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METHODS FOR THE ESTIMATION OF VAPOR PRESSURES AND OXYGEN SOLUBILITIES OF FLUOROCHEMICALS FOR POSSIBLE APPLICATION IN ARTIFICIAL BLOOD FORMULATIONS.

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SUMMARY

A group additivity system has been generated which makes it possible to estimate, from the structural formulas alone, the energy of vaporization and the molar volume at 25°C of many fluorocarbons and their derivatives. From these two parameters and appropriate thermodynamic relations it is then possible to predict the vapor pressure and the solubility of oxygen in a fluorochemical liquid with sufficient accuracy to estimate its potential for application in fluorochemical emulsion artificial blood.

INTRODUCTION

Fluorochemical emulsion artificial blood has received much research attention in recent years, owing to its perceived potential use in human therapy, where it might help alleviate the shortage of safe donar blood[1]. The fluorochemical phase in these emulsions transports oxygen and carbon dioxide, and must also have a vapor pressure within certain limits. If the vapor pressure is too high at 37°C, gas emboli can form in the circulatory system; whereas too low a vapor pressure contributes to prolonged retention of the fluorochemical in the body[2]. Oxygen solubility is a point of special concern: although fluorochemicals dissolve much more oxygen than ordinary liquids, the oxygen capacity of all emulsions so far prepared is well below that of normal mammalian bloods at the oxygen tension of ambient air, and improved oxygen solubility is a goal of current research.

As one part of a program principally concerned with the synthesis and testing of new fluorochemicals, we have sought to estimate from chemical structure alone, gas solubilities and vapor pressures of fluorochemicals as an aid to optimize selection of compounds for synthesis.

EXPERIMENTAL

Details of the synthesis of the new fluorocarbon-hydrocarbon hybrid compounds described later in this paper will be reported in subsequent publications. All of the new compounds had elemental analyses and mass, ir and nmr (^{19}F and ^{1}H) spectra consistant with the assigned structures. Oxygen solubilities were measured by gas-solid chromatography using the method described by the 3M group[3]. The bulk of the computations were done on a Hewlett-Packard HP 67 programmable calculator and the programs for calculating vapor pressure and oxygen solubility are on file in the Hewlett-Packard Users' Program Library[4].

DISCUSSION AND RESULTS

For more than 50 years, Hildebrand and co-workers have studied the nature of the solubility of gases in liquids and the process of vaporization[5,6]. In the following sections it will be shown how the thermodynamic relations governing these phenomena in conjunction with a group additivity system make it possible to estimate the vapor pressure and oxygen solubility of liquid fluorochemicals from their chemical structure. Therefore it is possible to ascertain before synthesis whether or not a compound will have physical properties appropriate for an artificial blood constituent.

A. Estimation of the Energy of Vaporization and Molar Volume by the Group Additivity Method

A number of group additivity methods already exist in the literature which assume that molecular properties can be partitioned among the individual functional groups and structural components of a molecule. Thus,

simply by summing the group parameters, it is possible to estimate molecular properties from chemical structure alone. An extensive group additivity system for estimating both the energy of vaporization (ΔE_v^{298}) and molar volume (V) of organic liquids has been developed by Fedors[7]. Based upon examination of a large amount of data on simple liquids, he assumed that:

$$\Delta E_v = \sum_i \Delta e_i \tag{1}$$

$$V = \sum_i \Delta v_i \tag{2}$$

where the Δe_i and the Δv_i are the atomic or group contributions to the energy of vaporization and molar volume at 25°C. The deviations between the experimentally measured values and those estimated by this method for a number of liquids were found to be less than 10 percent. The group contributions given by Fedors, although extensive, include only the parameters CF_3- and -CF_2- for fluorochemicals.

Our search of the literature uncovered adequate ΔH_v^{298} or vapor pressure/temperature data for only 19 perfluorochemicals, but extensive boiling point and density data was found. However, the following empirical relationship proposed by Hildebrand and Scott[8] relates the heat of vaporization of nonassociated liquids at 25°C to the boiling point (T_b^0K) at one atmosphere:

$$\Delta H_v^{298} = 0.020 T_b^2 + 23.7\ T_b - 2950 \tag{3}$$

When equation 3 was tested on the 19 perfluorochemicals for which ΔH_v^{298} was known, the calculated and experimental values were often in disagreement by several hundred calories. Subsequently, it was brought to our attention[9] that no fluorochemical data were included in calculating the constants in equation 3. Using the data collected by us, the following relation for perfluorochemicals ensues:

$$\Delta H_v^{298} = 0.0724\ T_b^2 - 17.17\ T_b + 5309 \tag{4}$$

or in terms of the boiling point:

$$T_b^\circ K = \frac{17.17 + [294.9-0.2896 \ (5309-\Delta H_v^{298})]^{1/2}}{0.1448} \tag{5}$$

Equation 4 is based on least-squares computer curve fit for the 19 liquid perfluorochemicals whose ΔH_v^{298} and boiling point values were found in the literature or calculated by us from vapor pressure/temperature data. The perfluorinated compounds include eleven straight and branched alkanes, one dimethyl cyclobutane ring, one cyclopentane, two cyclohexanes, decalin, a methyl decalin and two tertiary amines. Figure 1 is a plot of equations 3
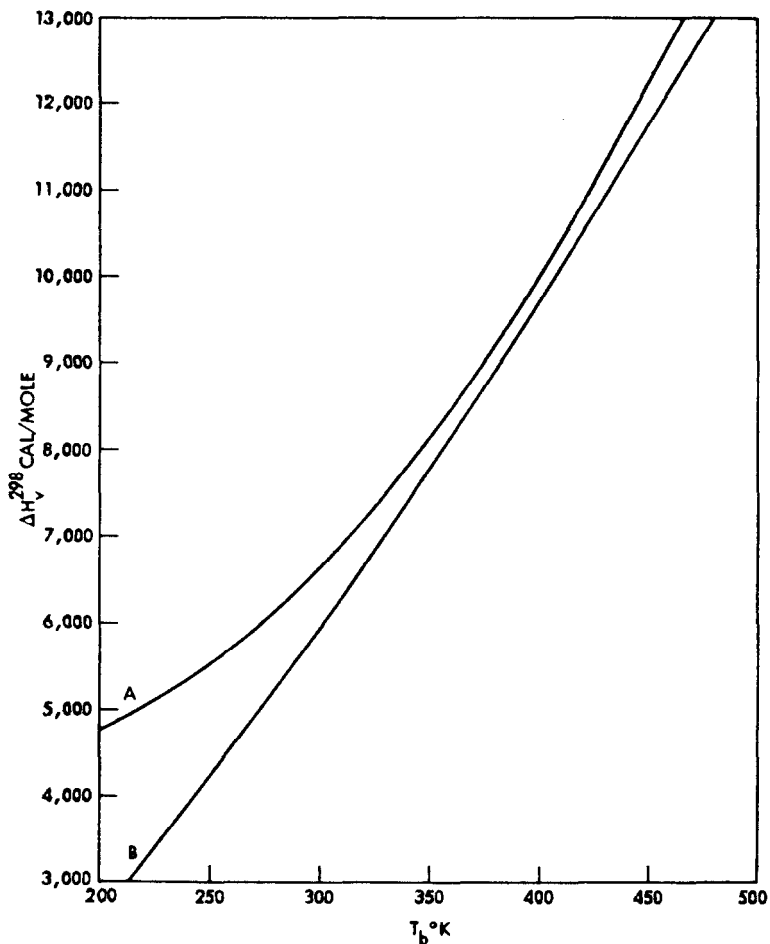

Figure 1. Relationship between ΔH_v^{298} and T_b for: (A) fluorochemicals and (B) nonfluorinated liquids.

and 4. As can be seen, perfluorochemicals have higher heats of vaporization than hydrocarbons of the same boiling point. This is especially true of those with boiling points below 300°K, after which perfluorochemicals parallel non-fluorinated liquids fairly closely.

With the assumption that equation 4 is a good first approximation to estimating ΔH_v^{298} for perfluorochemicals, we calculated ΔH_v^{298} for a large number of such compounds from their literature boiling points. For example, by taking the boiling points for perfluorobutane and perfluoropentane, one can calculate their individual ΔH_v^{298} which can be used to calculate ΔE_v^{298} from:

$$\Delta E_v^{298} = \Delta H_v^{298} - RT \tag{6}$$

The difference between the two ΔE_v^{298} values is an estimate of the group contribution of a $-CF_2-$ to the energy of vaporization. By using the boiling points for straight chain fluorocarbons from C_3-C_{13}, 10 values for Δe_i of a $-CF_2-$ were calculated, which were then averaged. Also, from the density data the molar volumes were calculated from:

$$V = \frac{MW}{D} \qquad MW = \text{molecular weight; } D = \text{density} \tag{7}$$

and the Δv_i for $-CF_2-$ calculated in a similar way. Table I contains a list of fluorochemical group additivity values calculated in this work, as well as some hydrocarbon values published by Fedors[7].

By summing the individual group parameters, obtained by inspection of the structural formula of a compound, the energy of vaporization and molar volume can be estimated before it is synthesized. Also, by calculating ΔH_v^{298} from equation 6 and using this value in equation 5, a reasonable estimate of the boiling point may be made. Similarly, the density of the compound can be estimated from the molar volume by equation 7.

The predicted and reported boiling points for a number of perfluorochemicals are presented in Table II.

TABLE I

Group Contributions to the Energy of Vaporization and Molar
Volume at 25°C

Group	Δe_i^{298} cal/mole	Δv_i cm^3/mole
CF_3-	1933	54.8
$-CF_2-$	783	23.1
$-CFH-$	422	18.6
$-CF-$	-396	-15.0
$-C-$ (Perfluoro)	-1515	-38.3
$-N-$ (Perfluoro 3° Amine)	-914	-16.3
$-O-$ (Perfluoro Ether)	8	19.0
Ring: 5 atoms	2023	37.7
Ring: 6 atoms	2272	39.9
CH_3-	1125	33.5
$-CH_2-$	1180	16.1
$-CH-$	820	-1.0
$-HC=$	1030	13.5
$-C-$	350	-19.2
$-O-$	800	3.8

B. Estimation of Vapor Pressure

Material that have vapor pressures over about 40 torr at 37°C tend to
have adverse physiological effects when used as the gas carrying phase of
artificial blood substitute formulations. Therefore it is desirable to
have some method of predicting the vapor pressure before synthesis is
attempted.

TABLE II

Calculated Boiling Point and Vapor Pressure for Some
Fluorochemicals

Compound	(1) CALCD. ΔH_v^{298}	(2) CALCD. B.P. °C 760 torr	(4) LIT. B.P. °C 760 torr	(3) CALCD. V.P. @25°C	(4) LIT. V.P. @/T°C
$CF_3CF_2CF_2CF_2CF_3$	6807	32	29	519	646/25
$CF_3CF_2CF_2CF_2CF_2CF_3$	7590	59	57	202	220/25
	8316	81	76	92	106/25
	10608	141	142	11.1	6.6/25
	11362	158	160	6.1	2.1/25
$CF_3CHF[OCF_2CF(CF_3)]_2F$	8782	94	104	57	56/37.5
$(CF_3)_2CFO(CF_2)_5CF_3$	9918	124	121	19.9	39/37.5
$[(CF_3)_2CFOCF_2CF_2]_2$	10680	142	135	10.5	13/37.5
$CF_3CHF[OCF_2CF(CF_3)]_3F$	11110	152	152	7.4	10/37.5
$CF_3CHF[OCF_2CF(CF_3)]_4F$	13438	201	194	1.4	1.9/37.5
$[(CF_3)_2CFO(CF_2)_4]_2$	13812	208	199	1.1	3/37.5
$CF_3CHF[OCF_2CF(CF_3)]_5F$	15766	244	224	0.4	0.4/37.5
$(CF_3CF_2CF_2CF_2)_3N$	12524	183	174	2.6	2.5/37.5

1. from the values in Table I.
2. from equation 5.
3. from equation 9 using the α and β values for perfluorochemicals.
4. from Ref. [16].

From Hildebrand's general rule that compounds have equal entropies of vaporization at equal molar volumes of their vapor[10], the entropy of vaporization for non-polar liquids can be predicted from a relation developed by K. Sato[11].

$$\Delta S_v = \frac{\Delta H_v}{T} = \alpha R(\frac{P}{T})^{\beta-1} \tag{8}$$

In terms of the vapor pressure (P in torr), equation 8 becomes:

$$P = T\left(\frac{\Delta H_v}{\alpha RT}\right)^{\frac{1}{\beta-1}} \tag{9}$$

where T is the temperature in ^oK at which the vapor pressure is desired and R is the gas constant in cal mole^{-1} $^oK^{-1}$. Thus, equation 9 provides a useful way of estimating the vapor pressure of a non-polar liquid from its heat of vaporization when the constants α and β are known. Sato originally calculated α and β from vapor pressure/temperature data for 10 non-polar liquids containing hydrogen.

New values of α and β for perfluorochemicals have been calculated by the same procedure in this work. BY plotting dP/dT vs. P/T from vapor pressure/temperature data, a family of overlapping curves was generated. The deviations of the vapor from ideality were corrected for by fitting the data for each substance to an equation of the form:

$$\frac{dP}{dT} = \alpha\left(\frac{P}{T}\right)^{\beta} \tag{10}$$

and then taking the average of the α and β values. Using these new constants, the vapor pressure of perfluorochemicals calculated from equation 9 matches their literature vapor pressure much more closely than when Sato's original α and β values are used. Sato's constants and our values for perfluorochemicals are:

Non-polar liquids: α = 11.8822 β = 0.8810
Perfluorochemicals: α = 12.2497 β = 0.8846

Thus, by estimating ΔE_v^{298} of a perfluorochemical from the group additivity values in Table I, calculating its ΔH_v^{298} with equations 6, and

using equation 9 with the α and β constants for perfluorochemicals the vapor pressure of the compound can be estimated before it is synthesized. Alternatively, if the boiling point of the compound is known, its ΔH_v^{298} can be estimated from equation 4 and its vapor pressure predicted from equation 9. Table II also contains vapor pressures of some perfluorochemicals calculated from equation 9 and corresponding experimentally measured values. It is believed that the accuracy of vapor pressures predicted by this method is sufficiently reliable to make decisions on the utility of new perfluorochemicals as artificial blood constituents before they are synthesized.

C. Estimation of Oxygen Solubility.

In selecting gas-carrying materials for artificial blood formulations it is desirable to have a method of making estimates of oxygen and, to a lesser degree, of carbon dioxide and nitrogen solubility in candidate materials. It is possible, using regular solution theory as developed by Hildebrand and others, to make useful predictions of the solubility of a number of gases in a wide range of solvents.

There are two equations based on regular solution theory that are frequently used to calculate gas solubilities[12]. The first is:

$$-\log x_2 = -\log x_2^i + \frac{0.4343\bar{V}_2(\delta_1-\delta_2)^2}{RT} \tag{11}$$

where the subscript 1 refers to the solvent and 2 refers to the solute. R is the gas constant (cal mole^{-1} $^\circ$K^{-1}), T($^\circ$K) is the temperature at which the gas solubility is to be estimated, $\bar{V}_2$ is the partial molar volume of the gas in the solvent, δ is the solubility parameter defined as:

$$\delta = \left(\frac{H_v-RT}{V}\right)^{1/2} = \left(\frac{E_v}{V}\right)^{1/2} \tag{12}$$

and x_2^i is the "ideal" gas solubility calculated from:

$$\log x_2^i = \frac{\Delta H_v}{4.574}\left(\frac{1}{T} - \frac{1}{T_b}\right) \tag{13}$$

where ΔH_v is the heat of vaporization of the gas at the boiling point, T_b, and T is the temperature at which the gas solubility is to be determined. Equation 11 gives the best results when gas and solvent molecules are similar in size. For solutions where the molecules differ greatly in size a correction of the Flory-Huggins type based upon the ratio of molar volumes is introduced which alters equation 11 to [13]:

$$-\log x_2 = -\log x_2^i + \frac{0.4343 \, \overline{V}_2 \, (\delta_1 - \delta_2)^2}{RT} + \log \left(\frac{\overline{V}_2}{\overline{V}_1} \right)$$
$$+ 0.4343 \left(1 - \frac{\overline{V}_2}{\overline{V}_1} \right) \tag{14}$$

In terms of natural logs, equation 14 is:

$$\ln x_2 = \ln x_2^i = \frac{\overline{V}_2 \, (\delta_1 - \delta_2)^2}{RT} - \left[\ln \left(\frac{\overline{V}_2}{\overline{V}_1} \right) + \left(1 - \frac{\overline{V}_2}{\overline{V}_1} \right) \right] \tag{15}$$

The application of equations 14 and 15 has been described by Gjaldbaek in a number of publications[14]. The pertinent constants for equation 15 when calculating oxygen solubility are:

$$x_2^i = 17.638 \times 10^{-4}; \ \overline{V}_2 = 46 \ \text{ml./mole; and} \ \delta_2 = 5.70 \ (\text{cal./cm}^3)$$

The value of $\overline{V}_2$ = 46 ml/mole for oxygen is the measured value obtained by Horiuti[15] in benzene and is the value normally used. However, Horiuti's measurements of the partial molar volume of oxygen in other solvents have shown that this quantity depends on the solvent and varies from 56 ml/mole in diethyl ether to 31 ml/mole in water, while in pure liquid oxygen at the boiling point it is 28 ml/mole.

When $\overline{V}_2$ was changed so that values of oxygen solubility calculated from equation 15 agree for 24 liquid fluorocarbons reported by Clark[16], it was found that $\overline{V}_2$ varies over the range of 30-50 ml/mole. It can be seen from Figure 2 that a reasonable correlation exists between calculated values of $\overline{V}_2$ for these compounds and logarithms of their entropies of vaporization at 25°C, if the cyclic structures are treated separately.

The equations of the least squares fit for the data and their correlation coefficients are:

Open chain compounds:

$$\overline{V}_2 \;=\; -19.85 + 15.90 \; \ln\Delta S_v^{\,298} \quad,\quad r^2 \;=\; 0.8999 \tag{16}$$

Cyclic Compounds:

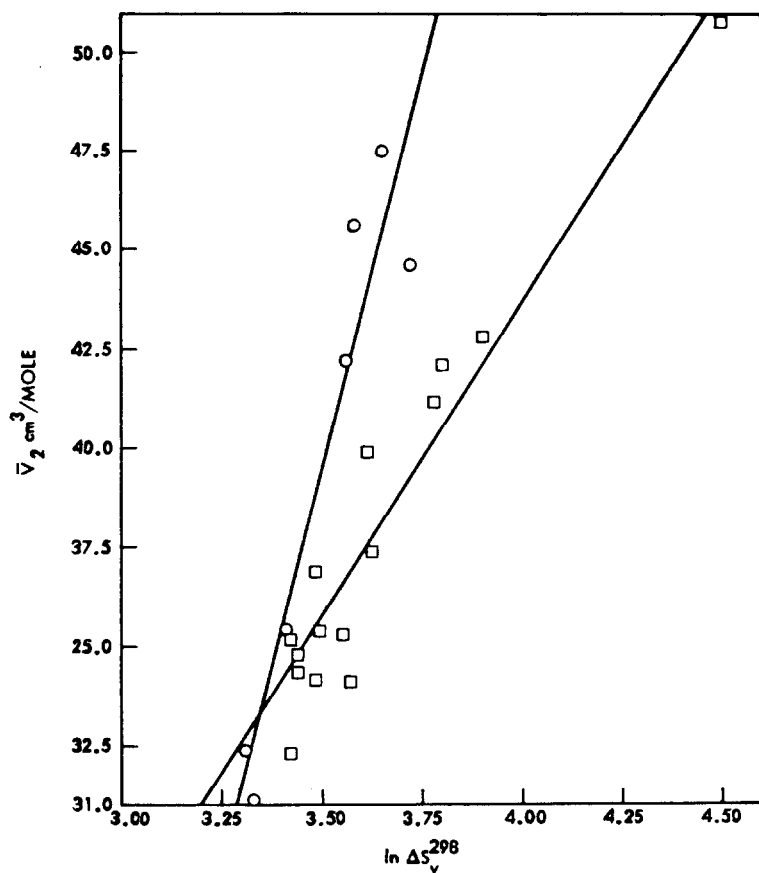$$\overline{V}_2 \;=\; -100.15 + 39.90 \; \ln\Delta S_v^{\,298} \qquad r^2 \;=\; 0.8910 \tag{17}$$


Figure 2. Relationship between $\ln\Delta S_v^{298}$ and $\overline{V}_2$ for Cyclic (O) and Open Chain (□) Fluorochemicals.

By using equation 16 or 17 in conjunction with equation 15, it is possible to predict the oxygen solubility of 22 compounds to ±4 ml. and 14 of these to within ±2 ml. of their experimentally determined values. Since equations 16 and 17 are empirical and we have not measured the partial molar volume of oxygen in these solvents, no physical interpretation of this relationship is attempted. Some compounds with their calculated oxygen solubility and corresponding experimentally measured values are presented in Table III.

TABLE III

Calculated Oxygen Solubility of Fluorochemicals

Compound	[1] b.p. °C	[2] D_4^{25}	[3] ΔH_v^{298}	[4] V	[5] δ	[6] ΔS_v^{298}	[7] $\overline{V}_2$ calc.	[8] O_2 solub. calcd/lit.
⟨F⟩	76.3	1.788	8150	195.7	6.21	27.34	31.85	58.1/57.2
$CF_3CHF[OCF_2CF(CF_3)]_2F$	104.4	1.656	9147	272.9	5.60	30.68	34.59	52.4/55.7
$CF_3(CF_2)_7Br$	140.5	1.890	10,595	264.0	6.16	35.54	36.92	49.1/52.7
$(CF_3)_2CF(CF_2)_4Cl$	108	1.77	9283	228.2	6.17	31.14	35.82	52.7/52.7
$(CF_3)_2CFO(CF_2)_5CF_3$	121	1.721	9789	292.9	5.60	32.83	35.66	50.6/52.5
⟨O⟩∿	102	1.783	9057	233.3	6.02	30.38	36.06	51.3/52.2
$(CF_3)_2CF(CF_2)_4Br$	120	1.977	9749	227.1	6.35	32.70	35.60	51.1/51.4
$CF_3CHF[OCF_2CF(CF_3)]_3F$	152	1.738	11,096	355.6	5.43	37.22	37.66	47.0/47.3
$(CF_3)_2CF(CF_2)_6Cl$	151	1.83	11,051	275.4	6.16	37.07	37.59	48.0/45.6
$[(CF_3)_2CFO(CF_2)_4-]_2$	199	1.820	13,342	423.1	5.49	44.75	40.59	43.2/41.8
⟨F F⟩	160	1.972	11,455	259.6	6.47	38.42	45.43	39.9/38.4
$CF_3CHF[OCF_2CF(CF_3)]_9F$	399	1.848	26,477	873.4	5.44	88.80	51.48	32.9/33.3

1,2:   Literature values from [16].   5:   From ΔH_v^{298} and eq. 12.

3:   From lit. b.p. and eq. 4   6:   From ΔH_v^{298}

4:   From lit D_4^{25} and eq. 7.   7:   From ΔS_v^{298} and eqs. 16 or 17

8:   From eq. 15 and 18.

Therefore, to estimate the solubility of oxygen in a fluorochemical from its structure alone, ΔE_v^{298} and V are estimated from Table I. δ_1 is calculated from equation 12, ΔH_v^{298} is calculated from equation 6, and ΔS_v^{298} (= ΔH_v^{298}/T) then determined. From ΔS_v^{298} and either equation 16 or

17, $\overline{V}_2$ is estimated. Then, using the estimated δ_1, $\overline{V}_2$, V_1 and the constants x_2^i and δ_2 in equation 15, the mole fraction of oxygen, x_2, is obtained. This can be converted to cm^3 of O_2/100 ml. of liquid at 25^{0}C by:

$$\text{cm.}^3\ O_2/100\ \text{ml. of liquid} = \frac{100 \cdot x_2 \cdot 24465}{V_1} \tag{18}$$

TABLE IV

Sample Calculations of Physical Properties from Chemical Structure

	From Table I	ΔE_v^{298} cal/mole	V^{298} cm^3/mole
	7 x CF$_2$ =	5481	161.7
	3 x CF =	-1188	-45.0
	1 x CF$_3$ =	1933	54.8
	2 x 6 atom ring =	4544	79.8
		10,770	251.3

1. ΔE_v^{298} = 10,770 cal/mole

2. V_1^{298} = 253.1 cm^3/mole

3. δ_1 = 6.55 from eq. 12

4. $\Delta H_v^{298} = \Delta E_v^{298}$ + RT = 10,770 + 592 = 11,362 cal/mole

5. T_b^0K = 431 or 158^{0}C from eq. 5

6. D_4^{25} = 2.04 from eq. 7

7. P torr = 6.1 from eq. 9 using perfluorochemical α, β values.

8. $\Delta S_v^{298} = \frac{\Delta H_v^{298}}{298.15}$ = 38.11 cal/mole-^{0}K

9. $\overline{V}_2$ = 45.11 cm^3/mole from eq. 17

10. Mole fraction of dissolved O_2 @ 25^{0}C: X_2 = 4.111 x 10^{-3} from eq. 15.

    cm^{3}O$_2$/100 cm^3 of liquid = 40.0 from eq. 18.

Table IV presents a sample calculation of all the physical properties discussed above for perfluoremethyldecalin. Table V shows the calculated and measured physical properties of some fluorocarbon-hydrocarbon hybrid compounds prepared in our own research efforts. Because these compounds have high hydrogen content, the agreement between calculated and measured physical properties is not quite as good as those for totally fluorinated materials.

TABLE V

Properties of Fluorocarbon-Hydrocarbon Hybrids

	$^1\Delta H_v 298$	^1v	$^2D_4^{25}$ calc/found	$^3T_b \,^oC$ calc/found	$^4cm^3 O_2/100\ cm^3$ calc/found
$CF_3CF_2CF_2(CF_3)_2CCH_2CH_2CH_3$	9927	238.0	1.52/1.52	124/121	46.5/46.7
$CF_3CF_2CF_2(CF_3)_2CCH_2CH_2CH_2CH_3$	11,107	254.1	1.48/1.47	152/138	41.3/46.6
$CF_3CF_2CF_2(CF_3)_2CCH_2CH(CH_3)_2$	10,692	254.4	1.48/1.45	143/132	43.1/43.6
$CF_3CF_2CF_2(CF_3)_2COCH_3$	8367	209.6	1.67/1.62	83/97	56.3/48.1
$CF_3CF_2CF_2(CF_3)_2COCH_2CH_3$	9547	225.7	1.61/1.57	115/109	48.4/49.9
$CF_3CF_2CF_2(CF_3)_2COCH_2CH_2CH_3$	10,727	241.8	1.56/1.51	144/125	42.6/45.8
$(CF_3)_3CCH_2CH_2C(CF_3)_3$	11,520	284.4	1.64/solid	161/solid	40.2/-
$(CF_3)_3CCH_2CH_2CH_2C(CF_3)_3$	12,700	300.5	1.60/solid	186/solid	36.7/35.8
$(CF_3)_3CCH_2CH=CHCH_2C(CF_3)_3$	13,580	311.4	1.58/solid	204/solid	34.3/-
$(CF_3)_3CCH_2CH_2CH_2CH_2CH_2C(CF_3)_3$	15,060	332.7	1.53/solid	231/solid	31.1/-
$CF_3CF_2CF_2(CF_3)_2COH$	8728	182.3	-/1.77	-/93	-/44.3
$CF_3CF_2CF_2(CF_3)_2CN=O$	8040	205.1	-/1.70	-/73	-/decomp.

1: From Table I.
2: From eq. 7.
3: From eq. 5.
4: From eq. 15, 17 and 18 (The hybrids are similar to the cyclic fluorochemicals in their O_2 solubility behavior).

In summary, the design of fluorochemical phases for use in artificial blood should have a vapor pressure of less than 40 mm Hg at 37.5^oC and an oxygen solubility as high as possible. In this paper we report methods for predicting vapor pressure and oxygen solubility for perfluorochemicals based on chemical structure alone; thereby making it possible to guide synthetic strategy in the design of artificial blood substitutes.

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