

## PERFLUOROCARBONS – USEFUL TOOLS FOR MEDICINE\*

St. Rüdiger, U. Groß, E. Kemnitz

Institute of Chemistry, Humboldt-University, Berlin, Germany

**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, intravascularly 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 resource. 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 ( $\text{CoF}_3$ ), 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-

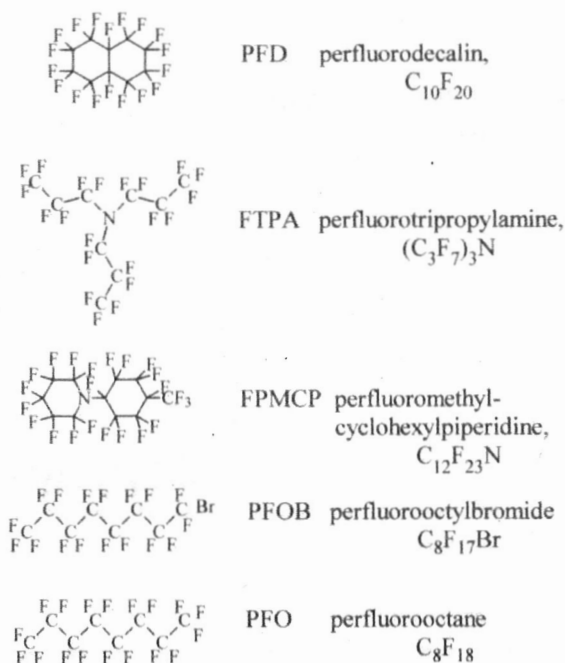


Fig. 1. Examples of perfluorocarbons used for medical applications.

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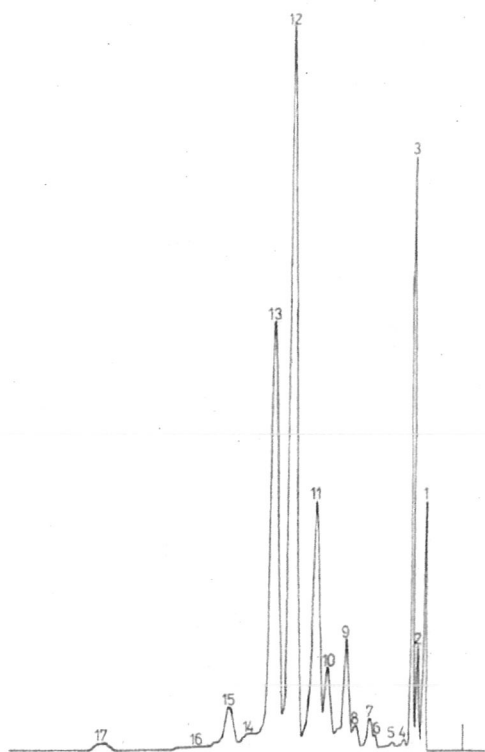


Fig. 5. Gaschromatogramm of crude perfluorodecalin. Peaks No. 12 and 13 correspond to cis- and trans-perfluorodecalin. (From Rüdiger S, Radeck W (1988) unpublished).

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 ultra-purification 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 MEDICAL 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  $\chi_p$ , but the lowest polarizability  $\alpha_v$ , 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 enzyme 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

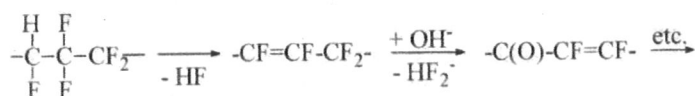


Fig. 6. Typical reactions of toxic impurities.

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 1998 end of 1998	Phase II – temporary tissue oxygenation in 250 surgical patients Clinical trials with more than 340 patients 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]	$a_v$ [ $\text{\AA}^3$ ]	$r_v$ [ $\text{\AA}$ ]	$\chi_p$
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

X	$D^0(\text{C-X})$ [kcal/mol]	
	$\text{CH}_3\text{CH}_2\text{-X}$	$\text{CF}_3\text{CF}_2\text{-X}$
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 peculiarities 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  $2 \text{ g/cm}^3$ , 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  $\text{O}_2$ -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-

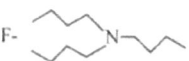


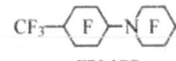

perfluorocarbon	other liquid
 FTBA 40	water 2.9
 PFD 45	ethanol 24.2
 FBTHF 49	benzene 22.5
 FPMCP 43	acetone 28
 PFOB 53	ethyl ether 44.7

Fig. 7. Oxygen solubility of selected perfluorocarbons and some other liquids (mL O<sub>2</sub>/100 mL liquid at 760 mmHg O<sub>2</sub>).

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 emul-

sions 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 valuable 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

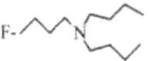

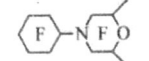
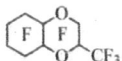
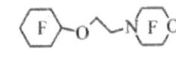

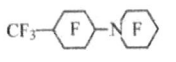
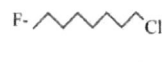


 FTBA 59	 PFD 22
 FDMCM 53.3	 FMDBD 21.2
 FCOM 44.2	 FMCH 8.2
 FPMCP 39	 PFOCl -7.5
 PFO 37	 PFOB -24.5

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

emulsions can also be stabilized by entrapping the PFC droplets in, e.g., swollen micelles of lecithin. Among the several factors affecting emulsion stability, PFC-lipophilicity as well as PFC-diffusion through water play an important role, properties which are well-balanced in only some PFCs as, e.g., in PFOB.

A drawback of PFCs is that they are very poor solvents for all but fluorophilic substances. Therefore, it is almost impossible to obtain therapeutically or diagnostically useful concentrations of pharmaceuticals dissolved in a PFC. To overcome this disadvantage, other developments are needed, which are discussed in detail below.

The high specific gravity of PFCs resulting from the replacement of the light hydrogen atoms by the comparatively heavier fluorine atoms is helpful in the light of liquid ventilation to introduce PFC in the lungs [15] even in case these are (partly) filled with water, and for the use of PFCs in ophthalmology [16]. In ophthalmology, PFC is used to flatten a detached and possibly folded retina at the eye's background that it becomes re-attached.

Surprisingly, PFCs having molecular weights which are about three times higher than those of the respective hydrogenated compounds boil at nearly the same temperature. The low boiling points together with low heats of evaporation are further indices for very low intermolecular interactions. As a consequence, PFCs can be very easily evaporated, thus leaving the lungs in case of liquid ventilation within short time although the body temperature is far below their respective boiling points.

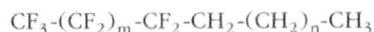
There are further PFC properties worth to be mentioned because of medical relevance. Thus, the low acoustic velocity makes them a valuable ultrasound contrast agent, for instance as stable gaseous PFC-in-water dispersions [18]. Furthermore, fluorine atoms are as suited as hydrogen for nuclear magnetic resonance experiments. Because fluorine resonates at another (lower) frequency range than hydrogen (provided the magnetic field is the same), conventional magnetic resonance tomographs are not useful, unfortunately. However, on an experimental level, excellent  $^{19}\text{F}$  images have been obtained already [19].

The great interest in perfluorocarbons for medical uses arose with the advent of PFC-based blood substitutes, as they were called at that time. Scientists, at the beginning mostly chemists, all over the world were confronted with the very difficult task to find or develop a PFC representing a good compromise between sufficient intravascular dwell time, fast excretion from the patient, and long term stability of its aqueous emulsion using physiologically tolerable emulsifier. Hundreds of compounds were tested in this respect, some taken from industry, most were specially synthesized (see, e.g., Fig. 1).

Perfluorooctyl bromide ("PFOB" or "Perflubron") is the PFC-constituent of a blood substitute introduced by Alliance Pharmaceuticals, USA, which is the nowadays most advanced tested one. In accor-

dance with the explanations given above, the bromine atom in PFOB (see Fig. 1) is a weak-point at which comparatively easily a chemical attack is possible. Correspondingly, some authors [33] question the broadly accepted physiological inertness. As mentioned above, manufacturing of medical grade PFCs is a laborious task. Therefore, once that a manufacturing line for an ultra-pure PFC is implemented, the PFC is available for testing of all kinds of medical uses as in case of PFOB. However, it is neither the only one nor necessarily the best one for a special purpose, but possibly the only one available in larger quantities of medical grade.

Despite the large number and great variety of PFCs tested, their physico-chemical characteristics lay within rather narrow limits. One way to extend these limits is the introduction of Br- or Cl-atoms in the molecule, as in PFOB (perfluorooctylbromide) or in perfluoro-( $\alpha,\omega$ -dichlorooctane). Another way to extend these limits is in going from "true" perfluorocarbons to perfluorocarbon derivatives, the molecules of which consist of at least two different parts, one a fluorocarbon, and the other a hydrocarbon. Such compounds are known since 1964 [20], the synthetic route is given in Fig. 3. A typical example of these perfluoroalkylalkanes, or so-called  $\text{R}_\text{F}\text{-R}_\text{H}$  diblock compounds is shown in the following.



Surprisingly, such compounds can be physiologically acceptable, too, like PFCs [21]. However, in contrast to PFCs, because of their structure these compounds have a certain interfacial activity [22], making them valuable co-surfactants for PFC-in-water as well for water-in-PFC emulsions. In addition, by selecting the respective length of both the perfluoro- and the hydrocarbon part, one has the possibility to design a PFC-like compound having desired boiling point, specific density and lipophilicity. One can design tailor-made compounds which fit best for ophthalmology [23] but also for emulsification [24], and which open a minor possibility for making solutions of compounds of medical interest [25].

#### USE OF PFCs FOR LIQUID VENTILATION

Since PFC liquids dissolve large amounts of respiratory gases, their suitability for liquid ventilation is under study for several years [26]. Experiments with both experimental schemes, filling the lungs partially with PFC (Partial Liquid Ventilation, PLV), and filling the lungs totally with PFC (Total Liquid Ventilation, TLV), have demonstrated that oxygenation and carbon dioxide washout can be maintained sufficiently [27], though the latter method involves greater technical problems to be solved. In addition to maintaining respiration, PFCs are able to replace water or aqueous liquids, e.g. in case of lung edema, and to inflate an immature lung in, e.g., newborn infants.



Concerning the selection of appropriate PFCs, the requirements a PFC to be used for liquid ventilation has to meet are similar to those in case of blood substitutes, though not identical. An obvious precondition is its physiological inertness, depending on ultra-high purity of the PFC, as in case of blood substitute, too. Despite its general importance, gas solubility is not a characteristic to be taken into account selecting a PFC because of the low variability mentioned above. The vapor pressure and correspondingly the boiling temperature of a PFC could be expected to be crucial because low boiling PFCs (i.e. with high vapor pressure) are known to cause gas emboli, and might cause hyperinflation of the lung when administered intravenously in emulsified form [28]. However, if administered intratracheally, PFCs having boiling points even below 37°C have been reported in the patent literature to be advantageously [29]. The lipophilicity of a PFC can be of importance for liquid ventilation, too. In case of the elimination of fluorocarbons as components of blood substitutes from the body, the rate determining step is the dissolution of PFC in circulating lipid carriers [30, 14]. These carriers transport the PFC to the lung, where it is eliminated into the air. The higher the lipophilicity of the PFC the higher the transportation and excretion rate. If, however, the lung contains already substantially amounts of the PFC, depending on the lipophilicity of the latter they will become dissolved in circulating lipids. As a consequence, the PFC will probably be found in all parts of the body especially in adipose tissue [31]. The therapeutic benefit of liquid ventilation would be greatly improved if the PFC administered can be used as carrier for other therapeutic agents, too. Interesting agents are, e.g., antiinflammatory or antiinfectious agents, other types of drugs, lung surfactants, or nutrients, to mention some. In this respect one could make use of the large surface of the lung (about 160 m<sup>2</sup>) for the resorption of water insoluble agents, which are conventionally difficult to administer. However, as specified above, PFCs are very poor solvents so that therapeutical useful concentrations of a solute are very unlikely to be obtained. Therefore, special developments are necessary to make use of PFCs as carriers, e.g. development of PFCs or better fluorocarbons specifically adapted to dissolve a drug, or implementing water-in-PFC emulsion for transporting water soluble agents, or developing stable dispersions of the therapeutic agent in PFC. Although first attempts in this field are already reported [32], the problems encountered are far from being solved.

### OUTLOOK

The principal suitability of perfluorocarbons and related compounds for medical use is known for long. Up to now, there are so many papers published and patents filed covering all aspects of synthesis of fluorocarbons and their use in biology and medicine that it is impossible to review

them comprehensively. From a chemical point of view, there are a great many fluorocarbons suitable for medical use because of their physical-chemical properties. However, the medical researcher who wants to test a fluorocarbon should be sure that the material is of real medical grade, to get reliable and comparable results. Such highly purified compounds are very limited available on the market, unfortunately.

Despite the great variety of medical applications already tested, the inherent potential of the fluorocarbons is by far not exhausted. Future investigations will probably not be focussed predominantly on the oxygen solubility but on other aspects of their use, some of which are discussed above.

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*Address for correspondence:*

Dr. Stephan Rüdiger  
Institute of Chemistry  
Humboldt-University  
Hessische Str. 1-2  
D-10115 Berlin, Germany  
Phone +49 30 2093 7328  
Fax +49 30 2093 7277  
e-mail stephan=ruediger@chemie.hu-berlin.de