

A CORRELATION OF VAN DER WAALS CONSTANTS WITH ANESTHETIC POTENCY

R. J. WULF, B.S., AND R. M. FEATHERSTONE, PH.D.

RESPECT for the ideas presented in the classic review on theories of anesthesia by Butler (1) breeds timidity on the part of the authors in attempting to "explain" anesthesia on a physical basis. However, studies of xenon, an anesthetic agent (2), have focused attention on some hitherto unreported correlations between anesthetic potency and some physical properties related to atomic and molecular structure.* These observations are presented here not as an "explanation" of anesthesia, but to call attention to the fact that some properties of atoms and molecules correlate much better with clinical anesthetic potency than others previously cited. Some of these properties approach the problem at what seems to be a more fundamental level.

Boyle's Law (pressure, P , times volume, V , equals a constant for an ideal gas), although used as a criterion for an ideal gas, is not followed by a real gas.† Numerous attempts (3) have been made to formulate an expression which would agree more closely with the experimental data and one of these was formulated by the Dutch physicist, Johannes D. van der Waals (1873-1923). He considered that in a real gas the attraction between molecules, which is not considered in the concept of an ideal gas, would be equivalent to a slight increase in the pressure applied to a gas. Since any given molecule is affected by a number of others within its sphere of action, this number will be proportional to the density of the gas. Hence the correction should be proportional to the square of the density or inversely proportional to the square of the volume. For this reason van der Waals replaced the pressure, P , in Boyle's Law by the term $\left(P + \frac{a}{V^2}\right)$.

He also considered that the volume would be reduced in a real gas because of the space occupied by the molecules themselves, and should be replaced by the smaller term $(V - b)$. Making these corrections to

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* Some of these observations were reported by R. M. Featherstone during a symposium on "Chemical Bonding and the Molecular Level of Drug Interaction," conducted in September, 1955, at a meeting of the American Society for Pharmacology and Experimental Therapeutics, in Iowa City, Iowa.

† A real gas is the type that actually occurs naturally; for example, oxygen, nitrogen, and xenon.

Boyle's Law the following relationship is established for one mole of a real gas:

$$\left(P + \frac{a}{V^2}\right)(V - b) = RT$$

where: P = pressure in atmospheres, V = volume in liters, R = gas constant (0.08207), T = temperature in degrees Kelvin, and "a" and "b" are the constants and are discussed below. (Equation is true for one mole of gas.)

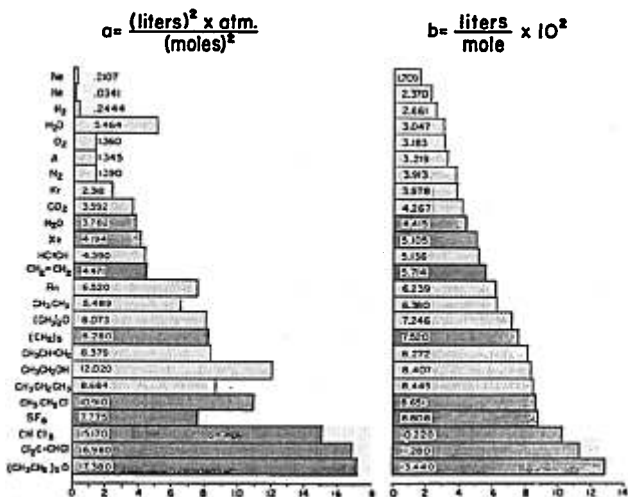


FIG. 1. Anesthetic and nonanesthetic gases in order of increasing van der Waals "b." Values for "a" and "b" for SF₆, Cl₂C=CHCl and (CH₃)₂S are calculated from critical temperature and critical pressure values by the following relationships (12):

$$P_c = \frac{a}{27b^2} \quad T_c = \frac{8a}{27Rb}$$

where P_c = critical pressure, T_c = critical temperature, and R = gas constant. All other values from Lango's Handbook of Chemistry (7).

The constants "a" and "b" in the van der Waals equation may then be considered as a measure of the attractive forces of the molecules for one another and the volume of the molecules, respectively. All reactions or interactions between any atoms or molecules are dependent on these fundamental properties, but perhaps no one has ever found a series of drugs which seems to illustrate it so clearly as do the

anesthetic agents. The data in figure 1 are arranged in order of increasing van der Waals "b" constants and show that the correlations of both the van der Waals constants, "a" and "b," with anesthetic potency are very pronounced. Figure 1 lists many substances which do not possess anesthetic properties at ordinary pressures, as well as inert gases and organic compounds which do produce anesthesia. All those substances in the latter class are indicated by greater shading in figure 1. In view of the closeness of the "a" and "b" constants of xenon to those of nitrous oxide and ethylene, the order of anesthetic potency of this inert gas is not surprising. The inordinately high "a" constants for water and ethanol may be explained by their high potentials for hydrogen bonding. Similarly, the low "a" constant of SF₆ may be attributed to the differences in bonding among the six fluorine atoms (4). This factor may play an important role in the anesthetic action of SF₆, since Virtue (5) has classified this gas with the nitrous-oxide-xenon-ethylene group. Radon is included to complete the inert gas series. Theoretically, by the considerations presented in this paper, radon would be an excellent anesthetic agent if it possessed no radioactivity.

The significance of van der Waals "b" can be clarified by considering further what it actually measures. Most simply, it may be stated that it is a measure of the volume occupied by the molecules of one mole of the substance. Upon closer examination it may also be shown to be a measure of the polarizability of the molecules (3), polarizability being a measure of the ease with which the negative electrons can be shifted from a normal charge distribution about the positive nucleus or aggregation of nuclei (6). Polarizability, α , is defined by the following equation: $m = \alpha F$, where m is the electrical moment of the induced dipole produced by a field of strength F acting on a molecule. Polarizability may be determined from the molecular refraction, (R), by the following relationship:

$$[R] = \left[\frac{4\pi N}{3} \right] \alpha = \frac{n^2 - 1}{n^2 + 2} \frac{M}{d}$$

where N = Avogadro's number, n = index of refraction, M = molecular weight, and d = density; then

$$\alpha = \frac{[R]}{\frac{4}{3} \pi N}$$

or in order to convert values of molecular refraction, $[R]$, into polarizability it is necessary to divide $[R]$ by $\frac{4}{3} \pi N = 2.52 \times 10^{24}$.

The molecular refraction of an atom or molecule may also be determined from empirically deduced atomic and structural refractive

constants (7). These values are found to be very close to experimental values and for our purposes entirely sufficient. Figure 2 shows the correlation between anesthetic potency and molecular refraction obtained upon plotting such determinations.

Meyer and Overton (8, 9, 10) found that the chemically inert anesthetics had activities which were for the most part proportional to their oil-water partition coefficients, figure 3, and suggested that their action was due to their entry into the lipid portion of the cell. The

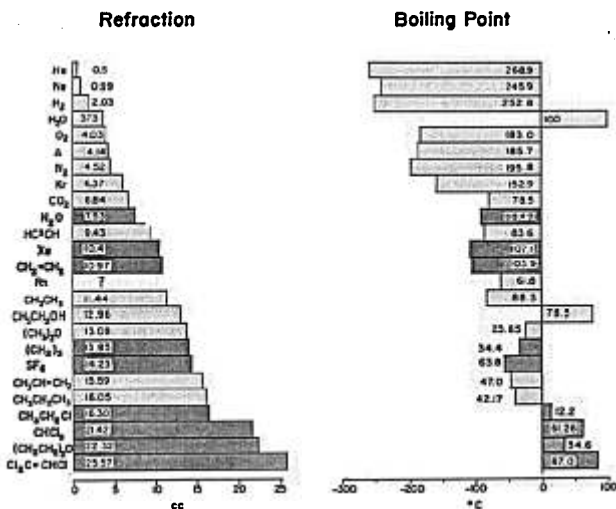


FIG. 2. Refraction and boiling point data. Refractions: Values for elements from Lange's Handbook of Chemistry (7). Values for compounds from tables in Ingold's, Structure and Mechanisms in Organic Chemistry (17). Note: H₂O, CH₃CH₂OH and SF₆ occupy approximately the same positions in the list as when using van der Waals "b." Boiling points: All values from Lange's Handbook of Chemistry (7).

amount of gas which dissolves in a liquid (oil or water) depends on the temperature and pressure, as well as on the nature of the gas and the liquid solvent. Solubility is therefore dependent upon the attraction and repulsion between the solute (gas) and solvent (water or oil) molecules which are measurable by van der Waals constants and also the "chemical reactions" such as hydrogen bond formation. Experimentally it has been found that at a given temperature and pressure the solubilities of a series of gases in a given liquid generally increase in the order of their ease of liquefaction, that is, in proportion to their

critical constants † or van der Waals constants "a" and "b." Large discrepancies (possibly SF₆) can usually be attributed to "chemical reactions" between the molecules of solute with those of solvent. It is primarily because water has such peculiar solvent properties that the aqueous concentrations make an undesirable scale upon which to base comparisons of narcotic effectiveness. Therefore, it is not surprising to observe many single anesthetics and groups of agents which fall out of line when one considers the possibilities of these "chemical reactions" which would "mask" the more fundamental property of van der Waals constants "a" and "b." Thus the Meyer and Overton theory in general does not have great validity (fig. 3).

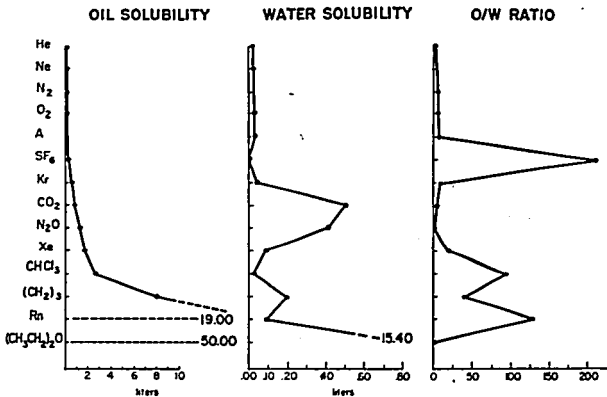


FIG. 3. Meyer-Overton theory of narcosis. Solubilities are expressed in Bunsen coefficients, i.e., the volume of gas, reduced to 0 C and 1 atmosphere pressure, dissolved by unit volume of solvent at the temperature of the experiment under a partial pressure of 1 atmosphere of the gas. References: N₂O, CHCl₃, (CH₂)₃, (CH₃CH₂)₂O (2); SF₆ (5); He, Ne, N₂, O₂, A, Kr, CO₂, Xe, Rn (18).

The Traube theory (11) is based upon a correlation between potency and the ability to lower surface tension of water. Traube therefore concluded that anesthetic action was at some surface in the cell. A closer examination of the data will show the following to be true. Absorptions may be classified as two general types (12). The first, van der Waals absorption, is characterized by relatively low

† van der Waals constants "a" and "b" may be calculated from the critical constants of a gas by the following relationships:

$$T_c = \frac{8a}{27Rb} \quad P_c = \frac{a}{27b^2}$$

where P_c = critical pressure, T_c = critical temperature, and R = gas constant.

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heats of absorption (5 to 10 kcal. per mole of gas). These heat changes are of the same order of magnitude as heats of vaporization and the forces by which the absorbed gas molecules are held to the surface of the solid are therefore similar to the forces of attraction between molecules in a liquid, again measurable by van der Waals "a" and "b." Another characteristic of this type of absorption, under given conditions, is that the absorption is roughly related to the ease of liquefaction of the gas. The second type, "chemabsorption," is characterized by heats of absorption of from 10 to 100 kcal. per mole. It occurs, however, in limited cases and is generally observed at moderately high temperatures only. Again the measurement of absorption depends primarily on the interaction forces between molecules with large discrepancies being due to the "chemical reactions." Thus the Traube theory offers further experimental proof for the correlation of anesthetic potencies with these fundamental van der Waals forces.

Ferguson (13) also pointed out in his interpretation of data on anesthetics that all of the previous theories were not really independent. The physical properties measured, vapor pressure, solubility, oil-water partition coefficients, and absorbability were in reality measures of the tendency of a substance to distribute itself between two phases and that when equilibrium existed the chemical potential would be the same in all phases. Brink and Posternak (14), in an extension of Ferguson's work, elaborated upon the idea that the work required per mole in the transfer of the narcotic from the pure liquid to the narcotized cell is the same for all those substances that have been shown to cause equal degrees of narcosis at equal thermodynamic activities. They also make speculations as to the significance of their work and suggest the probability that narcotics produce their effect in regions of the cell into which they can fit, much as they fit into their own pure liquid. This is consistent with our discussion of the importance of the van der Waals constants "a" and "b" and the correlation found with anesthetic potency.

One other correlation that points out the importance of the forces between the molecules themselves in anesthesia is the boiling point relationship. The boiling point of a compound may be taken as a rough measure of the attractive forces between molecules, since the boiling point is that temperature at which the thermal agitation of the molecules is sufficient to overcome the attractive forces between them (6). A plot of a selected series of gases (fig. 2) in order of ascending temperature to cause boiling correlates surprisingly well with the anesthetic potency of the various gases. This is another indication that anesthesia correlates with the fundamental properties, van der Waals "a" and "b" of the atom or molecule. Again, the hydrogen bonding potentials of water and ethanol account for their deviations from approximate linearity.

It appears then that in most of the previous "explanations" of

anesthesia attempts were made to utilize the fundamental properties of the atoms and molecules themselves. It is also observed that in most cases this was "concealed" or "masked" by interactions with a solvent, surface, or unknown substance in the central nervous system before reaching the actual site of action. These difficulties are overcome by looking at the atom or molecule itself, much in the same way that Ferguson (13) did when he applied the changes in partial free energy or chemical potential to the analysis of various narcotics. It may also be pointed out that "activities" were used in place of concentrations in the work of Ferguson because of the nonideal nature of the agents involved.

From these observations it must then be realized that the van der Waals constants are actually a measure of far greater importance than a mere statement of their volume or the attraction between molecules. There are in fact a great many general properties of the atoms or molecules all lumped into the two constants which correct for the non-ideality of a real gas. This interpretation of the meaning of the "a" and "b" terms also brings one to realize that it is not actual "attraction" and "volume" that we are concerned with but that it is the sphere of influence of the molecule or atom which is responsible for its correlation with biologic action in solution.

The roentgen-ray diffraction studies of Schmitt and Palmer (15) point to some interesting experimental evidence of the importance of the correlation of anesthetic potency with van der Waals' constants "a" and "b." Measurements of the distances between layers of lipids extracted from dry nerve tissue and their expansion upon saturation with water and various anesthetic agents points to a possible mode of action. Schmitt and Palmer have measured the varying thicknesses of water layers between bimolecular leaflets of mixed lipids as a function of the relative amount of water with which the lipids were emulsified. In the discussion which followed presentation of our data * the question was raised as to whether the effects of narcotics on the lateral spacing of the lipid molecules may not so upset the permeability of membranes as to cause the interruption of the normal nerve impulse along the membrane. Goldacre (16), in working with amoebae, also postulated and perhaps demonstrated such phenomena.

When these physical chemical constants are considered in relation to the part they may play in the anesthetic process, the following picture emerges as a possibility. Figure 4 shows the effect of arranging the anesthetic and nonanesthetic agents in order of increasing volume. It is, of course, purely hypothetical in that in the cell we would expect water, oxygen and nitrogen to be present between the lipid layers normally, but it is highly conceivable that, upon the administration of an anesthetic, the separation of the lipid layers would be dependent upon the molecular volume as evidenced by a measure of "b." It is interesting to note that atoms or molecules which are normally present

or those that do not cause anesthesia are of relatively the same volume. It must also be kept in mind, however, that any "chemical reaction" between the atoms or molecules and the lipid layers would again effect the importance of the anesthetic potency correlation with the molecular volume. Figure 4 would seem to give more weight to the suggestion of Brink and Posternak (14) that narcotics produce their effect in the regions of the cell into which they can fit, much as they fit into their own pure liquids.

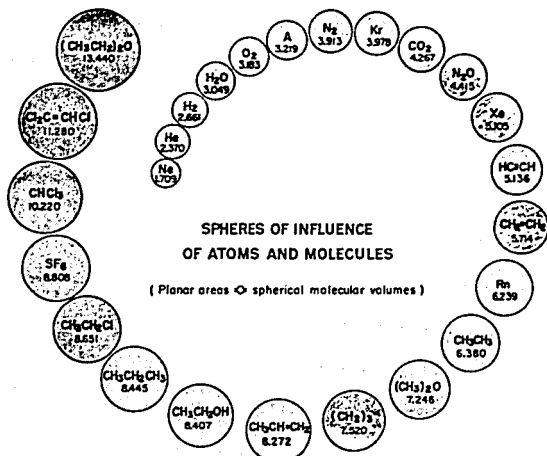


FIG. 4. Spheres of influence of atoms and molecules. All values for "b" or molecular volume are the same as those used in figure 1.

SUMMARY

Definite correlations between anesthetic potency or nonpotency of a series of atoms and molecules and their van der Waals physical chemical constants have been shown. These observations indicate that the attributes of many molecules which are important in bringing about "anesthesia" may be well expressed by the concept of "approximation to ideality." This concept has been given substance through the development of an equation by van der Waals, which contains correction terms for the major deviations from ideality. The increasing potency of clinical anesthetic agents has been shown to parallel in general the increasing magnitude of these constants. The inert gas xenon has been shown to possess physical chemical properties which can be used to explain its classification with nitrous oxide and ethylene as an anesthetic agent.

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