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PERFLUOROCARBONS – USEFUL TOOLS FOR MEDICINE*

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Abstract: Perfluorocarbons (PFCs) combine rather unique chemical and physical properties together with physiological inertness. Due to this, they have become useful tools in medicine. Whereas the majority of applications benefit from their excellent oxygen solubility, there are several applications making use of other PFC properties. The great importance of PFC ultra-purity is especially emphasized.

Key words: perfluorocarbons, purification, oxygen transport, liquid ventilation, drug carrier

INTRODUCTION

Over the last 3 decades, perfluorocarbon compounds (perfluorocarbons, PFCs), originally invented in the 1940s in connection with the Manhattan-Project, have been attracting scientists all over the world because of their unique suitability for a variety of biological-medical applications [1].

"Blood substitute" is the perhaps most spectacular application of PFCs [2]. PFC-based, intravascularily injectable oxygen transporting liquids have already received approval for special purposes (Fig. 1). Since such liquids have to be miscible and compatible with human blood, they are composed of perfluorocarbon(s) finely dispersed, emulsified, in an aqueous solution of salts, because of the osmotic pressure, special polymers, because of the colloid-osmotic pressure, and glucose as energy ressource. Other important fields of PFC-use [3] are ophthalmology and liquid ventilation, in both applications neat perfluorocarbons are used.

NATURE AND SYNTHESIS OF PFCS

Perfluorocarbons are compounds consisting in a narrow sense of carbon and fluorine atoms only; in a broader sense all compounds are summed up under this term having all their hydrogen atoms replaced by fluorine, and containing single bonds only, and fluorine is bond to carbon only. Typical examples are shown in Fig. 1.

There are two principal ways for manufacturing PFCs. The one starts from hydrogen containing organic compounds having the skeleton (from carbon and possibly nitrogen and/or oxygen) of the aimed PFC. By special methods these compounds are perfluorinated, i.e. all hydrogen atoms are replaced by fluorine, and all multiple bonds are saturated. Industrial perfluorination methods comprise electrochemical fluorination (ECF), cobalt trifluoride fluorination (CoF_3), and to a certain extent also fluorination with elemental fluorine.

The other way starts from preformed fluorinated small "building blocks" which are combined to form the aimed PFC. Examples for both ways are given in Fig. 2 and 3.

PURIFICATION OF PFCS

Unfortunately, as quite normal in chemical synthesis, all these reaction do not proceed as smoothly, completely, and exclusively as given in the exam-

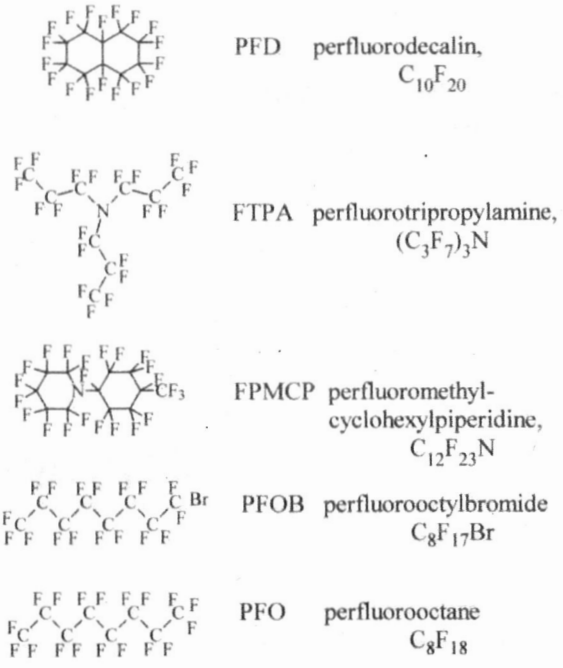

Fig. 1. Examples of perfluorocarbons used for medical applications.

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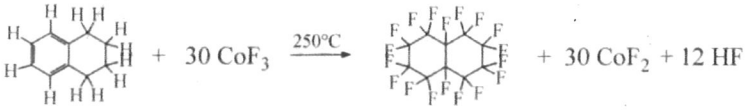
CoF_3-process



ECF-process

$$(CH_3CH_2CH_2)_3N + 42\ F^- \longrightarrow (CF_3CF_2CF_2)_3N + 21\ HF + 42\ e^-$$

$$42\ H^+ + 42\ e^- \longrightarrow 21\ H_2$$

Fig. 2. Perfluorinating routes to perfluorocarbons.

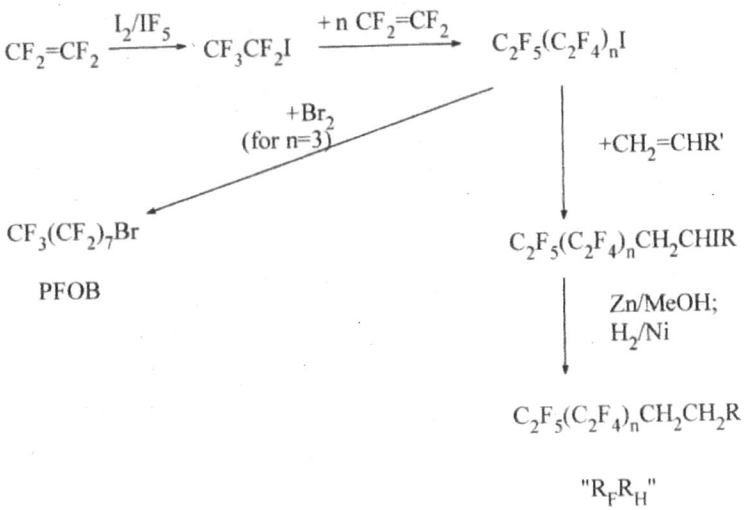


Fig. 3. Building block route to perfluorocarbons and to RFRH-diblock compounds.

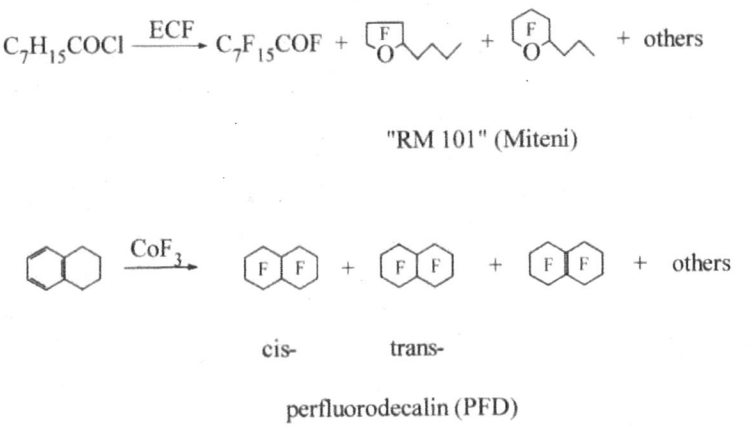


Fig. 4. Product mixtures obtained by industrial perfluorination reactions.

ples. Depending on their respective ways of manufacture, the crude PFCs contain different types of by-products. Of these not all are necessarily impurities. On the contrary, "by-products" which are perfluorinated, and the physico-chemical properties of which are close to those of the aimed (major) product, might be acceptable, too, depending on the medical field of application. Thus, e.g., ECF of octanoic acid chloride yields, besides the aimed perfluoro octanoic acid fluoride, hugh amounts of both perfluorobutyltetrahydrofuran and perfluoropropyltetrahydropyran. The latter two are commercialised as a mixture by Miteni, Italy, under the trade name RM 101, and can be

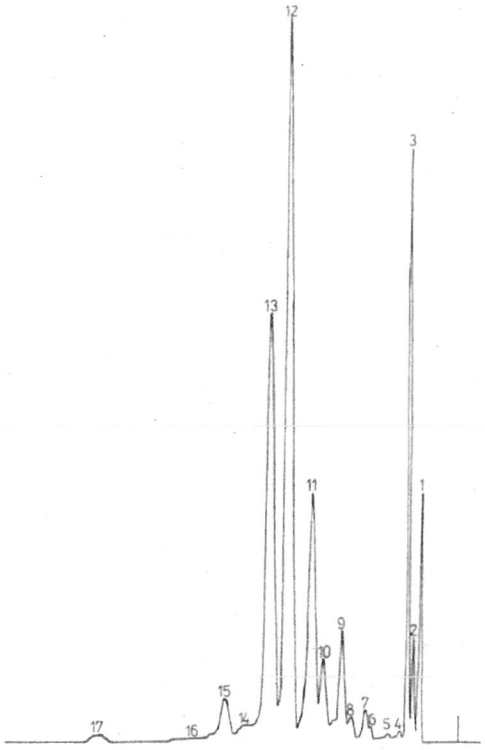


Fig. 5. Gaschromatogramm of crude perfluorodecalin. Peaks No. 12 and 13 correspond to cis- and trans- perfluorodecalin. (From Rüdiger S, Radeck W (1988) unpublished).

used for, e.g., liquid ventilation (Fig. 4). Another example is the use of cis- and trans- perfluorodecalin as mixture (Fig. 4) in, e.g., ophthalmology [4]. In case that their physico-chemical properties differ beyond acceptable limits, it opens in itself possibilities to separate them by, e.g., distillation or other means.

However, there are other types of impurities in the crude PFCs which are toxic, often in very low concentrations, and which have to be removed, therefore [5]. Fig. 5 shows a typical gaschromatogramm of crude perfluorodecalin, giving an impression of the variety of differently fluorinated compounds which can be found in the product mixture.

These potentially toxic impurities are compounds containing CHF and/or C=C within their molecules. Because of their high reactivity towards nucleophiles, these parts of the molecules are weakpoints of the otherwise stable fluorinated molecules (Fig. 6).

Reactions with nucleophilic agents, as shown in Fig. 6 with the hydroxyl ion, lead not only to multiple formation of hydrogen fluoride, but nucleophilic groups of biomolecules can react, too. As a consequence, complete removal of such impurities is an absolutely necessary and important task in preparing PFCs for medical use. Such an ultapurification requires the application of specifically designed multistep processes, combining chemical treatments with physico-chemical ones [6]. In principal, time-consuming reactions with very strong nucleophiles at high temperatures can be used, followed by phase separation, distillation, extraction, and chromatography. The quality control of the purified product, to confirm it is of medical grade, needs besides great experience of the personnel concerned with, advanced analytical techniques which have to be combined with or checked against biological tests. For the latter, several types of cell culture tests have been introduced and employed [5, 7].

The authors feel that quite often irreproducible results, and nonconformity between the results of different researchers might have their origin in the use of PFCs having different degrees of purity. These few remarks, already, should emphasize the necessity of chemists and medical scientists to work together in this field.

Properties and Medicall Use of PFCs

Perfluorocarbons have rather unique properties. These can be explained on a molecular basis by the specific properties of fluorine and the C-F bond, some of which shall be referred to very briefly (Table 1 and 2).

A comparison of fluorine with the other halogens and with hydrogen shows that fluorine has the highest ionization potential IP and highest electronegativity χ_p, but the lowest polarizability α_v, whereas its van der Waals radius r_v is not much larger than that of hydrogen.

As consequences of the high ionization potential of fluorine and especially of its low polarizability, the intermolecular interactions in liquid perfluorocarbons are very weak, and the surface energies are low. Due to its extraordinary high electronegativity, fluorine is always electron-withdrawing when bonded to carbon, causing a relatively high ionic character of the C-F bond making it stronger than any other C-X bond. There is another, most important peculiarity of the C-F bond, i.e., mammals do not have an enzym capable to cleave that bond.

The comparison of the bond strength data shows that fluorine is not only superior to hydrogen, but also that the bond strength increases in

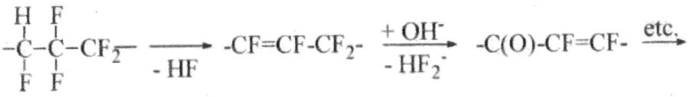


Fig. 6. Typical reactions of toxic impurities.

Table 1. Examples of Biomedical Applications for PFC Liquids and their Emulsions.

Product	Company	Year	Status and Purpose
Fluosol DA (PFD/FTPA)	Green Cross Corp. Japan	1990	Approval of emulsion for clinical use in coronary balloon angioplasty
Perftoran (PFD/FPMCP)	Russia	1996	Approval for haemorrhagic shock patients; perfusion of isolated human organs
Oxygent (PFOB)	Alliance Pharm. Corp. USA	1997	Phase II – temporary tissue oxygenation in 250 surgical patients
		1998	Clinical trials with more than 340 patients
		end of 1998	Phase III studies started
PFD, PFO	Bausch + Lomb USA/Europe	actual	Surgical tools in ophthalmology
Liquivent	Alliance Pharm. Corp. USA	actual	Liquid ventilation fluid under testing Phase III ongoing
Imagent	Alliance Pharm. Corp. USA	actual	Diagnostic imaging agent Phase III completed
Several PFCs	different suppliers	actual	Cell culture media supplements

Table 2. Atomic Properties of Fluorine in Comparison.

	IP [kcal/mol]	a_v [Å^3]	r_v [Å]	χ_p
H	313.6	0.667	1.20	2.20
F	401.8	0.557	1.47	3.98
Cl	299.0	2.18	1.75	3.16
Br	272.4	3.05	1.85	2.96
I	241.2	4.7	1.98	2.66

Data taken from Smart BE (1994) Characteristics of C-F Systems. In: Banks RE, Smart BE, Tatlow JC (ed) Organofluorine Chemistry, Principles and Commercial Applications. Plenum Press, New York, London.

Table 3. Bond Dissoziation Energies of Ethanes

	D°(C-X) [kcal/mol]	
X	CH_3CH_2-X	CF_3CF_2-X
H	100.1	102.7
F	107.9	126.8

Data taken as above

going from mono- to perfluorinated compounds.

Because of the comparatively small size of fluorine, all hydrogen atoms in an organic molecule can be replaced principally by fluorine with the molecular structure remaining. Due to the slightly greater fluorine atoms, the resulting perfluorocompounds are somewhat stiffer than the hydrogenated ones, and their carbon skeleton and with that their carbon-carbon bonds are completely shielded by fluorine, making them less accessible to any chemical attack. In summary, PFCs are of extraordinary chemical as well as thermal resistance.

The fluorine and C-F bond pecularities imply many specific properties of perfluorocarbons, several of them are valueable from a medical point of view.

Perfluorocarbons-

- are chemically highly inert, as a consequence they are physiologically acceptable, too;
- dissolve about 20 times more oxygen than water does, and even more carbon dioxide;
- have very low surface tension allowing them to wet any solid surface;
- are strongly hydrophobic but also oleophobic, consequently, they are immiscible with water, and very limited miscible with oleophilic liquids;
- are very poor solvents for all but fluorophilic solid substances;
- have specific densities near 2 g/cm^3, but their boiling points resemble those of the analogous hydrogenated compounds, so that they easily evaporate;
- are unusual compressible, hence, acoustic velocity in PFCs is low making them excellent contrast agents for ultrasound diagnosis.

As basis of any medical use, physiological acceptance of a PFC is a precondition, depending primarily on its purity only. Therefore, ultra-purification of the PFCs is absolutely necessary.
Among other specific properties, the high oxygen (and carbon dioxide) solubility is most widely employed. The O_2-solubility depends partly on molecular volume and structure, but it varies not so much that its variation have to be taken into consideration for a specific medical task (Fig. 7) [8].

The ability of PFCs to dissolve large amounts of oxygen was decisive for their use in "blood substitutes", for organ preservation, and for liquid ventilation. Unlike to blood, PFCs show a linear rela-

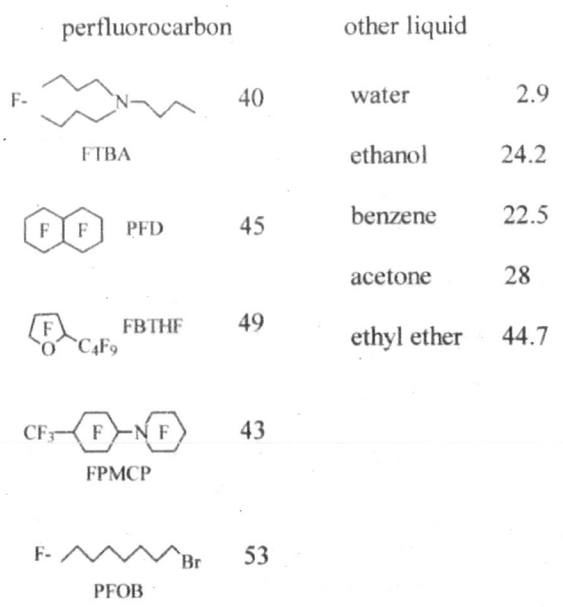


Fig. 7. Oxygen solubility of selected perfluorocarbons and some other liquids (mL O_2/100 mL liquid at 760 mmHg O_2).

tion between the amount of dissolved oxygen and oxygen partial pressure, i.e. the solubility follows Henry's Law. Oxygen is dissolved physically only, there are no specific interactions with the PFC [9]. On the contrary, due to the very weak intermolecular interactions in PFCs, there is sufficient free space between the PFC molecules to be occupied by oxygen or other low molecular gases. By the way, similar amounts of oxygen can be dissolved in, e.g., diethylether (Fig. 7).

The very low surface tension of PFCs makes it possible that PFCs wet any solid surface even polytetrafluoroethylene, Teflon®. However, its spreading behaviour on surfaces already wetted with water as they are within lungs has to be investigated experimentally.

PFCs are practically insoluble in water. Only to explain the droplet growth in PFC-in-water emulsions one has to take into consideration a very, very small but decisive solubility [10]. This implies the necessity to make PFC-in-water emulsions for intravascular use of PFC-based oxygen carriers. On the other hand, PFCs are very limited miscible with or soluble in lipophilic liquids, too, depending on the nature of the PFC tested as well as of the other solvent. The temperature above which two liquids become completely miscible, the critical solution temperature (CST), is a valueable characteristics indicating the difference in the respective Hildebrandt's solubility parameters [11]. By using a specific lipophilic liquid as a standard the experimentally determined CSTs are used to discriminate between PFCs regarding their lipophilicity and other properties depending on it as e.g. the excretion rate in case of intravascular use. In this respect, n-hexane, olive oil, as well as n-bromoalkanes have been used as reference liquids [12, 13, 14]. The lower the CST the higher the lipophilicity and the higher the excretion rate. CST(n-hexane)-values of some typical PFCs are shown in Fig. 8 [12, 13].

At this point some short remarks concerning the emulsification behaviour of PFCs are necessary. If one of two immiscible liquids is finely dispersed within the other, the resulting dispersion is thermodynamically (i.e. energetically) unstable and tends to decay into the two separate phases. The dispersion can be more or less stabilized by introducing surface active agents which become enriched at the liquid-liquid interface. Ideally, such agents should bear in their molecules two spatially separated groups, one, e.g., hydrophilic and the other, e.g., fluorophilic as in "fluorosurfactants". Such surfactants arrange themselves in the interface in a way that their hydrophilic part is orientated towards the water phase and the fluorophilic (i.e.hydrophobic) one towards the PFC. As a result, the free energy of the system can become that low that thermodynamically stable systems might be formed, eventually, as in case of the so-called microemulsions. When stable emulsions have to be made, consisting of water dispersed in PFC (water-in-PFC), special fluorosurfactants have to be used, whereas PFC-in-water

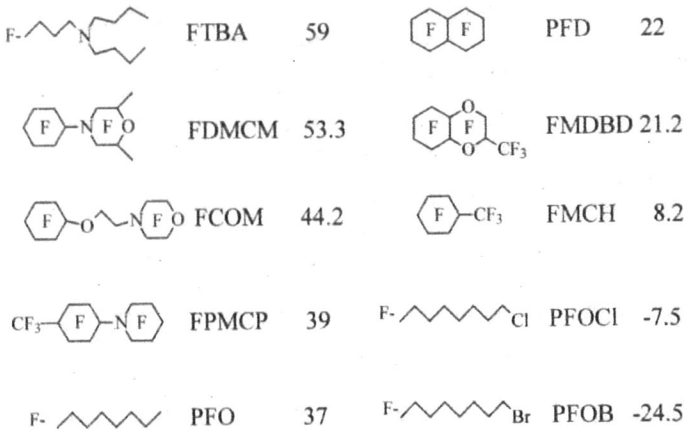


Fig. 8. Critical solution temperatures (CST) of selected perfluorcarbons in n-hexane (°C) (Data taken in part from [12]).

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