase. Specifically, the first term in the development is given by equation (14).[64] In

$$\Delta E_1 = \frac{\varepsilon - 1}{2\varepsilon + 1} \cdot \frac{\mu^2}{a^3} \qquad (14)$$

this equation, μ is the dipole moment of the solute and ε is the dielectric constant of the medium. A similar equation, based on the same premises, occurs in the estimation of solvent effects on excitation energies.[65] In early calculations, μ was estimated by roundabout means.[19] Ways were then found to incorporate the computation of the dipole moment[33] or the charge distri-

bution[26] in the molecular-mechanical calculation. As to 'a', experience shows that it is satisfactorily approximated by the radius of a sphere of volume equal to V_m, that is, the distance that we have labelled r_{in}. Now, if Δ for a given molecule can be estimated from data on germane molecules, 'a' it self may be computed internally: one has to use, in sequence, equation (12), or an eventually improved version thereof, and equation (1). The 'first-order approximation' that all conformers of a molecule have the same molecular volume[19,66,67] can thus be dispensed with.

Conclusion.—It is amazing that so little interest is being paid to details of the shape and size of simple molecules, while so much attention is currently accorded to van der Waals quantities of complex molecules. For molecules sizeable enough to interest the molecular biologist, reactivity has been investigated in terms of generalised indices of shape,[68] reagent accessibility,[23] and loss of accessible surface area,[69] packing density,[70] and cavity surface area.[71] For large molecules, notions of surface electrostatic properties have been developed and expressed in graphical form.[24,72] Volumes[73] and shapes[32,74] have been compared along series of substrates, and concepts of contact regions[75] and complementary surfaces[76] have been couched in terms of van der Waals identifiers. The foreground is thus in existence, but the background, populated by the more ordinary topics of organic stereochemistry, is virtually missing. Given that accurate geometries of simple molecules are now available from molecular mechanics, the systematic examination of fine details has come within reach. Rapid and cheap methods to evaluate the charge distribution can now be incorporated in the molecular-mechanics program,[77] and these allow for the extension of analysis from the static to the dynamic properties of molecules. The examples given above, in particular those of 1,2-dichloroethane and 1,2-dibromoethane, illustrate how important it is to use actually computed co-ordinates and not standard geometries.

Here we limited ourselves to saturated hydrocarbons and to very simple derivatives, and examined just the more evident manifestations of volume and shape. The main inference, obvious no doubt, but only too frequently unappreciated in the literature, is that van der Waals volumes cannot substitute for molecular volumes. Another observation is that V_w correlates with various molecular properties, and may be adopted in certain contexts as a topological index. Closer to everyday stereochemistry is the discernment of a descriptor, globularity, that has to do with conformational bias, and sheds light on the significance of terms in the force-field equation. A practical outcome of the analysis is the evaluation of the change in volume that attends conformational transition; this bears on the computation of conformational equilibria in solution. Needless to say, the various types of descriptor (V_w, S_w, Δ, R, *etc.*) await uses that we have bypassed or overlooked, for example, the analysis of solubility.[9,18] Also, application to less simple molecules is wont to uncover additional correlations.

Finally, it is proper to bear in mind that the actual numbers computed are sensitive to the choice of van der Waals radii and to the constants in the force-field program. In the discussion, accordingly, we stressed trends and generalities rather than numerical detail.

Appendix

Volume and Surface Area of the Overlap Disk.—The following is a straightforward even if somewhat laborious derivation (*cf.* ref. 10). See Figure 5. Let the radii of spheres O$_1$ and O$_2$ be r_1 and r_2, and the distance between their centres be $d < r_1 + r_2$. The overlap-solid ABCEA is made up of two solids of revolution, ABCA and ACEA. Since both are sections of
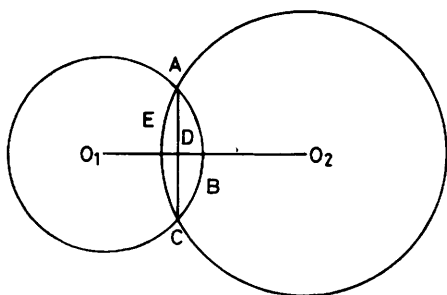
Figure 5. Two overlapping spheres

spheres, volume of each $= \pi[r^2 X - \frac{1}{3}X^3]_a{}^b$ and surface of each $= 2\pi r[X]_a{}^b$. The limits of integration are $O_1 D \equiv d_1$ and r_1 for ABCA, $O_2 D = d_2$ and r_2 for ACEA. To express d_1 and d_2 in terms of given quantities, use the rule of cosines. This provides equations (A1) and (A2), from which (A3) and (A4) follow. The definite integrals can then be evaluated. Final results for the entire solid ABCEA are given as equations (A5) and (A6).

$$r_1{}^2 = r_2{}^2 + d^2 - 2r_2 d\cos(AO_2O_1) \qquad (A1)$$

$$r_2{}^2 = r_1{}^2 + d^2 - 2r_1 d\cos(AO_1O_2) \qquad (A2)$$

$$d_1 = r_1\cos(AO_1O_2) = (r_1{}^2 + d^2 - r_2{}^2)/2d \qquad (A3)$$

$$d_2 = r_2\cos(AO_2O_1) = (r_2{}^2 + d^2 - r_1{}^2)/2d \qquad (A4)$$

$$V(ABCEA) = \pi[-3(r_1{}^4 + r_2{}^4) + 8d(r_1{}^3 + r_2{}^3)$$
$$-6d^2(r_1{}^2 + r_2{}^2) + 6r_1{}^2 r_2{}^2 + d^4]/12d \qquad (A5)$$

$$S(ABCEA) = \pi[-r_1{}^3 - r_2{}^3 + 2d(r_1{}^2 + r_2{}^2)$$
$$+ (r_1 r_2 - d^2)(r_1 + r_2)]/d \qquad (A6)$$

Volume and Surface Area of a Solid Made of Two Overlapping Spheres.—This is the solid in Figure 5. The volume and surface area of each separate sphere are $V_i = 4\pi r_i{}^3/3$ and $S_i = 4\pi r_i{}^2$ ($i = 1,2$), and the required quantities are $V = V_1 + V_2 - V(ABCEA)$ and $S = S_1 + S_2 - S(ABCEA)$. Using equations (A5) and (A6), the expressions (A7) and (A8) are obtained. For spheres of equal radii, $r_1 = r_2 = r$, these reduce to equations (A9) and (A10).

$$V = \pi[8d(r_1{}^3 + r_2{}^3) + 3(r_1{}^4 + r_2{}^4)$$
$$+ 6d^2(r_1{}^2 + r_2{}^2) - 6r_1{}^2 r_2{}^2 - d^4]/12d \qquad (A7)$$

$$S = \pi[(r_1{}^3 + r_2{}^3) + 2d(r_1{}^2 + r_2{}^2)$$
$$+ (d^2 - r_1 r_2)(r_1 + r_2)]/d \qquad (A8)$$

$$V = \pi(16r^3 + 12dr^2 - d^3)/12 \qquad (A9)$$

$$S = 2\pi r(2r + d) \qquad (A10)$$

Steric Change affects the Surface Area more than the Volume.—Start with equations (A9) and (A10), and denote by δ the thickness of the overlap-disk, $\delta = 2r - d$. If the internuclear distance d changes somewhat:

$$\frac{dS}{dV} = \frac{dS}{dd} \cdot \frac{dV}{dd} = \frac{8r}{(2r + d)(2r - d)}$$
$$= \frac{8r}{(4r - \delta)\delta} \sim \frac{2}{\delta}$$

or $\quad \dfrac{\Delta S}{S} = \dfrac{\Delta V}{V} \cdot \dfrac{2V}{S\delta}$

With typical numbers, the percentage change in S is about twice the percentage change in V.

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