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Molecular Volumes and the Stokes-Einstein Equation

The progress of science has owed much to the use of models: mental pictures helpful in explaining phenomena. It is instructive to examine the model of a solution used by Einstein in his explanation of diffusion rates, which resulted in the well-known Stokes-Einstein equation. This model is based on a naive physical picture of a solution, which is obviously in error when solute molecules are small. Nonetheless, the equation is found to be still valid for quite small solute molecules, and the model is a good example of the heuristic usefulness of an oversimplified picture. Part of the uncertainty about the limits of applicability of the Stokes-Einstein equation arises from uncertainty about the sizes of small molecules. In this paper we review the various ways in which the volumes of molecules have been estimated, consider the data in the literature on the diffusion coefficients of small molecules, and produce a correction factor permitting the Stokes-Einstein equation to be applied to the smallest solute molecules.

The Stokes-Einstein Equation

Einstein (1) was led to a theoretical derivation of Fick's laws of diffusion from a consideration of the Brownian movement of colloidal particles. The random motion of these particles leads to a net transfer from a region of high to a region of low concentration.¹ The driving force of this diffusion process may be regarded as osmotic pressure, exerting a driving force F on a particle which causes it to be accelerated to a final velocity v at which F is counterbalanced by the viscous drag of the medium

$$F = vf \quad (1)$$

f being the frictional coefficient of the particle. Einstein showed that the diffusion coefficient D° in infinitely dilute solution is given by the equation

$$D^\circ = kT/f \quad (2)$$

where k is Boltzmann's constant and T the absolute temperature.

While the value of f in general is unknown, G. Stokes (3) showed that for the special case of a spherical particle of radius r moving with uniform velocity in a continuous fluid of viscosity η , the frictional coefficient f_0 is given by

$$f_0 = 6\pi\eta r \quad (3)$$

Einstein pointed out that if one can assume that this equation also applies to spherical molecules, then their

¹ A good account of the diffusion process, and of transport processes in general, is given by Tanford (2).

diffusion coefficients should be given by the equation

$$D^\circ = kT/6\pi\eta r \quad (4)$$

We discuss this assumption below. Equation (4) has come to be known as the Stokes-Einstein equation.

The Stokes equation applied only to spherical particles. In 1936 Perrin (4) derived equations giving the frictional coefficients of prolate and oblate ellipsoids. These frictional coefficients (f) are greater than the frictional coefficients of a sphere (f_0) of equal volume, the difference depending on the ratio of the major (a) to minor axis (b) of the ellipsoid. This is shown graphically in Figure 1, in which the frictional ratio

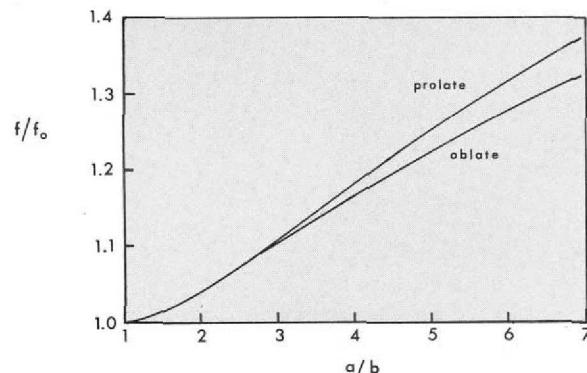


Figure 1. Variation of the frictional ratio (f/f_0) of a prolate or oblate ellipsoid with the axial ratio (a/b) of the ellipsoid.

(f/f_0) is plotted against the axial ratio (a/b). To apply to both spheres and ellipsoids, eqn. (4) must be modified to

$$D^\circ = kT/6\pi\eta r(f/f_0) \quad (5)$$

r now being the radius of a sphere having the same volume as the diffusing particle. For spheres $b/a = 1$ and $f/f_0 = 1$ and eqn. (5) reduces to eqn. (4).

The frictional ratios of ellipsoids having three unequal axes have been calculated (5), but for more irregular shapes they are at present unknown.

We turn now to the question: Was Einstein's assumption, that eqn. (3) could be applied to spherical molecules, a reasonable one?

Limitations of the Stokes Equation

Stokes (2, 3) assumed that a sphere moving in a fluid continuum carried along with no slippage the layer of fluid in contact with it. He could then show by the principles of classical hydrodynamics (assuming perfect streamline flow, etc.) that the movement of the sphere is impeded by a force due to pressure built up in front of it ($= 4\pi\eta r$), and a frictional force parallel to its sur-

face ($= 2\pi\eta r$), the two forces adding up to that given in eqn. (3).

This equation has been verified experimentally many times for directly observable particles, and Cheng and Schachman (6) found it still valid for spherical polystyrene latex particles in water, having a radius (shown by electron microscopy to be remarkably uniform) of only 1300 Å. This is about eight times greater than the radii of plant virus molecules, but very much greater than the radii (2–6 Å) of the molecules usually encountered in organic chemistry.

If the diffusing molecule is wetted by a monomolecular layer of water molecules, then the radius of the diffusing entity must be increased by the diameter of a water molecule (about 3 Å (7)). This increase would be negligible for spheres of 1300 Å radius, but very important for small molecules of 2–6 Å radius: in the latter case, the radii of the diffusing entities would be systematically higher than expected and the diffusion coefficients systematically lower. The discrepancy should increase as the molecules become smaller.

In fact, just the opposite behavior is observed: small molecules diffuse more rapidly than predicted by eqns. (4) or (5) (8–11, and references therein). It is obvious that most small molecules are *not* wetted by the solvent. Some authors (e.g., Frank (12)) have modified the Stokes equation to

$$f_0 = 4\pi\eta rv \quad (6)$$

by including only the first of the two impeding forces on the sphere (see above). However, other authors reject such attempts to retain part of Stokes's treatment, when the size of the diffusing particle is such that his assumption of a fluid continuum can no longer be credible. Eyring *et al.* (13) take account of the discontinuous nature of the liquid, and calculate from transition state theory that the numerical factor of eqn. (3) should be reduced from six to about one, although this calculation has been questioned (14). Most authors (reviewed by Ihnat and Goring (11)) content themselves with determining empirical correction factors for the Stokes law when applied to very small molecules. These correction factors are discussed below, but first it is necessary to review the differing ways in which various investigators have measured the volume, and hence the radius, of the diffusing molecule. It is shown that this determines the magnitude of the correction factor.

Different Measurements of Molecular Volume

We shall use different symbols to indicate the different methods of computing molecular volumes. Some of these are discussed in the following sections.

The van der Waals Volume v_w Calculated from Atomic Increments

Molecules pack themselves in a crystal so that attractive forces are just balanced by repulsive forces. The distances between atoms in neighboring molecules can be determined by X-ray diffraction, and it is found that the closest approach of two nuclei A and B in different molecules is determined by their so-called van der Waals radii, $r_w(A)$ and $r_w(B)$. It has become customary to picture the molecule as being enclosed by a

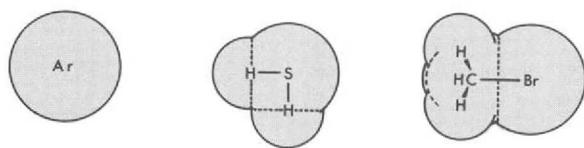


Figure 2. Van der Waals volumes of argon, hydrogen sulfide, and methyl bromide, using van der Waals radii of Bondi (15).

van der Waals surface, spherical about each atom (as illustrated in Figure 2 for argon, H₂S, and CH₃Br) which limits the approach of another molecule at ordinary temperatures. The van der Waals volume v_w of the molecule will then be the volume enclosed by this surface.

Such a volume may be dissected into contributions from the individual atoms—atomic increments—as pictured in Figure 2 for H, S, and Br. The increments for some of the common atoms are listed in Table 1.

Table 1. Van der Waals Increments of Atoms or Groups

Atom or Group	Increment (Å ³)	Atom or Group	Increment (Å ³)
—C—	5.6	O=	11.3
—C=	8.1	—O—	10.1
—C≡	11.6	—S—	17.9
—C—	13.4	—S≡	20.1
H— (attached to C) ^a	5.7	N—	7.2
H— (attached to C) ^b	5.3	—N+—	4.6
H— (attached to N)	5.2	—N=	8.6
H— (attached to N ⁺)	2.3	—N—	6.7
H— (attached to O)	7.2	N=	11.0
H— (attached to S)	6.6	P—	17.2
F—	9.9	—P+—	14.8
Cl—	19.8	—CO ₂ ⁻ (hydrated)	71.0
Br—	24.5	—NH ₃ ⁺ (hydrated)	11.5
I—	32.8	—NO ₂	27.9
O—	6.2		

^a Alkane, alkene, or alkyne.

^b Aromatic.

For the most part these increments come from the recent calculations of Bondi (15) but some come from earlier calculations of the author (16); the original papers should be consulted for an appreciation of the various assumptions involved in the calculations. The values in Table 1 are only approximate: thus the increment of 6.2 Å³ for singly-bonded oxygen represents a compromise between values ranging from 5.3 to 8.6 Å³.

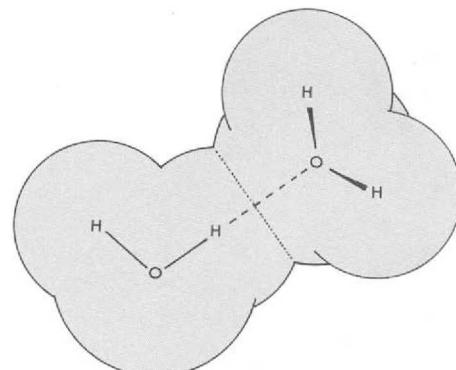


Figure 3. Van der Waals volume of two water molecules joined by a single hydrogen bond.

reported by Bondi, depending on whether the oxygen is found in cyclic, acyclic, or aromatic ethers. We shall use the increment of 6.2 \AA^3 also for singly-bonded oxygen in alcohols, carboxylic acids, and esters.

When the hydrogen bond A—H \cdots B is formed, the nuclei A and B can approach each other more closely than would be calculated by addition of the van der Waals radii of H and B and the bond length A—H. This is illustrated in Figure 3 for two water molecules HOH \cdots OH₂ having the relative orientation of water molecules in ice (17a) and in the organized regions of liquid water (17b), and in Figure 4 for two benzoic acid

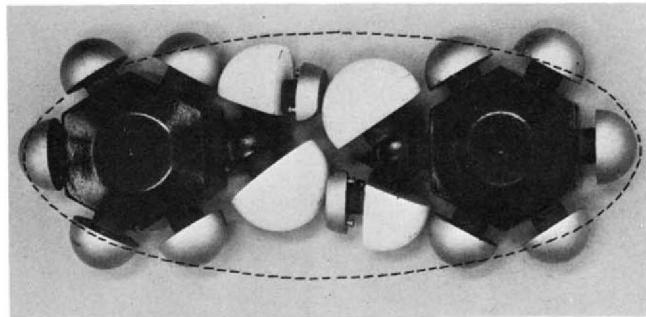
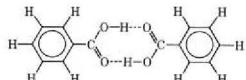


Figure 4. Model of the hydrogen-bonded dimer of benzoic acid



Constructed from Courtaulds space-filling atomic models (22). (Notice that the normal hydrogen atom is represented by a hemisphere and the atom involved in hydrogen-bonding by a disc, the latter allowing the two oxygen atoms to approach each other more closely.) Axial ratio of enclosing ellipse: 2.5.

molecules forming a dimer. A reduction of about 2 \AA^3 in total van der Waals volume is indicated for each hydrogen bond formed to oxygen or nitrogen.

We shall define the van der Waals radius r_w of a molecule by $r_w = (3v_w/4\pi)^{1/3}$, where v_w has been obtained by addition of the atomic increments of Table 1. This radius is shown in the scale drawing in Figure 5 of the methane molecule, for which r_w is 1.89 Å. This is a purely formal definition, and *not* the van der Waals radius (1.78 Å) as sometimes defined from the distance of closest approach (3.57 Å) of the centers of two methyl groups (15); the shorter distance of the latter is made possible by a gear-wheel type of meshing of the hydrogen atoms. A van der Waals radius defined as in this latter way gives the closest possible approach of atoms or groups in two different molecules, but the collision radius of the kinetic particle in the diffusion process will be on the average larger, because of the random orientation of the colliding particles. It would seem likely that this collision radius will be closer to our r_w , as

defined above, and we consider r_w to be the best available radius for use in eqns. (3–5), for small molecules such as methane. It becomes less appropriate for larger and more ramified molecules, for reasons discussed later.

The Volume v_{mod} Obtained from Measurements of Molecular Models

Some investigators (e.g., 18–21) have obtained the radii of molecules (and thence their volumes) by measurements of space-filling models, by measurements of scale-drawings of molecules, or by equivalent calculations. We shall designate a radius obtained in this way r_{mod} . For the near-spherical methane molecule, a possible r_{mod} (1.81 Å) is shown in Figure 5, and is not greatly different from our r_w of 1.89 Å. A larger radius (2.29 Å) would be obtained by taking the distance from the center of the molecule, along the line of the C-H bond, to the van der Waals surface of the hydrogen atom and equal to half the greatest possible distance between molecular centers on contact. A calculation along these lines was made by Robinson and Stokes (21) in obtaining the radius of the tetramethylammonium ion (no. 6 of Table 2). Such radii are systematically larger than our r_w , and we consider the latter closer to the collision radius of a molecule or ion.

Most models of methane made with presently-available atomic models would have r_{mod} (obtained as in

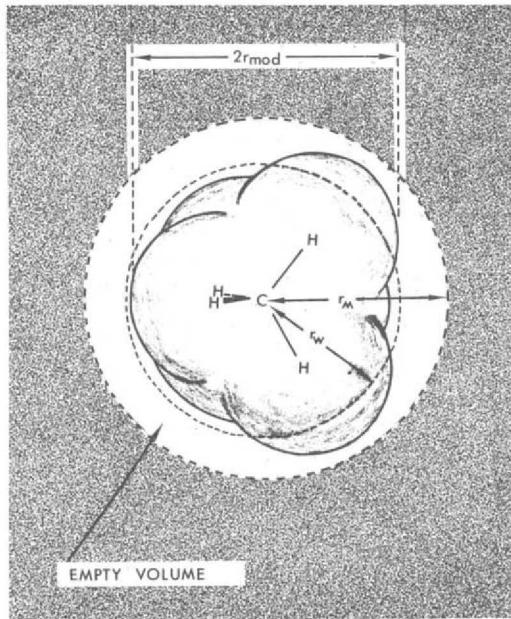


Figure 5. Drawing of the methane molecule from the parameters of Bondi (15).

Table 2. Comparison of van der Waals Radii Obtained by Measurements on Models (r_{mod}) and by Calculation from Atomic Increments (r_w)

Molecule or Ion	$r_w(\text{\AA})$	$r_{mod}(\text{\AA})$	r_w/r_{mod}	Type of Model Used	Reference
1. Methane	1.89	1.81	1.04	Fig. 5	This paper
2. Water	1.69	1.5	1.1	Stuart-Briegleb	(18)
3. Urea	2.35	2.3	1.0	Stuart-Briegleb	(18)
4. Glycerol	2.73	2.9	0.9	Stuart-Briegleb	(18)
5. Glucose	3.28	3.9	0.8	Stuart-Briegleb	(18)
6. Tetramethylammonium	2.84	3.47	0.82	Calc. ^a	(21)
7. Tetraethylammonium	3.39	4.00	0.85	Catalin	(21)
8. Pentaerythritol	3.12	3.2	1.0	Catalin	(19)
9. Citric Acid	3.31	3.5	0.95	Catalin	(20)

^aCalculated from a scale drawing similar to Figure 5.

Figure 5) smaller than 1.81 Å, because these models systematically underestimate van der Waals radii, particularly that of hydrogen, in order to allow models of slightly congested molecules to be assembled (22).² On the other hand, most molecules have a less spherical shape than methane, and hence r_{mod} has been obtained from the relation: $r_{mod} = (a b c/8)^{1/3}$, where a , b , and c are measurements of three axes of the model at right angles to each other (18). The r_{mod} thus obtained will be, for irregular and branched molecules, considerably larger than r_w . The opposition of these two effects will often result in r_{mod} being close to r_w for small molecules, as shown in Table 2. In general, we regard r_w as preferable: it is more easily obtained, and does not depend on an arbitrary choice of the axes a , b , and c to be measured.

The Volume v_M Obtained from Molar Volumes of Solids and Liquids

A molecular volume v_M may be obtained by dividing the molar volume V_M of a solid or liquid by Avogadro's number N .

If we accept the idea that the volume of a molecule is defined by a van der Waals surface as in Figure 2, then V_M is made up of the sum of the van der Waals volumes v_w of N molecules plus a varying amount of empty space between them which has been called the "free volume" or "empty volume"³ (23). Thus, at 0°K a crystal made up of close-packed spheres has only 74% of its total volume occupied by the spheres, and 26% occupied by empty volume,³ so that $v_M/v_w = 1.35$. This ratio may be expected to vary from compound to compound. Except for atoms of the noble gases,⁴ molecules are never exactly spherical, but always have bumpy surfaces, the methane molecule of Figure 5 being an example. Consequently, the proportion of empty volume in a crystal will depend on the shapes of the molecules composing it, and how well they fit together. The almost spherical molecule of methane is capable of reorientation in the crystal even at 1° K (25). Its density at 77.4° K (26) corresponds to an assembly of close-packed spheres of 2.12 Å radius, so that reorientation probably involves a concerted rotation of several molecules. However, less spherical molecules are capable only of vibrational motion in the crystal. The empty volume will be reduced by hydrogen-bonding between molecules, which will bring them closer together. On the other hand, it will increase with rising temperature because of the increasing amplitude of thermal vibrations.⁵ Hence no simple relation between v_M and v_w is to be expected. The variability of the

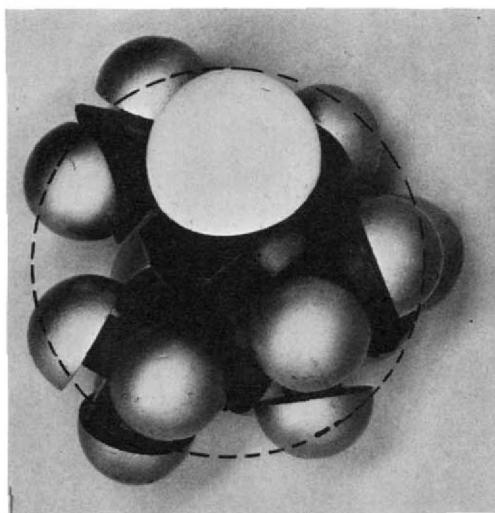


Figure 6. Model of the molecule of camphor constructed from Courtalds models. (These models underestimate the van der Waals radius of hydrogen, and so the actual molecule has a smoother van der Waals surface than indicated by the model.)

ratio v_M/v_w is shown in Table 3. The relatively non-polar compounds 2–7 have $v_M/v_w \approx 1.5$ and $r_M/r_w \approx 1.14$. The high ratio for camphor (1.57) arises from the fairly spherical shape of its molecules (Fig. 6) which enables them to rotate in the crystal (27) and hence occupy a large volume. Contrariwise, the fairly low ratio (1.41) for cholesterol is probably due to a flat shape which allows good packing in the crystal. The relatively polar molecules 8–14 of Table 3, held together by strong intermolecular hydrogen bonding or ionic bonding in the crystal, have $v_M/v_w \approx 1.34$ and hence $r_M/r_w \approx 1.10$. These ratios are probably pretty general for polar molecules. The five cellulose derivatives, investigated by Ihnat and Goring (11) in an important study discussed below, all have $v_M/v_w = 1.36 \pm 0.01$ ($r_M/r_w = 1.11$).

When a solid melts, the proportion of empty volume increases (except in a few cases such as that of ice), so that translatory motion of the molecules becomes possible. It further increases with increase of temperature, so that at the boiling point about half the volume of a liquid composed of approximately spherical molecules

² Most models are also based on a lower van der Waals for carbon than that adopted by Bondi (15). This results in a model of methane also being "bumpier" than indicated by Bondi's values. This can be seen by comparing the model of methane in Figure 8 (constructed with Stuart-Briegleb models) with the drawing in Figure 5.

³ This idea is obviously a simplification: there is a sense in which *all* the volume of a crystal is occupied. A molecule consists of positive nuclei embedded in an electron cloud of varying density, but without sharp boundaries. In our example of closely-packed spherical molecules, the empty volume between the molecules is in fact occupied by the outer regions of the electron clouds, at such low densities that they represent regions of intermolecular attraction. The points at which the spheres are in contact are in fact regions of interpretation of more dense electron clouds, and hence regions of intermolecular repulsion.

⁴ The densities of the noble gas solids at 0°K (24) are almost exactly those expected for close-packed spheres having the van der Waals radii suggested by Bondi (15).

⁵ The van der Waals increments of Table 1 are obtained from crystallographic data at ordinary temperatures, and not at 0°K, and hence all include about 10% of empty volume (15). Values of r_w computed from v_w are in consequence about 3% too large. This error is not significant for our present purposes.

Table 3. Molecular Volumes v_w and v_M of Some Solids

Compound	$v_w(\text{\AA}^3)$ ^a	$v_M(\text{\AA}^3)$ ^b	v_M/v_w
1. Methane	28.4	53.7 ^c	1.89
2. Naphthalene	123.4	185.4	1.50
3. <i>trans</i> -Stilbene	177.8	257	1.45
4. Camphor	161.0	253	1.57
5. Benzoic acid	107.9	160.1	1.49
6. Cholesterol	426.1	601	1.41
7. Propionamide	76.7	116.2	1.52
8. Urea	54.6	74.6	1.37
9. Adipic acid	133.6	177.8	1.33
10. Succinimide	85.2	116.1	1.36
11. Glycine	58.0	77.9	1.34
12. <i>m</i> -Aminobenzoic acid	110.8	150.8	1.36
13. Glucose	146.7	191.8	1.31
14. Sucrose	272.8	358	1.31

^a Calculated from atomic increments of Table 1.

^b Calculated from densities at 20° given in "Handbook of Chemistry and Physics," Chemical Rubber Co., Cleveland, 1960, except for methane.

^c Calculated from density at 77°K given in reference (26).

Table 4. Molecular Volumes v_w and v_M of Some Liquids (Temperature 20–25°C, Unless Otherwise Noted)

Substance (temp. °C)	$v_w(\text{Å}^3)^a$	$v_M(\text{Å}^3)^b$	v_M/v_w
1. Oxygen (-183°)	22.6	46.5	2.06
2. Nitrogen (-196°)	22.0	57.6	2.62
3. Carbon dioxide (-37°)	34.2	66.4	1.94
4. Carbon disulfide	51.8	100.1	1.94
5. Methane (-164°)	28.4	64.0	2.25
6. Ethane (-100°)	45.4	88.6	1.95
7. <i>n</i> -Pentane	96.4	192	2.00
8. <i>n</i> -Dodecane	215.4	368	1.71
9. Cyclohexane	102.0	179.4	1.76
10. Benzene	80.4	148.6	1.85
11. Ammonia (-79°)	22.8	34.5	1.51
12. Water	20.6	29.9	1.45
Water (+100°)	20.6	31.2	1.52
13. Methanol	36.1	67.0	1.86
14. <i>n</i> -Pentanol	104.1	179.6	1.72
15. Ethylene glycol	60.8	92.4	1.52
16. Glycerol	88.5	121.3	1.42

^a Calculated from atomic increments of Table 1.

^b Calculated from densities in "Handbook of Chemistry and Physics" Chemical Rubber Co., Cleveland, 1960.

is empty volume (i.e., $v_M/v_w \approx 2$) (23). The ratios v_M/v_w for a number of liquids at various temperatures are given in Table 4. It is evident that the proportion of empty volume decreases as the molecules of a liquid become more rod-shaped and less spherical (compare nos. 7 and 8, 13 and 14 in Table 4), and as they become more capable of hydrogen-bonding to each other (compare nos. 5 and 13; 13, 15, and 16).

Attempts are occasionally made to obtain the van der Waals radii of molecules or ions from molal volumes of liquids. From measurements of models of paraffins, Robinson and Stokes (21) proposed an empirical relation which in our symbols is

$$r_{mod} \approx 0.72 V_M^{1/3}$$

(with r_{mod} in Å and V_M in cm³ per mole). This relation leads to the ratio $r_M/r_{mod} \approx 1.02$, i.e., an r_{mod} about as great as r_M , and considerably greater than our r_w . This is a consequence of the high r_{mod} (as compared with r_w) obtained by Robinson and Stokes' method of calculation (see nos. 6 and 7, Table 2) and used in deriving the relationship above. Gorrell and Dubois (28) obtained molecular radii r'_w by assuming the LeBas volume V_M of a compound (obtained from LeBas increments⁶) to contain N spherical molecules in orderly cubic array, resulting in the relationship: $r'_w = \frac{1}{2}(V_M/N)^{1/3}$. To the extent that at the boiling point $V_M \approx 2V_w$, it can be shown that r'_w is close to our r_w . Spernol and Wirtz (31) obtained molecular radii by assuming relatively nonpolar liquids to be made up of spherical molecules in hexagonal close packing (i.e. assuming $v_M/v_w = 1.35$). As shown above, liquids have a variable proportion of empty volume, usually higher than allowed for

by this ratio, so that the radii of Spernol and Wirtz will usually be slightly greater than r_w . All of these differing methods of obtaining molecular volumes (and thence radii) would seem to be inferior to the simpler method of calculating v_w from atomic increments described in this paper.

Volume \bar{v}_M Obtained from Partial or Apparent Molal Volumes

Most recent measurements of diffusion rates have been carried out in aqueous solution, and some investigators have attempted to relate diffusion coefficients to radii r_M obtained from partial molal volumes \bar{V}_M

$$\bar{V}_M = N\bar{v}_M = 4\pi N\bar{r}_M^3/3$$

Such a volume refers to an infinitely dilute solution in water, but is not greatly different from the apparent molal volume (the increase in volume observed on dissolving one mole of substance in water to form a solution of low but finite concentration). We shall ignore this slight difference, and use the symbol \bar{V}_M for both partial and apparent molal volumes, and the symbol \bar{v}_M for the molecular volumes derived from them.

A comparison of the partial molecular volumes \bar{v}_M given in Table 5 for the solids nos. 5, 6, 8, 15, and 16 with the molecular volumes v_M (nos. 8, 7, 11, 13, and 14 of Table 3) shows the former to be very slightly smaller except in the case of propionamide ($\bar{v}_M/v_M = 1.02$). Similarly, the partial molecular volumes \bar{v}_M of the liquids 4, 12, and 13 of Table 5 are very slightly smaller than their molecular volumes v_M (nos. 10, 15, and 16 in Table 4). Evidently, the empty volume associated with the solute molecule in aqueous solution is roughly the same as the empty volume associated with this molecule in the solid or liquid state at ordinary temperatures. Polar molecules, such as urea and glycine, which have small empty volumes about them in the crystal ($v_M/v_w \approx 1.35$) because of the strong forces holding them together, have also small empty volumes (statistically) associated with them in aqueous solution ($\bar{v}_M/v_w \approx 1.3$) because of their strong attraction for the polar water molecules. On the other hand, less polar molecules such as benzene, which are liquid at ordinary temperatures ($v_M/v_w \approx 1.8$), do not attract water molecules strongly and so have large empty volumes

⁶ LeBas found molar volumes V_M at the boiling points to be approximately additive, and produced a set of atomic increments (29, 30).

Table 5. Volumes v_M and v_w of Molecules in Water Solution

Compound	$v_w(\text{Å}^3)$	$\bar{v}_M(\text{Å}^3)^a$	\bar{v}_M/v_w	$\bar{v}_T(\text{Å}^3)$	\bar{v}_M/\bar{v}_T
1. Methane	28.4	62.0 (32)	2.18	59.8	1.04
2. Ethane	45.4	85.0 (32)	1.87	86.4	0.98
3. Propane	62.4	111 (32)	1.77	112.0	0.99
4. Benzene	80.3	138 (32)	1.72	151.0	0.91
5. Urea	54.6	73.4 (9)	1.34	72.7	1.02
6. Propionamide	76.7	118 (9)	1.54	118.5	1.00
7. Glycolamide	67.4	93.4 (9)	1.39	95.7	0.98
8. Glycine	58.0	72.2 (10)	1.25	70.6	1.02
9. Alanine	75.0	101 (10)	1.34	97.2	1.04
10. Serine	82.7	101 (10)	1.22	101.0	1.00
11. α -Aminocaproic acid	126.0	180 (10)	1.43	166.6	1.08
12. Ethylene glycol	60.8	90.7 (9)	1.49	93.0	0.98
13. Glycerol	85.5	119 (9)	1.39	123.4	0.97
14. Erythritol	120.2	144 (9)	1.20	153.8	0.94
15. Glucose	146.7	186 (10)	1.27	209.7	0.88
16. Sucrose	272.8	348 (10)	1.27	366.7	0.95

^a Computed from data in literature (refs. in parentheses).

($\bar{v}_M/v_w \approx 1.7$) associated with the molecule also in aqueous solution. This empty volume in aqueous solution is shown for the methane molecule (which like all small, nearly spherical, nonpolar molecules has an abnormally large empty volume associated with it) in Figure 5.

About seventy years ago Traube (33) found that the apparent molal volumes of simple organic molecules in water are additive. Traube's increments in \AA^3 are as follows: C, 16.4; H, 5.1; N, 2.5; O (ether or carbonyl), 9.1; O (alcoholic hydroxyl), 3.8; O (carboxylic hydroxyl), 0.7. The addition of atomic increments plus a "covolume" of 22\AA^3 gives a molecular volume which we shall designate \bar{v}_T . The covolume may be regarded as the empty volume associated with the terminal atoms of a homologous series of compounds (16). (The "electrostriction" (30) of water by zwitterions such as glycine just cancels the covolume effect.) The values \bar{v}_T thus calculated are in surprisingly good agreement with \bar{v}_M , as shown by the last column of Table 5. The agreement becomes poorer when the molecule contains a long hydrocarbon chain (Table 5, no. 11) (presumably because of the effect of this chain in promoting "iceberg" formation and thus increasing volume (17)) or when it contains many hydroxyl groups (Table 5, nos. 13, 14, 15, 16), because of a breakdown of the open water structure about the molecule by hydrogen-bonding of water molecules to the hydroxyl groups.

The empty volume associated with a solute molecule can be much greater in solvents other than water. Thus in *n*-hexane a molecule of methane has \bar{v}_M of 99.6\AA^3 (32), or \bar{v}_M/v_w of 3.15. The lower \bar{v}_M in water has been attributed to the greater internal pressure in this solvent (32), but for most molecules \bar{v}_M is even lower in methanol (9), which is unlikely to have as high an internal pressure as water, and factors other than internal pressure must also be involved.

What Molecular Radius Should Be Used in the Stokes Equation?

Radii derived from each of the different molecular volumes defined above have been used at some time or another in calculating diffusion coefficients from eqn. (4). Intuitively, it seems reasonable that the collision volume of the kinetic particle itself, and not this volume plus an associated empty volume, which varies from solvent to solvent, should be used to furnish the radius for eqns. (3-5). For small molecules of $2\text{-}6 \text{\AA}$ radius this volume is best given by v_w .

Ihnat and Goring (11) have advanced the view that v_M better measures the diffusing entity.

Conceptually, the van der Waals volume is too small since it is unlikely that the solvent will behave as if it were an incompressible continuum surrounding the van der Waals surface and filling any voids within the molecule.

This is true to the extent that the empty volume surrounding a molecule and contributing to the total v_M is inaccessible to solvent molecules. We shall denote such inaccessible empty volume as "interior," as contrasted with accessible "exterior" empty volume.

An examination of molecular models shows that most of the empty volume associated with small molecules such as methane (Fig. 5) is exterior. As a molecule becomes larger and more ramified, we find a small

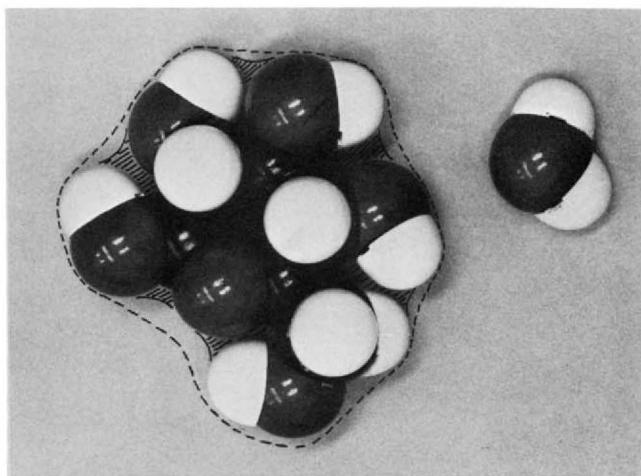


Figure 7. Model of a glucose and a water molecule, constructed with Stuart-Briegleb atomic models. Broken line about molecule indicates associated empty volume; shaded area indicates interior empty volume, inaccessible to the water molecule.

amount of inaccessible empty volume between the roots of the bulky groups. This is illustrated in purely qualitative fashion in Figure 7 for a glucose molecule. This illustration would seem to indicate that a fair proportion of the empty volume is "interior." It seems likely, however, that in fact for this molecule the proportion of empty volume is much less than indicated, because the Stuart-Briegleb models, which systematically underestimate the van der Waals radii of atoms (22, 34), make the molecule appear more "knobby" and less smooth than in actuality. This can be seen by a comparison of the Stuart-Briegleb model of methane in Figure 8 with the drawing in Figure 5. The latter is

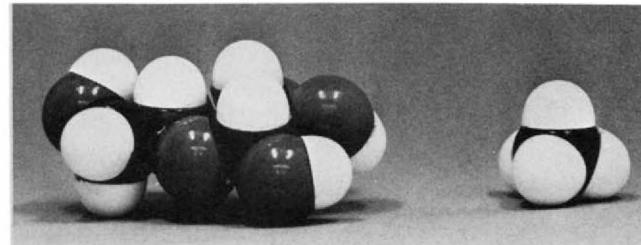


Figure 8. Model of a glucose molecule (viewed at right angles to view in Fig. 7) and a methane molecule, constructed with Stuart-Briegleb atomic models.

based on Bondi's latest estimates of van der Waals radii (15). An increase in the van der Waals radii of the carbon and hydrogen atoms in Figure 7 would fill in most of the crevices which account for interior empty volume and produce a much smoother molecule. The same is true, though to a lesser extent, for the tetramer of glucose, cellobetraose, shown in Figure 9.

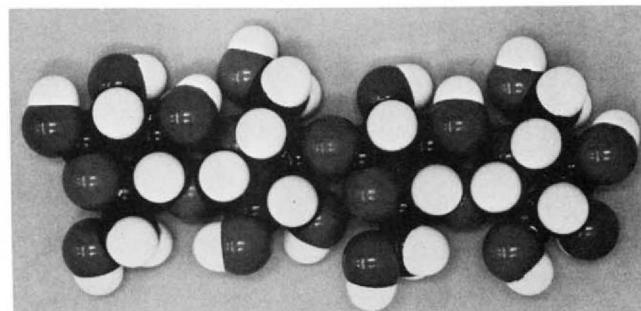


Figure 9. Stuart-Briegleb model of cellobetraose.

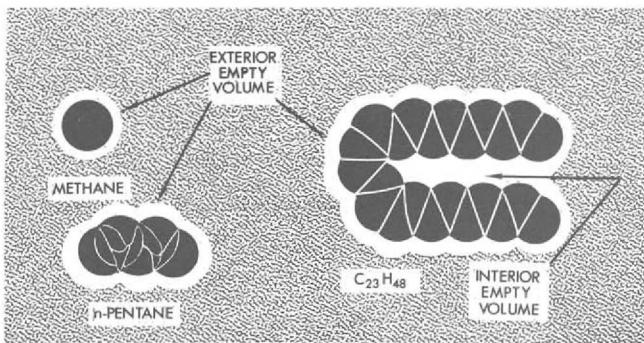


Figure 10. Representation of methane, *n*-pentane, and $C_{23}H_{48}$, showing the empty volumes associated with the molecules in solution. (Diagrammatic representation only; compare representation of methane in this figure with representation in Fig. 5.)

We conclude that for small molecules such as are considered in this paper the collision volume will have some value between v_w and v_M , but much closer to the former.

The reverse will become true for very large chain molecules repeatedly folded back on themselves. The empty volume associated with the molecule $C_{23}H_{48}$, folded back on itself once, is shown in Figure 10, and is still mainly exterior; however, for a very much longer chain folded back on itself many times the major part of the empty volume would become interior. Thus if one can assume $\bar{v}_M/v_w \approx 1.33$ for globular proteins (35), about 15% of the empty volume associated with a spherical protein molecule of molecular weight 50,000 is at the surface of the sphere and 85% is within; of the 15% at the surface, a certain proportion would be "interior" (in our sense) if the surface is folded to produce inaccessible crevices. The polystyrene latex particles of Chang and Schachman (6) include about 37% empty volume, but because of their size only 0.2% of this empty volume is at the surface of the spherical particles. Thus for very large molecules the collision volume becomes essentially v_M or \bar{v}_M rather than v_w .

If v_w gives the more reasonable estimate of the collision volume of a small solute molecule, one may ask why investigators of diffusion phenomena have used one or other of the less suitable measures of molecular volume discussed above. However, it has been a case of *faute de mieux*, since convenient methods of calculating v_w have become available only comparatively recently (15, 16).

Empirical Correction Factors for the Stokes Equation

We may now examine the applicability of eqns. (3)–(5) to small molecules, using the van der Waals radii r_w for r in these equations (see refs. 35–37 for other examples of the use of r_w in this way). We find that for molecules below a certain size the experimental diffusion coefficient is systematically higher than calculated from eqn. (5), and that the discrepancy increases as the molecule gets smaller. It becomes necessary (as already mentioned) to apply a correction factor, so that in effect the numerical factor 6 of eqns. (3)–(5) is reduced. It is convenient, for presentation of data, to treat this numerical factor as an unknown n , by rewriting eqn. (5)

⁷ Only molecules which appeared from the inspection of models to be roughly spherical or ellipsoidal have been considered. The difficulty of obtaining (f/f_0) for very irregular molecules has already been discussed (36, 37).

Table 6. Numerical Factor n of Equation (7), Applied to Diffusion in Carbon Tetrachloride

Molecule (lit. ref.)	$r_w(\text{\AA})$	Shape ^a	(f/f_0)	n
1. Hydrogen (38)	1.35	pro	1.00	1.10
2. Deuterium (38)	1.35	pro	1.00	1.38
3. Nitrogen (38)	1.74	pro	1.00	2.44
4. Argon (38)	1.88	sph	1.00	2.13
5. Methane (38)	1.89	sph	1.00	2.76
6. Methanol (39)	2.13	pro	1.00	2.59
7. Carbon tetrafluoride (38)	2.21	sph	1.00	3.22
8. Ethanol (39)	2.33	pro	1.01	3.14
9. Iodine (10)	2.50	pro	1.00	3.87
10. Cyclopentane (40)	2.53	obl	1.01	4.38
11. Carbon tetrachloride (38)	2.73	sph	1.00	3.77
12. Phenol (39)	2.77	pro	1.04	3.65
13. Tetrahydrofuran (39)	2.79	obl	1.01	3.50
14. N,N-Dimethylacetamide (39)	2.86	obl	1.03	4.00
15. Cyclohexane (40)	2.90	obl	1.01	4.06
16. Carbon tetrabromide (10)	2.91	sph	1.00	4.63
17. Benzyl alcohol (39)	2.93	pro	1.04	3.66
18. Cycloheptane (40)	3.05	obl	1.01	3.72
19. Naphthalene (39)	3.08	pro	1.03	3.81
20. Hexachloroethane (39)	3.14	pro	1.00	4.59
21. Biphenyl (39)	3.30	pro	1.07	3.82
22. Anthracene (39)	3.41	pro	1.06	3.92
23. Hexachlorobenzene (39)	3.42	obl	1.07	4.29
24. Acetic acid (dimer) (39)	2.98	pro	1.07	3.20
25. Benzoic acid (dimer) (39)	3.70	pro	1.16	3.82
26. Palmitic acid (dimer) (39)	5.20	pro	1.58	3.94
27. Hexadecanol (39)	4.11	pro	1.32	3.60
28. <i>n</i> -Pentane (41)	2.84	pro	1.06	3.07
29. <i>n</i> -Hexane (41)	3.00	pro	1.08	2.98
30. <i>n</i> -Heptane (39, 41)	3.15	pro	1.11	3.14
31. <i>n</i> -Octane (41)	3.28	pro	1.13	3.11
32. <i>n</i> -Decane (41)	3.51	pro	1.17	3.26
33. <i>n</i> -Dodecane (39, 41)	3.72	pro	1.23	3.30
34. <i>n</i> -Hexadecane (39, 41)	4.07	pro	1.32	3.50
35. <i>n</i> -Octadecane (41)	4.23	pro	1.36	3.66
36. <i>n</i> -Eicosane (39)	4.38	pro	1.40	3.56
37. <i>n</i> -Octacosane (39)	4.88	pro	1.56	3.59

^a pro = prolate ellipsoid; sph = sphere; obl = oblate ellipsoid

in the form

$$n = kT/\pi D^0 \eta r_w (f/f_0) \quad (7)$$

and investigate the dependence of n on r_w . (The "correction factor" by which the right hand side of eqns. (3)–(5) must be multiplied then becomes $n/6$.)

Calculations from the diffusion data for 37 widely different molecules in carbon tetrachloride give the results listed in Table 6 and plotted in Figure 11. The shapes of these molecules were obtained by inspections of models made with the Courtaulds atomic models (cf., Figs. 4 and 6), the axial ratios a/b obtained by measurements of these models, and the frictional ratios (f/f_0) thence obtained by reference to Figure 1.⁷ Compounds 1–23 of Table 6 are composed of relatively

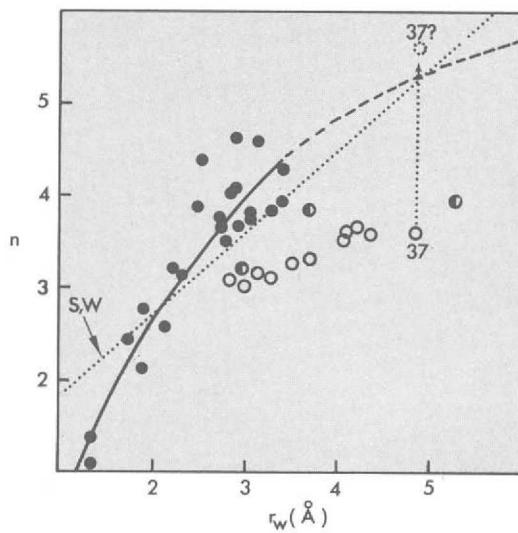


Figure 11. Variation of numerical factor n of modified Stokes eqn. (7) with van der Waals radius r_w of molecules diffusing in carbon tetrachloride. Solid circles: compounds 1–23 of Table 6; half-open circles: compounds 24–26; open circles: compounds 27–37. Theoretical curve according to Spernol and Wirtz (31) labelled S. W.

compact molecules having shapes not grossly different from spherical, and hence have frictional ratios approaching unity. Values of n for these compounds are shown as solid circles in Figure 11, and decrease rapidly for molecules having $r_w < 3 \text{ \AA}$, being almost unity for H_2 , the smallest molecule investigated. The curve drawn through these points is not wildly displaced from the curve calculated by the equation of Sernhol and Wirtz (31), showing the utility of the latter for rough calculations of diffusion coefficients of molecules having r_w between 2–4 Å.

Compounds 24–26, in the concentration range investigated, exist as dimers in carbon tetrachloride; Figure 4 pictures the model of compound 25. Compounds 24 and 25 have well-defined shapes, but compounds 26–37 are made up of flexible molecules of varying chain length. The points for compounds 27–37 (open circles in Fig. 11) all lie below any reasonable curve for n , which should approach the value 6 as the molecule becomes large enough. Longsworth (39) explains this behavior by assuming that these molecules do not diffuse as rigid particles, but by movement of segments of the flexible chain. Alternatively, one may explain the high values of D° by assuming that the flexible molecules are coiled up into more spherical shapes having (f/f_0) approaching unity. The effect of changing (f/f_0) for compound 37 from 1.56 to 1.00 is shown in Figure 11: the value of n rises from that indicated by point 37 to that indicated by point 37?, much closer to the value expected.

A very large volume of data on diffusion coefficients in water is available, and analysis of some literature

Table 7. Numerical Factor n of Equation (7), Applied to Diffusion in Water

Molecule (lit. ref.)	$r_w(\text{\AA})$	Shape	(f/f_0)	n
1. Helium (44)	1.40 ^a	sph	1.00	1.94
2. Oxygen (44)	1.73 ^a	pro	1.00	2.44
3. Argon (45)	1.88 ^a	sph	1.00	5.36
4. Nitrogen (45)	1.84 ^a	sph	1.00	3.56
5. Carbon dioxide (46)	1.98 ^a	pro	1.01	3.79
6. Nitrous oxide (46)	1.96 ^a	pro	1.01	3.49
7. HDO (9)	1.70	sph	1.00	3.82
8. H_2O^{18} (47)	1.70	sph	1.00	3.37
9. Methane (48)	1.89 ^b	sph	1.00	4.15
10. Ethane (48)	2.21	pro	1.00	4.39
11. Propane (48)	2.46	pro	1.01	4.90
12. <i>n</i> -Butane (48)	2.66	pro	1.03	5.60
13. Formamide (49)	2.20	obl	1.01	4.21
14. Acetamide (9)	2.45	obl	1.01	4.75
15. Propionamide (9)	2.66	pro	1.02	4.96
16. Urea (50)	2.35	obl	1.02	4.45
17. Thiourea (51)	2.50	obl	1.01	4.28
18. Methylurea (9)	2.62	pro	1.02	4.72
19. 1,3-Dimethylurea (9)	2.80	pro	1.03	5.12
20. Glycolamide (52)	2.75	pro	1.02	4.59
21. Lactamide (53)	2.91	obl	1.01	5.06
22. Methanol (44)	2.36	pro	1.00	3.94
23. Ethanol (44)	2.58	pro	1.01	4.54
24. <i>n</i> -Propanol (44)	2.77	pro	1.03	5.06
25. <i>n</i> -Butanol (44)	2.93	pro	1.06	4.89
26. <i>t</i> -Butanol (44)	2.93	sph	1.00	5.74
27. Glycine (8)	2.88	pro	1.02	4.75
28. Alanine (8)	3.03	obl	1.01	5.30
29. β -Alanine (8)	3.03	pro	1.03	5.05
30. Sarcosine (8)	3.06	pro	1.04	4.79
31. Serine (8)	3.24	obl	1.01	5.12
32. α -Aminoisobutyric acid (8)	3.17	sph	1.00	5.30
33. Glycylglycine (8)	3.28	pro	1.06	5.35
34. Diglycylglycine (8)	3.62	pro	1.12	5.46
35. Ethylene glycol (9)	2.86	pro	1.01	4.42
36. Glycerol (9)	3.23	pro	1.03	4.72
37. Erythritol (9)	3.56	pro	1.03	5.04
38. Pentaerythritol (19)	3.64	sph	1.00	5.32
39. Glucose (54)	3.86	obl	1.03	5.50
40. Cellulose (11)	4.65	pro	1.04 ^c	5.90
41. Cellotriose (11)	5.24	pro	1.07 ^c	6.27
42. Cellotetraose (11)	5.72	pro	1.09 ^c	6.30
43. Cellopentaose (11)	6.14	pro	1.19 ^c	6.29
44. Cellohexaose (11)	6.49	pro	1.24 ^c	6.31

^a Obtained from reference (15).

^b Compare with collision radius of 1.95 Å calculated by Flynn and Thodos (A. I. Chem. E. J., 8, 362 (1962)) from viscosity data; similar calculations for other compounds give 2.26 Å (ethane), 2.57 Å (propane), 2.85 Å (*n*-butane).

^c Taken from reference (11).

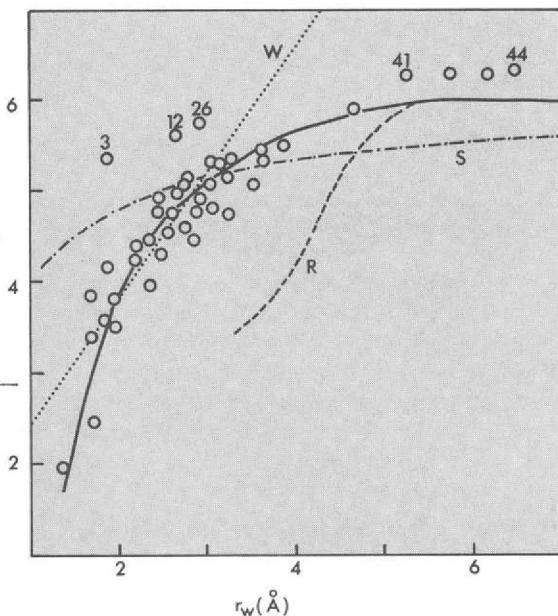
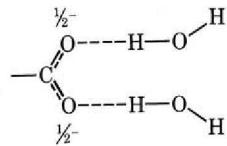


Figure 12. Variation of numerical factor n of modified Stokes eqn. (7) with van der Waals radius r_w of molecules diffusing in water. Correction curves of Sernhol and Wirtz (ref. (31)) ((W), Schultz and Solomon (ref. (18)) (S), and Robinson and Stokes (ref. (21a)) (R) are also shown.

data using eqn. (7) is presented in Table 7 and in Figure 12. While the analysis of data for diffusion in carbon tetrachloride neglected any possible solvation of the solute molecules, an attempt was made to take account of possible hydration of solute molecules in water: hydration of polar solutes has long been known to be important, although its extent is often in dispute (10, 11, 18, 21a). We have assumed that each hydroxyl group in a molecule is bonded, on an average, to one water molecule, with a consequent increase of about 18.6 \AA^3 in van der Waals volume of the diffusing particle (cf., Fig. 5); this value lies between the two volume increases assumed by Ihnat and Goring (11) to explain their diffusion and their viscosity results. We have further assumed that each ionized carboxyl group is, on an average, bonded to slightly more than two water molecules, as shown



Its hydrated volume has been taken to be 71 \AA^3 rather than 29.5 \AA^3 as computed from the increments of Table 1. The justification for this value is given elsewhere (36, 37). No hydration of the charged ammonium group or of the amide group is assumed; it is possible that some hydration of these groups takes place, but is offset by their effect in causing a breakdown of the local water-structure, so that the molecule finds itself in a zone having less than the macroscopic viscosity (36, 42, 43).

No account was taken of any effect of hydration on the shape of the molecules; it is likely to be small but perhaps not negligible (11). The frictional ratios are close to unity for all molecules having $r_w < 3.5 \text{ \AA}$ (i.e., for the majority of molecules in Table 7), and no great error would be involved in regarding these molecules as spherical.

It is apparent from Figure 12 that when r_w decreases below 5 Å, the numerical factor of eqn. (7) must be reduced below the Stokes value of six. Most of the points cluster about the solid line of Figure 12, with a scatter no worse than might be expected considering the rather naive model adopted. Thus no attempt has been made to take account of the possible effects of some of the polar molecules in causing a loosening of the water structure (36, 37, 42, 43). The large deviations of the three points 3, 12, and 26, and of the four points 41–44 probably arise from two different effects. The first three points are for molecules (argon, *n*-butane, *t*-butanol) known to have a great propensity for "iceberg" formation (17b, 21c), which effectively increases the size of the hydrodynamic particle (55). The last four points are for the elongated molecules of Ihnat and Goring (11), and the high value of n indicates that either r_w or (f/f_0) (or both) are too small: the former because (as Ihnat and Goring suggest), the effective volume of the hydrodynamic particle is greater than our v_w because of inaccessible, "interior" empty volume about the particle; the latter because the molecule is more irregular than the ideal prolate ellipsoid for which Perrin (4) calculated the frictional ratio (f/f_0), as seems highly probable from an inspection of the models (see Fig. 9 for cellotetraose).

Also shown in Figure 12 are the curves given by three other empirical corrections which have been proposed for the Stokes equation. The equation of Spernol and Wirtz (31) was obtained by analyzing the experimental data for diffusion coefficients of relatively nonpolar solute molecules in nonpolar solvent molecules of roughly comparable size, but it proves also to be a good approximation for water solutions of wide variety of solute molecules, polar and nonpolar, having van der Waals radii between 2 and 3 Å. The correction curves of Schultz and Solomon (18) and of Robinson and Stokes (21a), which are designed to cover aqueous solutions, but which are based on the analysis of a rather limited amount of data, are much less successful.

A comparison of Figure 12 with Figure 11 would seem to show that the Stokes equation is valid for molecules dissolved in water having radii down to about 5 Å, but that it becomes valid in carbon tetrachloride only when molecules are considerably larger. However, while the large molecules examined in aqueous solution were relatively stiff, the large molecules examined in carbon tetrachloride solution were flexible chains and capable of segmental diffusion. The study of the diffusion of large, rigid molecules in carbon tetrachloride would be interesting.

For molecules in water having $r_w < 5$ Å, the Stokes equation must be modified by using a numerical factor n less than 6 in eqn. (7); values of n read from the solid curve of Figure 12 for different values of r_w are given in Table 8. In apparent contradiction to these results, van Holde (56) found that application of the unmodified Stokes equation to the sedimentation in the

ultracentrifuge of osmium tetroxide yielded a molecular radius of 2.1 Å, in good agreement with a computed molecular radius of 2.2 Å. The latter computation, however, is in error, because it assumes a van der Waals radius of 0.55 Å, instead of 1.50 Å (15), for the oxygen atoms. A more realistic radius r_w for osmium tetroxide, known to be a tetrahedral molecule (57) and hence (like methane: Fig. 5) approximately spherical, would be about 3 Å. This would be about the value obtained from the sedimentation coefficient using a numerical factor of about 4 instead of 6 in the Stokes equation.

Conclusion

The Stokes equation, long known to apply to the viscous drag impeding the movement of such objects as steel balls falling in a bath of heavy oil, and shown by Cheng and Schachman to apply to the sedimentation in water of particles having a radius only eight times greater than that of a virus molecule, seems to be still valid when the particle in water solution is a molecule of only 5 Å radius. However, we have shown that for particles of this size the notion of particle volume, unambiguous in the case of the steel ball, becomes hazy. By adopting a simple notion of the volume of a molecule it has been possible to produce an empirical correction factor for the Stokes equation to enable one to apply it to molecules down to 2 Å in radius. Such a relationship has practical utility, but any explanation of it must start from a model of the solution differing from that of Stokes, and taking account of the discontinuous nature of the solvent.

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Table 8. Dependence of Numerical Factor n (Equation (7)) on van der Waals Radius r_w

r_w (Å)	n	r_w (Å)	n
1.5	2.2	3.5	5.4
2.0	3.9	4.0	5.6
2.5	4.8	4.5	5.8
3.0	5.1	5.0	6.0

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