Fluorocarbons as blood substitutes: critical solution temperatures of some perfluorocarbons and their mixtures

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Abstract

The exhalation of perfluorocarbons (PFCs) from the organism after administration of perfluorocarbon-based blood substitutes is discussed in terms of their lipid solubilities, which may be correlated with their critical solution temperatures (CSTs) with n-hexane, of which a number of measurements are reported here. The critical solution temperatures of some binary mixtures of PFCs with n-hexane are also reported. These are linearly dependent on the compositions of the mixtures of perfluorocarbons. The application of this simple relationship enables the extrapolation of the CST of the pure component (such as perfluoro-n-octyl bromide) for which the CST may not otherwise be easily determined. The observed CSTs of derivatives of PFCs, in which a fluorine atom has been replaced by a more polarizable atom, are strongly dependent upon the respective molar refraction.

Introduction

Among the most important characteristics of PFCs in blood substitute compositions are their so-called lipid solubilities (more correctly, their solubilities in lipids), because these are considered to be the predominant factor in PFC excretion. According to the model of excretion, the portion of PFC entrapped in the reticuloendothelial system (RES) follows a pathway from the cell membranes of the organs, especially the liver, to the blood stream and lungs to be exhaled. Transport in the blood vessels takes place via macrophages and dissolved in lipid blood components, respectively.

The ease of phagocytosis across the cell membrane of macrophages seems to be the rate-determining step of excretion. This stage of the exhalation process is proportional to the lipid solubility of PFCs, which is found to correlate well with the critical solution temperature (CST) in mixtures with n-hexane. A convenient, and acceptably accurate, measure of the CST of a PFC (or mixture of PFCs) in admixture with n-hexane is that temperature at which a mixture containing equal volumes of the PFC and n-hexane just becomes completely miscible. This measure was introduced in the discussion of PFC exhalation by Moore and Clark [1] and has been considered in the present work. While these authors injected neat PFCs intraperitoneal in mice, Yamanouchi and co-workers [2] obtained more satisfactory results by in-

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traveneous injection of 52 PFCs as emulsions. They confirmed the correlation between the half-life time in the animal and CST according to the equation:

$$\log t_{1/2} = 0.055(\pm 0.007)\mathrm{CST} - 15.51(\pm 2.12)$$

where $t_{1/2}$ is expressed in days and CST in Kelvin; the correlation coefficient r is 0.917. Apart from excretion, there is some evidence of PFC interaction with enzymes, e.g. the induction of cytochrom P450 and the liver monooxygenase system [3]. A precondition for such activities is a definite lipid solubility, which enables the PFC to penetrate cell membranes.

In the past, the use of PFC mixtures in blood substitutes were discussed in the light of existence of two individual compounds. In fact, the real situation seems to be much more complex. Obraztsov [4] has observed that the cytochrom P450–PFD (perfluorodecalin) complex in liver microsomes is destroyed in the presence of excess perfluoromethylcyclohexylpiperidine (PMCP) or perfluorotributylamine (FTBA) emulsions. Obviously, this is caused by re-extraction of PFD from lipids. Subsequently, the expiration rate of PFD is significantly reduced in rabbit when a PMCP emulsion is administered in addition. On the other hand, after intraveneous injection of lipid emulsion the expiration rate of PFD increases 2–4 times. It seems very likely that all these observations are a result of different lipid solubilities.

Experimental

The PFCs used were carefully distilled to obtain individual compounds of high purity and then checked by GC methods. The PFCs or their mixtures (1 ml) and the same volume of n-hexane were placed in a test tube (10 mm i.d.). By means of a bath, the temperature of the mixture was increased very slowly. When the two phases disappeared, the CST was recorded by means of a thermometer placed directly in the liquid. Often, it was more accurate to observe the appearance of the two phases when going from a higher to a lower temperature. Mixtures which were completely miscible at room temperature were chilled until phase separation took place.

Results and discussion

The CSTs of a variety of perfluorocarbons in n-hexane have been measured. Most of these are unknown and the corresponding perfluorocarbons were first prepared in our laboratory. The lower molecular weight and lower boiling compounds are also of interest due to their potential ability for oxygen supply in formulations for topical application. Their CSTs should also provide a measure of the tendency of perfluorocarbons bearing oxygen to penetrate into the skin.

Table 1 lists the critical solution temperatures of PFCs in mixtures with n-hexane at temperature intervals from −44 °C (PFOI) up to 59 °C (F-TBA).

TABLE 1

Critical solution temperatures of perfluorocarbons in admixture with n-hexane

No.	Compound	Lit.	Abbre-viation	Structure	CST (°C)
1	*F*-decalin		PFD		22
2	*F*-triethylamine		F-TEA		23.6
3	*F*-dibutylmethylamine		F-DBMA		46
4	*F*-tributylamine		F-TBA		59
5	*F*-cyclohexylmethylmorpholine	[5]	F-CMM		39.5
6	*F*-methylcyclohexylpiperidine		PMCP		39
7	*F*-cyclohexyloxyethylmorpholine	[6]	F-COM		44.2
8	*F*-cyclohexylmethylhexamethylenimine	[5]	F-CMHI		52.8
9	*F*-cycloheptylmorpholine	[7]	F-CHM		40
10	*F*-2,6-dimethyl-4-cyclohexylmorpholine	[8]	F-DMCM		53.3
11	*F*-ethoxyethylpiperidine	[9]	F-EEP		38.3
12	*F*-2-ethoxydecalin	[10]	F-EOD		40
13	*F*-methylcyclohexane		F-MCH		8.2
14	*F*-ethylcyclohexane		F-ECH		17.9
15	*F*-propylcyclohexane	[5]	F-PCH		25.8
16	*F*-1,4-dioxabicylo-4,4,0-decane	[11]	F-DBD		11.5
17	*F*-methyldioxabicyclo-4,4,0-decane	[11]	F-MDBD		21.2
18	*F*-ethoxymethyldioxabicyclo-4,4,0-decane	[11]	F-EDBD		32.6
19	*F*-butyltetrahydrofuran		F-BTF		29
20	*F*-hexane		F-HEX		20
21	*F*-octane		PFOF		37
22	*F*-1*H*-octane		PFOH		21.3
23	*F*-octyl chloride		PFOCl		−7.5
24	*F*-octyl bromide		PFOB		−24.5
25	*F*-octyl iodide		PFOI		−44

The CSTs of mixtures of PFD and fluorinated amines (F-TBA, F-DBMA, F-CMM) with n-hexane were also measured and show a linear relationship in respect of their composition, as shown in Fig. 1. As far as the overall exhalation rate of the fluorocarbon mixture is concerned, the individual lipid solubility of a high boiling compound, e.g. F-TBA, is increased by the addition of a low CST fluorocarbon such as PFD or PFOB. Thus, the adjustment of PFC mixtures to definite CSTs may be used to regulate their expiration.

Additionally, the linearity of the graphs shown in Fig. 1 allows extrapolation to obtain unknown CST values of individual compounds. Thus, the CST of perfluorooctyl bromide, a possible candidate in future blood substitutes, cannot be measured experimentally, because its melting point is 6 °C. However, from the extrapolation of PFOB mixtures (Fig. 2), a critical solution temperature of −24.5 °C may be determined.

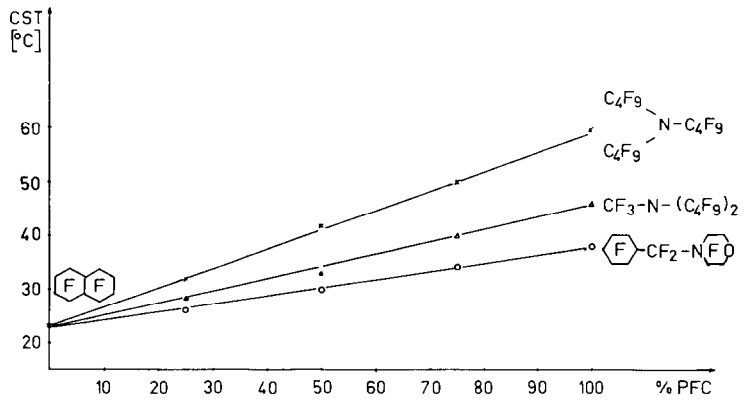

Fig. 1. Critical solution temperatures of PFD mixtures with n-hexane.

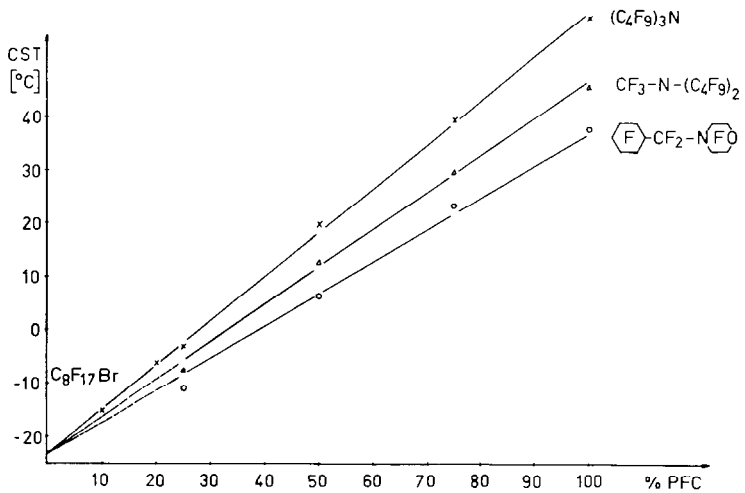

Fig. 2. Critical solution temperatures of PFOB and its mixtures with n-hexane.

Using the same method, the CST of perfluorooctyl iodide (PFOI) with n-hexane has been determined as −44 °C. From this it is clear that the existence of a more polarizable halogen in a perfluoro compound increases the lipophilicity. Substitution of X in $C_8F_{17}X$ (X = H, F, Cl, Br, I) and the corresponding change in CST is shown in Fig. 3 as a function of the electron polarizability. The latter is described by the molar refraction *MR*, calculated according to the Lorentz–Lorentz equation from the refractive index (see Table 2).

The low CST value of PFOB in relation to other fluorocarbons (see Table 1) should be further investigated relative to its transpiration rate, because it does not fit the Yamanouchi equation [2] (the calculated half-life time of 0.34 h is irrelevant). In contrast to the views of Yamanouchi *et al.* [2], it appears that the CSTs of fluorocarbons are dependent on other factors besides the number of carbon and fluorine atoms. The existence of polarizable atoms in the molecule appears to have a remarkable influence. Unfortunately,

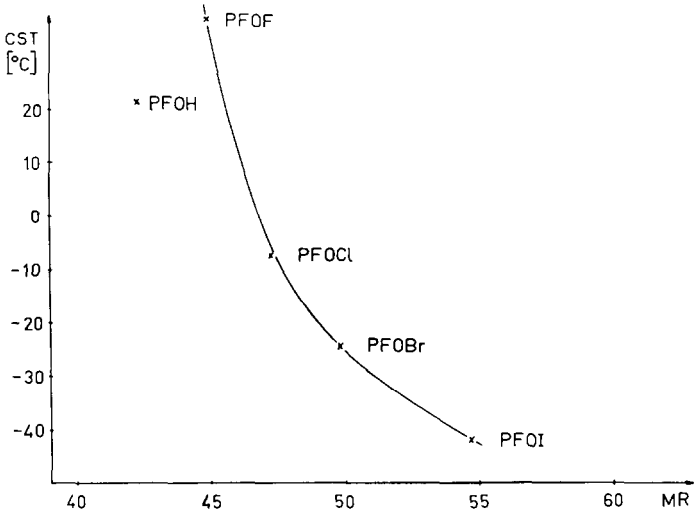

Fig. 3. CSTs of $C_8F_{17}X$ fluorocarbons (X = H, F, Cl, Br, I) as a function of their molar refractivities *MR*.

TABLE 2

Molar refraction as a function of the electron polarizability of perfluorooctyl derivatives ($C_8F_{17}X$)

Perfluorooctyl derivative $C_8F_{17}X$	Refractive index, $[n]_D^{20}$	Molar refraction, *MR* (cm^3)
X = H	1.283	42.24
F	1.286	43.93
Cl	1.297	47.18
Br	1.310	49.82
I	1.336	54.76

the degree of interaction between the heteroatoms of interest, i.e. nitrogen and oxygen, is not quite clear at present. To some extent, their polarizability appears to be too low to influence the CST to any great extent. The concept of molar refraction cannot be applied to all heteroelement-containing fluorocarbons, because of its molecular structure dependence. One conclusion to this work is that contrary to Yamanouchi *et al.* [2], values of $t_{1/2}$ and CSTs cannot be generally predicted for all fluorocarbons without taking into account additional molecular parameters.

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References

1 R. E. Moore and L. C. Clark Jr., *Proc. 5th Int. Symp. Perfluorochemical Blood Substitutes, Mainz 1981*, W. Zuckschwerdt Verlag, München, 1982, p. 50.
2 K. Yamanouchi, M. Tanaka, Y. Tsuda, K. Yokoyama, S. Awazu and Y. Kobayashi, *Chem. Pharm. Bull., 33* (1985) 1221.
3 V. V. Obraztsov, A. A. Sklifas and N. I. Kukuschkin, *Pharmakol. Toxikol. (Russ.), 52* (1989) 60.
4 V. V. Obraztsov, *J. Fluorine Chem.*, in press.
5 U. Gross, St. Rüdiger and U. Jonethal, *DD Pat. 280 130* (1988) [*Chem. Abs., 114* (1991) 152 967].
6 St. Rüdiger, H. Meinert, U. Jonethal, W. Radeck, G. Zielinski, V. Platonov and N. Popkova, *DD Pat. 254 219* (1986) [*Chem. Abs., 110* (1989) 179 568].
7 S. Schramm, U. Jonethal, M. Kupfer and St. Rüdiger, *DD Pat. 275 079* (1986) [*Chem. Abs., 113* (1990) 180 292].
8 S. Schramm, W. Radeck, L. Kolditz, U. Gross, St. Rüdiger and H. Meinert, *DD Pat. 275 078* (1986) [*Chem. Abs., 113* (1990) 180 293].
9 A. Dimitrov, W. Radeck, St. Rüdiger and V. E. Platonov, *J. Fluorine Chem., 52* (1991) 317.
10 W. Radeck, U. Gross and St. Rüdiger, *J. Fluorine Chem., 54* (1991) 184.
11 W. Radeck, St. Rüdiger and U. Gross, *DE Pat. 4 101 446* (1991).