THE VARIATION OF THE OIL-WATER DISTRIBUTION RATIO OF DIVINYL ETHER WITH CONCENTRATION *

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The distribution ratio or partition coefficient ‡ of anesthetic substances between olive oil and water has been related to their anesthetic potency in the classical Meyer-Overton (1, 2, 3, 4, 5) lipoid theory of narcosis. A review of this theory has been given by Henderson (6) who points out many of the discrepancies in the literature. The recent discussion of the lipoid theory given by Beecher (7) fairly gives its present status. One of the fundamental difficulties in evaluating this theory is the lack of concordance between various determinations of the partition coefficient. For example, the figures for chloroform vary from the value 30–33 given to it by Overton (2) to the questionable value of infinity given in the International Critical Tables (8). Kurt Meyer found the partition coefficient for chloroform to be 70 at 20°, while a more recent determination by Lindenburg (9) gives the value of 100.

A serious source of error which has not been generally recognized is that the oil-water distribution ratio of anesthetic agents is a constant only in ideally dilute solutions. Both Höber (10) and Winterstein (11) have called attention to this variation of distribution ratios with changes in concentration in criticism of the Meyer-Overton theory. While Gordon and Reid (12) measured the variation of the distribution ratio with changing concentration of a number of organic acids between cottonseed oil and water, we have not found any work in the literature in which this variation of distribution ratios has been studied in oil-water systems with an anesthetic agent as the distributed substance.

A critical discussion of the factors which cause deviation from the distribution law will not be entered into here, but reference may be made to the excellent summary of the subject in the chapter on heterogeneous equilibrium in H. S. Taylor's "Treatise on Physical Chemistry" (13). Since the distribution ratio varies with the concentration of the dis-

* From the Research Laboratories of Merck and Co., Inc., Rahway, N. J. Presented before the Division of Medicinal Chemistry of the American Chemical Society at Chapel Hill, North Carolina, April 1937.

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‡ In this paper the unqualified use of the term "distribution ratio" or "partition coefficient" refers to the conventional ratio of concentrations in terms of weight of solute per unit volume of solvent. The experimental ratios obtained in this paper were based on concentrations in terms of weight of solute per weight of solvent and are distinguished as "distribution ratios by weight."

TABLE 1

THE DISTRIBUTION RATIO BY WEIGHT OF DIVINYL ETHER BETWEEN OLIVE OIL AND WATER AT 37°

A Olive oil grams	*B* Divinyl Ether grams	*C* Conc. D.V.E. in water mg./gram	*D* Conc. D.V.E. in oil phase mg./gram	*E* Distribution ratio by weight
27.2	.745	.551	25.5	46.4
27.2	.895	.642	30.5	47.5
9.23	15.67	4.73	624.0	131.9
31.8	6.10	2.55	158.1	62.1
36.4	0.613	0.356	16.1	45.3
36.4	3.87	1.82	94.1	51.7
36.4	1.54	0.830	39.6	47.7
36.4	14.65	3.70	284.7	76.9

The distribution ratios by weight (column *E*) were obtained by dividing the concentration of divinyl ether (D.V.E.) in the oil phase (column *D*) by the analytically determined concentrations in the aqueous phase (column *C*). The concentration of divinyl ether in the oil phase was equal to the weight of divinyl ether present divided by the total weight of the oil phase. The former equalled the total weight of divinyl ether (column *B*) added minus the divinyl ether present in the aqueous phase and that in the air space. The amount of divinyl ether in the aqueous phase was equal to the concentration multiplied by the total weight of water which was 40 Gm. in all experiments except the fourth where it was 35 Gm. The amount of divinyl ether in the air space (which enters into the calculation as a minor correction not exceeding 2 per cent) was equal to the concentration of divinyl ether in the aqueous phase times 1.40,* multiplied by the air space which is the volume of the vessel, 95 cc., minus the total volume of oil, water and divinyl ether (density of olive oil 0.911; of divinyl ether 0.733).†

solved substance it is necessary to consider the conditions under which the ratios have been determined before using them in any quantitative discussion of the lipoid theory of narcosis.

It is our object to show quantitatively the variation with concentration of the distribution ratio of divinyl ether between olive oil and water. It will be shown that, for divinyl ether, the ratio obtained at concentrations corresponding to those found in the blood of anesthetized animals does not differ significantly from the figure obtained by the extrapolation of the ratio to infinite dilution.

Although there are several indirect methods for determining partition coefficients, we decided to equilibrate divinyl ether with olive oil and water and determine the actual ratio by a direct analysis of the aqueous phase. Since it was necessary to determine the coefficient at 37°, and divinyl ether boils at 28.3°, certain practical difficulties arose

* The distribution ratio water-air may be calculated without serious error by assuming that divinyl ether behaves as a perfect gas and that the partial pressure of divinyl ether above a saturated solution is equal to the vapor pressure of pure divinyl ether [1034 mm. at 37°, Miles and Menzies (17)]. This is permissible because the solubility of water in divinyl ether is only 0.1 per cent (as determined by Weaver's method to be published elsewhere) involving a vapor pressure correction of only 2 to 4 millimeters. The gram molecular volume at 1034 mm. and 37° is 18.73 liters, the molecular weight is 70.05, hence 1 liter of gaseous divinyl ether contains 3.74 grams. Since 1 liter of water saturated with divinyl ether at 37° contains 5.25 grams the distribution ratio water-air is 1.40.

† In the eighth experiment this correction was not applied due to breakage of the duplicate vessel before its volume was ascertained.

which were solved by the following technic. A cucumber-shaped vessel of about 95 cc. capacity was used which had, near one end, a narrow outlet through which were introduced appropriate amounts of purified olive oil, water and divinyl ether. The divinyl ether was contained in an ampule when small amounts were being used. The vessel was then stoppered with a selected soft cork. After breaking the ampule the vessel was cradled in a thermostat and slowly rocked until equilibrium was attained. No trouble was experienced with leaks which could have readily been detected by bubbles forming at the cork. After tipping the

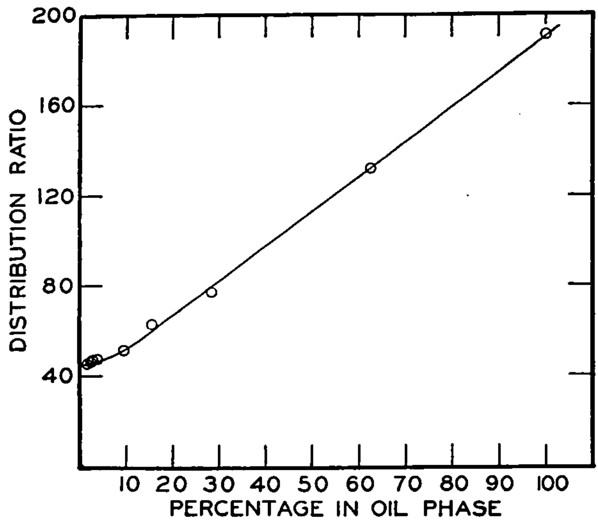

FIG. 1. Distribution ratio by weight of divinyl ether between olive oil and water plotted as a function of the concentration of divinyl ether in per cent in the oil phase.

vessel on end, a sample of the aqueous layer could be withdrawn through the cork with a fine needle attached to a calibrated hypodermic syringe. The syringe was cooled with ice water before withdrawing the needle and the sample immediately transferred to the aerator of the iodine pentoxide train for analysis (14). In this way several check samples could be taken for each run.

Table 1 gives the results obtained. Figure 1 shows the distribution ratios by weight of divinyl ether between oil and water plotted against the percentage concentrations of divinyl ether in the oil phase. Above a concentration of 10 per cent divinyl ether the ratio is a linear function of the concentration, and below this concentration the ratio approaches the value 45.3.

In Figure 1, the last point on the curve is this ratio at a concentration of 100 per cent divinyl ether in the "oil phase." The solubility of divinyl ether was determined in the same manner as the distribution ratios and found to be 5.25 mg. per cubic centimeter. The "concentration" of divinyl ether in the "oil phase," here pure divinyl ether, was obviously, 1000 mg. per gram. The limiting value of the distribution ratio by weight is hence 190.5. Had the densities of the oil phase been known, a similar curve could have been obtained for the more usual partition coefficient or distribution ratio by volume. This curve would have been somewhat flatter since the density factor would lower the ratio by

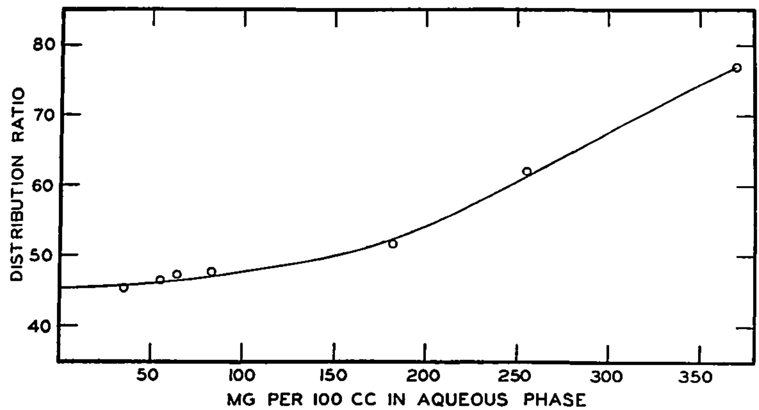

FIG. 2. Distribution ratio by weight of divinyl ether between olive oil and water plotted as a function of the concentration of divinyl ether in the aqueous phase.

about 10 per cent at 0 concentration and by about 20 per cent at the high end of the scale, the density of olive oil being 0.911 and that of pure divinyl ether 0.773.

In Figure 2 the distribution ratio by weight is plotted against the concentration of divinyl ether in the aqueous phase. The average concentration of divinyl ether in the blood at the time of abolition of the corneal reflex in dogs has previously been found to be 28 mg. per 100 cc. (18). The distribution ratio by weight in this range, as can be seen in Figure 2, is about 45.5 and at 0 concentration is about 45.3. These distribution ratios by weight may be converted to the conventional distribution ratios by volume by multiplying 0.911, since at these concentrations the density of the oil phase can be taken the same as that of the olive oil and the aqueous phase as unity. Thus the distribution ratio by volume or partition coefficient at anesthetic concentrations is 41.6, while the value obtained by extrapolation at 0 concentration is 41.3. Since the analytical errors involved in the determination are of the order of 3 per cent, this variation is of no significance.

Leake and Chen (15), recognizing the fundamental importance of the partition coefficient, in their original communication on unsaturated ethers reported a value of 2.5 ± 0.2 for the oil-water partition coefficient of divinyl ether determined gravimetrically at 20°. Apart from the temperature difference in the determination, this low value may be accounted for by assuming the presence of considerable amounts of water soluble impurities in the original few cubic centimeters of material supplied to them, the reported boiling point of which was 36–39°. Pure divinyl ether as prepared by Ruigh and Major (16) boiled at 28.3° ± 0.2°, a value confirmed by Miles and Menzies (17) (28.35° ± 0.04°).

Calculation of the theoretical concentration of an anesthetic agent in the lipoids of the brain [Kurt Meyer's lipoid constant, C_{lip}, (3)] may be made from blood concentrations when the oil-blood distribution ratio is known. In the case of divinyl ether, attempts to determine this ratio directly met with failure due to the formation of emulsions. It will probably be necessary to use indirect methods to obtain this ratio.

If, however, we assume that the difference in ratios oil-blood and oil-water is due mainly to the lipoid content of the blood we might make an analogy with cyclopropane. Orcutt and Seevers (19) found with cyclopropane that the oil-water coefficient was 34.3 and the oil-blood coefficient 15.3. If the same relation holds with divinyl ether, the oil-water ratio of which is 41.3, one would expect the oil-blood ratio to be somewhat less than half. Multiplying the assumed ratio, 20, by the anesthetic concentration of 0.28 g. per liter obtained in dogs, we find that the theoretical lipoid concentration to be 5.6 g. per liter or C_{lip} is 0.08 moles per liter. This calculation shows at least that divinyl ether follows the general scheme of Kurt Meyer who found an average anesthetic concentration of 0.06 moles per liter of brain lipoid using mice for his experimental animal.

SUMMARY

A study has been made of the variation with concentration of the distribution ratio by weight of divinyl ether between olive oil and water.

The distribution ratio by volume or partition coefficient was found by extrapolation to be 41.3 at infinite dilution. This did not differ significantly from the value obtained at concentrations corresponding to those found in the blood of anesthetized dogs.

The solubility of divinyl ether in water at 37 C. has been found to be 5.25 Gm. per liter.

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SECTION ON ANESTHESIA OF THE INDIANA MEDICAL ASSOCIATION

CLAYPOOL HOTEL—INDIANAPOLIS—WEDNESDAY, SEPTEMBER 24, 1941

12:30 Luncheon in honor of Paul M. Wood, M.D., New York, N. Y.
2:00 Lillian B. Mueller, M.D., Indianapolis, Ind.
Subject: A Simple Device for Administering Intravenous Barbiturates.
2:10 Paul M. Wood, M.D., New York, N. Y.
Subject: Facts and Fallacies Concerning Modern Anesthesia.
2:30 Discussion by E. P. Buckley, M.D., Jeffersonville, Ind.
2:40 Merrill E. Liston, M.D., South Bend, Ind.
Subject: Preliminary Medication.
3:00 Discussion by F. W. Ratcliff, M.D., Lafayette, Ind.
3:10 J. M. Whitehead, M.D., Indianapolis, Ind.
Subject: Anesthetic Agents and Anesthetic Failures.
3:30 Discussion by Paul M. Wood, M.D., New York, N. Y.
3:40 Round table discussion.
4:00 Election of section officers.