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Solubility of Inhalation Anesthetics in Various Media

A New Correlation

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SUMMARY

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A new correlation for the solubility of inhalation anesthetics and other gases and vapors in lipid phases, polymers, and other media is derived from thermodynamic considerations. The correlation is applicable to solute concentrations in Henry's law limit, such as is the case for clinical concentrations of anesthetics. Ostwald solubility coefficients for a variety of anesthetics and light gases in lipids, rubber, and silicone rubber were correlated over a range of 6 orders of magnitude in solubility values. The proposed correlation should prove useful for estimating solubility coefficients of gases and vapors in a variety of media, as well as the temperature dependence of these coefficients.

INTRODUCTION

A knowledge of the solubility of inhalation anesthetics in various solvent media is of scientific interest and is also necessary for certain biomedical applications. Thus, studies of some proposed mechanisms of general anesthesia require information on the solubility of inhalation anesthetics and of inert gases in lipid phases, which are taken as models of the lipoid region of the neuronal membrane (1, 2). The solubility of anesthetics in blood and various tissues is of clinical importance, and that in silicone rubber has been studied in connection with a method of anesthesia via arteriovenous shunts (3, 4). More recently, the solubility of several inhalation anesthetics in silicone rubber, polyethylene, and polytetrafluoroethylene membranes has been measured in relation to the continuous *in vivo* analysis of anesthetics in blood by mass spectrometry (5).

The object of this communication is to present a simple correlation of solubility coefficients in Henry's law limit for a large number of gases and vapors, including inhalation anesthetics, in some of the above solvents. The correlation is based on thermodynamic considerations and should be applicable to many other solvents. The prediction of the concentration dependence of solubility coefficients is also discussed.

THEORETICAL CONSIDERATIONS

The solution of a gas in a condensed phase can be visualized as a two-step isothermal process (6, 7) comprising: (a) condensation of the gas to a hypothetical pure liquid with a molar volume equal to the partial molar volume the former would have in solution, followed by (b) mixing of the hypothetical liquid with the solvent.

The change in the Gibbs free energy of the solute (designated i) in the first step, $\Delta G_{(1)}$, is (per mole):

$$\Delta G_{i(1)} = RT \ln(f_i^L/f_i^G) \tag{1}$$

where R is the universal gas constant, T is the absolute temperature, f_i^L is the fugacity of the solute in the hypothetical liquid state, and f_i^G is the fugacity of the solute in the gas phase. The fugacities are to be taken at the temperature and pressure of the solution.

If the solute is a small molecule, the change in its Gibbs free energy in the second step can be described by the Flory-Huggins relation (8) in the form:

$$\overline{\Delta G}_{i(2)} = RT\,[\ln \phi_i + (1 - \phi_i) + \chi\,(1 - \phi_i)^2] \tag{2}$$

where ϕ_i is the volume-fraction concentration of a solute i, and χ is the Flory-Huggins interaction parameter. $\Delta G_{i(2)}$ is, more specifically, the difference between the chemical potentials of the solute in solution and in the hypothetical liquid state defined above, i.e., the change in the partial molar Gibbs free energy. Equation 2 is applicable to solvents of long-chain molecules.

The total change in the free energy of the solute, $\Delta_i G$, in the above process is zero, i.e.,

$$\Delta G_i = \Delta G_{i(1)} + \overline{\Delta G}_{i(2)} = 0 \tag{3}$$

because, at the end of the process, the solution is taken to be in thermodynamic equilibrium with the gas phase. Substituting Eqs. 1 and 2 into Eq. 3, one obtains:

$$\ln (f_i^G/f_i^L) = \ln \phi_i + (1 - \phi_i) + \chi\,(1 - \phi_i)^2. \tag{4}$$

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At high dilutions, when the solubility of the gaseous solute is within Henry's law limit ($\phi_i \rightarrow 0$), one has:

$$\lim_{\phi_i \rightarrow 0} \left(\frac{f_i^G}{\phi_i} \right) = H_{i,k}. \tag{5}$$

Equation 5 defines Henry's law constant $H_{i,k}$ for solute i in solvent k. Under these conditions Eq. 4 becomes:

$$\ln (H_{i,k}/f_i^L) = 1 + \chi. \tag{6}$$

One can also describe the solubility in terms of the Ostwald coefficient, S:

$$S = V_i^G/V_k^L \tag{7}$$

where V_i^G is the volume of gaseous solute at system temperature T and partial pressure P_i dissolved in a volume V_k^L of solvent. At sufficiently low pressures it can be assumed that the gaseous solute is an ideal gas, i.e., that

$$S = \frac{n_i RT}{P_i V_k^L} \tag{8}$$

where n_i is the number of moles of solute dissolved at temperature T and partial pressure P_i, and R is the universal gas constant. At high dilutions, in Henry's law limit, Eq. 8 becomes:

$$S_0 = \lim_{n_i \rightarrow 0} S = \lim_{V_i^L \rightarrow 0} \left(\frac{V_i^L RT}{v_i^L P_i V_k^L} \right) \tag{9}$$

where V_i^L ($\cong n_i v_i^L$) is the total volume of solute i in the solution, assuming that the excess volume of mixing is negligible, and v_i^L is molar volume of the pure liquid solute. If T is higher than $T_{i,C}$, the critical temperature of the solute, then v_i^L is a hypothetical quantity. Furthermore:

$$\phi_i = V_i^L/V \cong V_i^L/V_k^L \tag{10}$$

where ϕ_i is the volume fraction of the solute, and V is the volume of the solution. Equations 5, 9, and 10 yield:

$$S_0 = \lim_{\phi_i \rightarrow 0} \left(\frac{RT}{v_i^L} \right) \left(\frac{\phi_i}{P_i} \right) = \frac{\alpha}{H_{i,k}} \tag{11}$$

where $\alpha = RT/v_i^L$. At low pressures Eq. 5 becomes

$$\lim_{\phi_i \rightarrow 0} (P_i/\phi_i) = H_{i,k}$$

since $f_i^G \rightarrow P_i$. Substituting Eq. 11 into Eq. 6 yields:

$$\ln (S_0 f_i^L) = \ln \alpha - (1 + \chi). \tag{12}$$

Prausnitz and Shair (7) and also Yen and McKetta (9) have shown that f_i^L can be correlated by means of the principle of corresponding states:

$$f_i^L = P_{i,C} F(T/T_{i,C}) \tag{13}$$

where $P_{i,C}$ is the critical pressure of the solute, $T/T_{i,C}$ is the reduced temperature of the solute, and F is an undefined function. As a first approximation, the Flory-Huggins parameter χ can be assumed to be proportional to the reciprocal of the reduced solute temperature, $T_{i,C}/T$ (10). The term $\ln \alpha$ in Eq. 12 is a relatively weak function of temperature. Equations 12 and 13 then yield:

$$\ln (S_0 P_{i,C}) = F'(T_{i,C}/T) \tag{14}$$

which is the desired correlation. Hence, a plot of $\ln (S_0 \cdot P_{i,C})$ versus $T_{i,C}/T$ should be a unique curve for various solutes and a given solvent. Values of $\ln (S_0 P_{i,C})$ for various pressures and temperatures should fall on this curve if the assumptions used to derive Eq. 14 are fulfilled. The subscript i is deleted in the following section.

RESULTS AND DISCUSSION

Allott *et al.* (11) have reviewed and analyzed the literature on the solubility of inhalation anesthetics in lipids (oil) at 37°, and their results are summarized in Table 1. The critical temperature and pressure of the anesthetics and of other gases are given in Table 2; these data were obtained from the compilation of Perry and Chilton (12). Some anesthetics are thermally unstable at higher temperatures, and consequently their critical temperature and pressure cannot be measured. In such cases, the desired critical properties were estimated by the method of Lydersen (13, 14). The data of Table 1 were employed to test the validity of Eq. 14, and the results are shown graphically in Fig. 1. A few light gases have been included in the correlation for comparison. It is seen that, when oil is used as a solvent, a satisfactory linear correlation is obtained between $S_0 P_c$ and T_c/T on semilog graph paper. This correlation extends over a range of $S_0 P_c$ values of almost five orders of magnitude and can be represented by the least-squares equation:

$$\log (S_0 P_c) = 2.8754\ (T_c/T) - 0.79048\ (0.02500\ \text{SD}) \tag{15}$$

where S_0 is dimensionless (see Eq. 7), T_c and T are in ° K, and P_c is in atmospheres. Although the Ostwald coefficients used here were obtained at 37°, Fig. 1 and Eq. 15 are valid, in principle, at any other temperature and can be employed for predictive purposes.

Allott *et al.* (11) did not indicate the nature of the oil (or oils) used to obtain the solubility data of Table 1. More recently, the solubility of a number of inhalation anesthetics in olive oil was determined in this laboratory at 37° by means of a Cahn microbalance.[1] These data, together with the solubilities of several light gases in olive oil (15, 16) are reported in Table 1 and have been used to test Eq. 14. The results of this test are shown in Fig. 2. As can be seen, the correlation appears to be satisfactory over a range of $S_0 P_c$ values of 6 orders of magnitude and can be represented, for olive oil, by the least-squares relation:

$$\log (S_0 P_c) = 2.8799\ (T_c/T) - 0.74763\ (0.01562\ \text{SD}) \tag{16}$$

Another test of Eq. 14 was made with the data of Lowe and Hagler (17) for the solubility of inhalation anesthetics in extracted fat of human origin at 37° (see Table 1 and Fig. 3). The proposed correlation is again satisfactory and can be represented by the least-squares relation:

$$\log (S_0 P_c) = 3.2629\ (T_c/T) - 1.42285\ (0.01596\ \text{SD}) \tag{17}$$

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[1] S. A. Stern, S.-P. Shiah, and R. M. Jobbins, unpublished data.

TABLE 1

Ostwald solubility coefficients for inhalation anesthetics and light gases in lipid phases and rubbers

No.	Solute	Temperature	Ostwald solubility coefficient in				
			Oil[a]	Olive oil[b]	Human fat[c]	Silicone rubber[d]	Rubber[e]
1	Argon	24.8°	-	0.148	-	-	-
2	Carbon monoxide	24.5	-	0.091	-	-	-
3	Carbon dioxide	24.9	-	1.412	-	-	-
4	Chloroform	37.0	400	385.3	394.0	175	-
	Chloroform	23.0	-	-	-	-	300.0
5	Cyclopropane	37.0	11.5	-	13.0	1.29	-
	Cyclopropane	23.0	-	-	-	-	6.6
6	Diethyl ether	37.0	65	69.3	73.5	72.6	-
	Diethyl ether	23.0	-	-	-	-	58.0
7	Divinyl ether	37.0	60	-	59.3	-	-
	Divinyl ether	23.0	-	-	-	-	45.0
8	Ethrane (Enflurane)	37.0	98	87.8	-	57.6	-
9	Ethylene	37.0	1.27	-	-	-	-
10	Fluroxene	37.0	48	-	53.8	-	-
	Fluroxene	23.0	-	-	-	-	20.0
11	Halopropane	37.0	320	-	-	-	-
	Halopropane	23.0	-	-	-	-	136.0
12	Halothane	37.0	220	196.3	182.0	97.6	-
	Halothane	23.0	-	-	-	-	120.0
13	Krypton	37.0	0.45	-	-	-	-
14	Methoxyflurane	37.0	950	930.8	820.9	530	-
	Methoxyflurane	23.0	-	-	-	-	630.0
15	Neon	24.5	-	0.0214	-	-	-
16	Nitrogen	37.0	0.07	-	-	-	-
	Nitrogen	24.5	-	0.073	-	-	-
17	Nitrous oxide	37.0	1.4	-	-	(3.3)	-
	Nitrous oxide	23.0	-	-	-	-	1.2
18	Oxygen	25.1	-	0.127	-	-	-
19	Teflurane	37.0	29	-	-	-	-
	Teflurane	23.0	-	-	-	-	8.0
20	Trichloroethylene	37.0	900	-	634.0	393	-
	Trichloroethylene	23.0	-	-	-	-	830.0
21	Xenon	37.0	1.8	-	-	-	-

[a] Ref. 11.

[b] Data for Ar, CO, CO_2, Ne, N_2, and O_2 are from ref. 16. Data for anesthetics were obtained in this laboratory.

[c] Ref. 17.

[d] Ref. 5. Value for N_2O is stated to be uncertain.

[e] Ref. 18.

Equation 14 is found to provide a satisfactory correlation of solubility coefficients in Henry's law limit also when the solvent is a polymeric substance. For example, Fielding and Salamonsen (5) have determined the Ostwald solubility coefficient, S_0, for several anesthetics in medical-grade silicone rubber, at clinical concentrations of the anesthetics. Their data at 37° are summarized in Table 1. These data are satisfactorily correlated by Eq. 14, as is shown in Fig. 4. The straight line in this figure can be represented by the least-squares relation:

$$\log (S_0 P_c) = 2.8975 \, (T_c/T) - 0.99311 \, (0.00522 \text{ SD}) \qquad (18)$$

The Ostwald solubility coefficient for nitrous oxide is stated by Fielding and Salamonsen to be essentially an estimate, because the solubility of this gas in silicone rubber at 37° was near the sensitivity limit of their measurements. Figure 4 suggests that the reported Ostwald coefficient for nitrous oxide is too high. Therefore, this value was not used in the above least-squares relation.

Equation 14 should also correlate the solubility of inhalation anesthetics and of various gases and vapors in many other types of polymers, such as other synthetic rubbers, natural rubber, Teflon, polyethylene, and polypropylene. For example, Titel and Lowe (18) have determined Ostwald coefficients for a number of inhalation anesthetics in rubber from chromatographic retention times. The measurements were made at 23° with a rubber of unspecified origin. The data of Titel and Lowe are summarized in Table 1. A test of Eq. 14 using these data is presented in Fig. 5; a straight line is obtained, which can be represented by the least-squares relation:

$$\log (S_0 P_c) = 3.1824 \, (T_c/T) - 1.73119 \, (0.0584 \text{ SD}) \qquad (19)$$

The scatter of the data in Fig. 5 suggests that the experimental error in these measurements was somewhat larger than in the other data of Table 1. In the case of semicrystalline polymers, the correlation refers to the amorphous region only. In general, Eq. 14 should be applicable to gas-solvent systems that are nonpolar or weakly polar. Hence, Eq. 14 may not provide a satisfac-

TABLE 2

Critical properties of inhalation anesthetics and other gases

No.	Solute	Formula	Boiling point	Critical properties	
				Temperature	Pressure
					atm
1	Argon	Ar	87.4° K	151.1° K[a]	48[a]
2	Carbon monoxide	CO	66	134[a]	35[a]
3	Carbon dioxide	CO_2	194.6	304[a]	73[a]
4	Chloroform	$CHCl_3$	334.4	534.1[a]	52.4[a]
5	Cyclopropane	C_3H_6	239.2	394.9[b]	52.9[b]
6	Diethyl ether	$(C_2H_5)_2O$	307.8	466.8[a]	36.0[a]
7	Divinyl ether	$(CH_2CH)_2O$	301.4	463.1[b]	41.9[b]
8	Ethrane (Enflurane)	$CHClFCF_2OCHF_2$	329.7	470[b]	33.1[b]
9	Ethylene	C_2H_4	169.3	282.8[a]	50.5[a]
10	Fluroxene	$CF_3CH_2OCHCH_2$	315.8	463.8[b]	31.4[b]
11	Halopropane	$CHF_2CF_2CH_2Br$	347.1	519.7[b]	34.3[b]
12	Halothane	$CH_3CHClBr$	323.3	496.4[b]	52.1[b]
13	Krypton	Kr	121.35	209.3[a]	54.3[a]
14	Methoxyflurane	$CHCl_2CF_2OCH_3$	377.9	559.8[b]	40.2[b]
15	Neon	Ne	27.9	44.3[a]	25.9[a]
16	Nitrogen	N_2	77.4	126.0[a]	33.5[a]
17	Nitrous oxide	N_2O	182.5	309.6[a]	71.7[a]
18	Oxygen	O_2	90.1	154.3[a]	49.7[a]
19	Teflurane	CF_3CHFBr	281.1	431.1[b]	38.9[b]
20	Trichloroethylene	CCl_2CHCl	360.4	570.9[b]	45.7[b]
21	Xenon	Xe	164.0	289.7[a]	58.2[a]

[a] Ref. 12.

[b] Predicted values (13, 14).

tory correlation for systems containing strongly polar and/or hydrogen-bonded molecules, such as water. Interestingly, good linear plots of log (S_0P_c) versus T_c/T are obtained for anesthetics in blood and in a number of water-containing tissues, e.g., from brain (white), pancreas, and adrenal glands (18); it is possible that agreement with Eq. 14 is fortuitous in these cases.

It should be noted that, although all plots of Eq. 14 examined above are linear, the equation does not predict the form of the dependence of log (S_0P_c) on T_c/T. This dependence can be determined from a more detailed thermodynamic analysis (19). However, the correlation represented by Eq. 14 has the merit of great simplicity, particularly in the cases where it is linear. This correla-

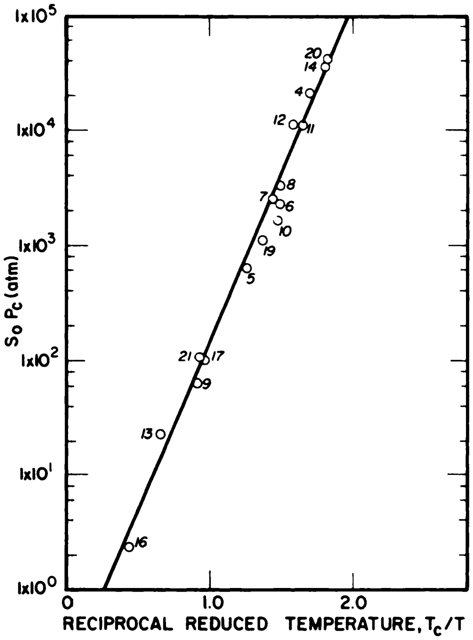

FIG. 1. *Correlation of Ostwald solubility coefficients of inhalation anesthetics and other gases in oil*

4, Chloroform; 5, cyclopropane; 6, diethyl ether; 7, divinyl ether; 8, Ethrane; 9, ethylene; 10, Fluroxene; 11, halopropane; 12, halothane; 13, krypton; 14, methoxyflurane; 16, nitrogen; 17, nitrous oxide; 19, Teflurane; 20, trichloroethylene; 21, xenon.

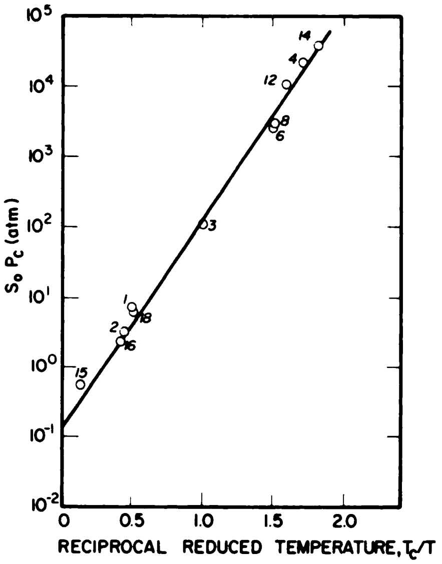

FIG. 2. *Correlation of Ostwald solubility coefficients of inhalation anesthetics and other gases in olive oil*

1, Argon; 2, carbon monoxide; 3, carbon dioxide; 4, chloroform; 6, diethyl ether; 8, Ethrane; 12, halothane; 14, methoxyflurane; 15, neon; 16, nitrogen; 18, oxygen.

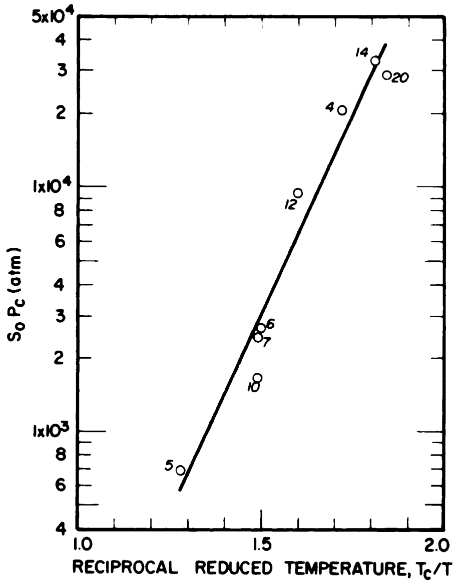

Fig. 3. *Correlation of Ostwald solubility coefficients of inhalation anesthetics in human fat*

4, Chloroform; 5, cyclopropane; 6, diethyl ether; 7, divinyl ether; 10, Fluroxene; 12, halothane; 14, methoxyflurane; 16, trichloroethylene.

tion should therefore prove useful for estimating solubility coefficients of gases and vapors in a variety of media, when a few experimental data for other solutes in these media are available. Moreover, by using the correlation in conjunction with a method described earlier by Suwandi and Stern (20), it is possible to estimate also the concentration dependence of gas solubility coefficients outside Henry's law limit.

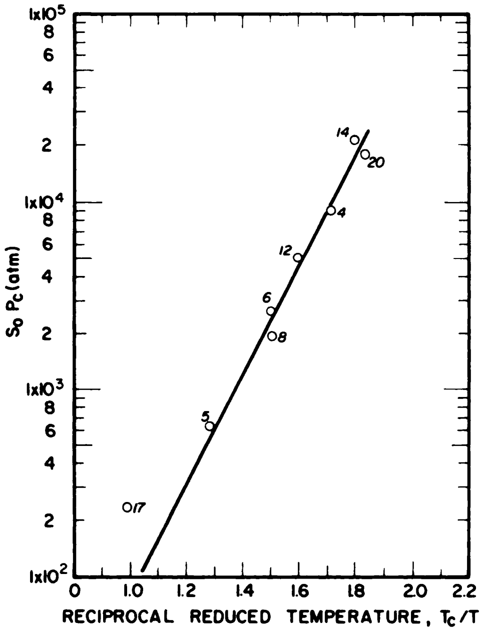

Fig. 4. *Correlation of Ostwald solubility coefficients of anesthetics in silicone rubber*

4, Chloroform; 5, cyclopropane; 6, diethyl ether; 8, Ethrane; 12, halothane; 14, methoxyflurane; 17, nitrous oxide; 20, trichloroethylene.

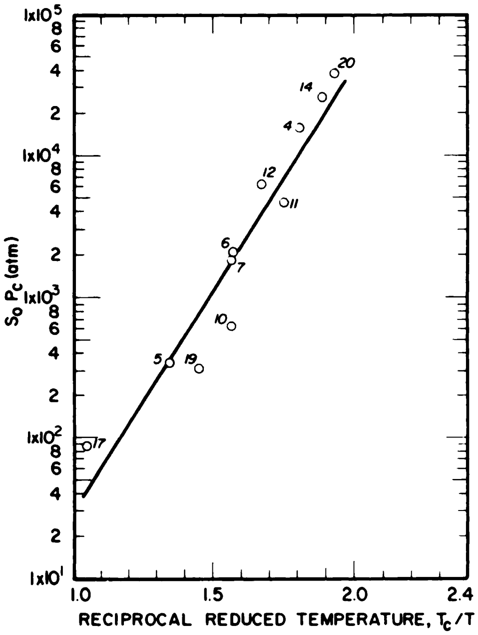

Fig. 5. *Correlation of Ostwald solubility coefficients of inhalation anesthetics in rubber*

4, Chloroform; 5, cyclopropane; 6, diethyl ether; 7, divinyl ether; 10, Fluroxene; 11, halopropane; 12, halothane; 14, methoxyflurane; 17, nitrous oxide; 19, Teflurane; 20, trichloroethylene.

Finally, the proposed correlation also permits the prediction of the temperature dependence of solubility coefficients. For example, by differentiating Eq. 15 for the solubility of various gases in oil, one obtains:

$$\frac{d\log S_0}{dT} = -2.8754 \left(\frac{T_c}{T^2}\right) \tag{20}$$

The temperature dependence of the Ostwald coefficient can be expressed by the van't Hoff equation (11):

$$S_0 = S'_0 \exp(-\Delta H/RT) \tag{21}$$

Table 3

Comparison of calculated and experimental enthalpies of solution of inhalation anesthetics and light gases in oil

Solute	Enthalpy of solution, ΔH (kjoules·gmole^{-1})		% Difference[b]
	Calculated from Eq. 22	Experimental[a]	
Chloroform	−29.4	−38.9	24.4
Cyclopropane	−21.7	−20.0	−8.5
Diethyl ether	−25.7	−29.7	13.5
Divinyl ether	−25.5	−31.0	17.7
Ethrane (Enflurane)	−25.9	(−30.6)	18.1
Ethylene	−15.6	(−11.1)	−40.5
Fluroxene	−25.5	−31.4	18.8
Halopropane	−28.6	−33.0	15.4
Halothane	−27.3	−37.4	27.0
Krypton	−11.5	−5.8	98.3
Methoxyflurane	−30.0	−39.2	21.4
Nitrogen	−6.9	−0.3	−2200
Nitrous oxide	−17.0	(−11.6)	−46.6
Teflurane	−23.7	−19.0	−24.7
Trichloroethylene	−31.4	−38.8	19.1
Xenon	−15.9	−10.3	−54.4
Mean (without N_2)			6.44

[a] Ref. 11. Values are for 37°. Parentheses indicate estimated values.

[b] 100 (Expt-Calc.)/Expt.

TABLE 4

Comparison of calculated and experimental enthalpies of solution of inhalation anesthetics in silicone rubber

Solute	Enthalpy of Solution, ΔH (kjoules·gmole^{-1})		% Difference[b]
	Calculated from Eq. 23	Experimental[a]	
Cyclopropane	−21.9	−11.9	−84.0
Ethrane	−26.1	−31.7	17.7
Diethyl ether	−25.9	−27.2	4.78
Halothane	−27.5	−29.3	6.14
Chloroform	−29.6	−34.1	13.2
Methoxyflurane	−31.1	−40.3	22.8

Mean: −3.23%

[a] Ref. 5.

[b] 100 (Expt.-Calc.)/Expt.

where S'_0 is a constant and ΔH is the apparent enthalpy of solution at constant pressure. Substituting Eq. 21 into Eq. 20, one further obtains:

$$\Delta H = -6.622\ RT_c. \tag{22}$$

Enthalpies of solution calculated from Eq. 22 are compared with experimental values (11) in Table 3. Except for simple solutes with low critical temperatures (compared to the ambient temperature), such as nitrogen, the over-all agreement probably is as good as can be expected considering the limitations of Eq. 14 and the magnitude of the experimental error. The "experimental" values for ethrane (Enflurane), ethylene, and nitrous oxide have been estimated by Allott *et al.* (11) from an empirical correlation and are therefore of unknown accuracy. In the case of solutes with low critical temperatures, the discrepancy between the predicted and observed enthalpies of solution may be due to the fact that the solubility of these substances *increases* as the temperature is raised (near ambient temperature) or is a very weak function of temperature. By contrast, relation 14 applies to substances whose solubility decreases with increasing temperature. Thus, in hydrocarbon solvents at room temperature, the solubility of the quantum gases (H_2, He, Ne) increases with temperature, and the solubility of oxygen, nitrogen, and argon is nearly independent of temperature (16, 21). Similarly, the solubility of the quantum gases in silicone rubber below 0° increases with temperature, and that of oxygen and nitrogen is for all practical purposes independent of temperature (21). It has also been reported that the solubility of helium, oxygen, nitrogen, argon, carbon monoxide, and methane in polyethylene and Hydropol at 25° either increases with temperature or exhibits a low temperature dependence (10).

The apparent enthalpy of solution for inhalation anesthetics in silicone rubber has been determined in the same manner from Eqs. 18 and 21, which yield:

$$\Delta H = -6.673\ RT_c \tag{23}$$

The predicted and experimental enthalpies are compared in Table 4. The agreement between these two sets of data is satisfactory, except for cyclopropane. It should be noted that all values of T_c used here were estimated (13).

The above considerations indicate that the proposed correlation, Eq. 14, is not applicable to the quantum gases (H_2, He, and Ne), that it is valid for nonpolar or weakly polar systems, and that it will be more reliable for solutes with critical temperatures near or above the ambient temperature. It would be interesting to test the validity of Eq. 14 with systems other than those examined in the present study.

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