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Quantitative Structure–*in Vivo* Half-Life Relationships of Perfluorochemicals for Use as Oxygen Transporters

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Quantitative structure–activity relationships of a series of perfluorochemicals (PFCs) for use as oxygen transporters were investigated in terms of their *in vivo* half-lives ($t_{1/2}$). The $\log t_{1/2}$ values can be correlated by a linear combination of lipophilic (*e.g.*, critical solution temperature (*CST*)), physicochemical (*e.g.*, molecular weight and vapor pressure (P_v)) and topological (*e.g.*, number of fluorines (*NOF*)) parameters on regression analyses. The most important excretion-rate-determining factor was the *CST*. The P_v alone of PFCs did not correlate well with $\log t_{1/2}$. However, a combination of *CST* and P_v produced the most meaningful and important correlation, indicating that P_v plays a pivotal role in the excretion and can be considered a kind of correction factor to the *CST*. The $t_{1/2}$ can thus be predicted from the combination of *CST* and P_v. It can also be predicted from structural information: the smaller the *NOF*, the shorter the $t_{1/2}$. The incorporation of hetero atom(s) such as nitrogen and oxygen in the PFC molecule, which has been considered to produce better emulsion stability but results in persistence in the body, had relatively little effect in terms of $t_{1/2}$. These results suggested that, taking the emulsifiability of hetero atom-containing PFCs into consideration, a cyclic F-ether and F-tertiary amine with fused ring(s), containing fewer fluorines than acyclic analogues, might be a good candidate compound as an oxygen transporter.

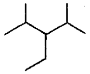
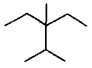
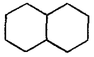
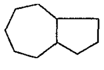
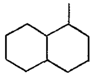
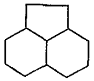
Keywords——oxygen transporter; perfluorochemical emulsion; structure–excretion relationship; regression analysis; lipophilicity; topological effect; physicochemical effect

Remarkable characteristics of perfluorochemical (PFC) liquids, low surface energy and biological inertness,[1)] have attracted considerable attention and resulted in biomedical applications as exemplified by an oxygen transporter candidate.[2)] One of the oxygen transport fluids, a mixed-PFC emulsion,[3)] exhibits potent usefulness as an oxygen-carrying plasma expander,[4)] but leaves room for improvement; *viz.*, it must be stored frozen to prevent deterioration of the emulsion particles, and one of the PFCs used is rather slowly excreted from the body.[5)] Faced with these problems, we have been concerned with the synthesis of novel PFCs which could give an emulsion storable in a liquid state as well as having a reasonably large excretion rate. The screening test performed by Yokoyama *et al.*[6)] has shown that bicyclic perfluoro-tertiary amines with fused rings such as F-4-methylquinolizidine possess favorable properties as candidate PFCs. In the present paper, a quantitative structure–*in vivo* half-life relationship study of PFCs is described, with the aim of providing a basis for the design of better PFCs.

Results

In our previous paper,[7)] we showed that PFCs are mainly excreted through the lung, and their expiratory excretion rates[8)] seem to correlate with their vapor pressures. With the use of

Table I. Structure–*in Vivo* Half-Life Constants for Perfluorochemicals

Compound													log $t_{1/2}$		
No. (Source[a])	Structure[b]	Molecular formula	CST (K)	δ	$\log P_v$	ΔS	M_r	M_v	F[c]	V_w	A_w	$^1\chi$	Obsvd.	Calcd[d] (|Δ|)	Calcd[e] (|Δ|)
1 (A)		C_9F_{20}	313.5	6.15	1.3513	33.72	488.09	255.54	1.57	2.41	5.15	4.091	1.4614	1.4921 (0.031)	1.5364 (0.075)
2 (A)		C_9F_{20}	316.0	6.12	1.2347	34.41	488.09	249.03	1.52	2.41	5.15	4.065	1.5175	1.6549 (0.137)	1.5364 (0.019)
3 (B, C)		$C_{10}F_{18}$	295.0	6.50	1.1031	35.69	462.11	237.47	1.54	2.56	4.94	3.966	0.5311	0.6551 (0.124)	0.8711 (0.346)
4 (L)		$C_{10}F_{18}$	295.7	6.56	1.1296	34.76	462.11	243.34	1.55	2.26	4.94	3.966	0.5311	0.6811 (0.150)	0.8711 (0.346)
5 (B)		$C_{11}F_{20}$	304.6	6.44	0.6808	38.43	512.12	259.70	1.67	2.51	5.47	4.377	1.543	1.2720 (0.271)	1.2351 (0.308)
6 (L)		$C_{12}F_{22}$	307.6	6.22	0.4621	38.08	562.13	277.60	1.73	2.56	6.00	N.A.	1.4415	1.4090 (0.033)	1.5931 (0.152)
7 (D)		$C_{12}F_{20}$	300.0	6.71	0.2303	40.70	524.13	256.67	1.72	2.56	5.63	4.071	1.0784	1.5703 (0.492)	1.0845 (0.006)
8 (B)		$C_{12}F_{20}$	300.0	6.55	0.6228	40.78	524.13	263.38	1.72	2.56	5.63	4.449	0.9237	1.0626 (0.139)	1.0845 (0.161)
9 (C)	$(C_3F_7)_3N$	$C_9F_{21}N$	317.6	5.79	1.2663	34.14	521.10	286.32	1.66	2.57	5.39	4.846	1.8117	1.7239 (0.088)	1.7907 (0.021)
10 (C)	$(C_4F_9)_2NCF_3$	$C_9F_{21}N$	314.8	5.78	1.2033	34.14	521.10	N.A.	N.A.	2.57	5.39	4.808	1.3608	1.6057 (0.245)	1.7907 (0.430)
11 (C)	$(C_3F_7)_2N$(*tert*-C_4F_9)	$C_{10}F_{23}N$	323.1	5.69	0.8445	37.23	571.11	299.48	1.76	2.82	5.92	5.019	2.0778	2.1370 (0.059)	2.1487 (0.071)
12 (C)	(iso-$C_4F_9)_2N(C_3F_7)$	$C_{11}F_{25}N$	328.5	5.75	0.3615	38.13	621.13	335.74	1.93	3.06	6.45	5.558	2.5374	2.5604 (0.023)	2.5066 (0.031)
13 (C)	$(C_4F_9)_3N$	$C_{12}F_{27}N$	328.9	5.77	0.0414	41.10	671.13	358.90	2.07	3.31	6.98	6.346	2.9498	2.6863 (0.264)	2.8646 (0.085)

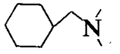
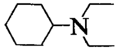
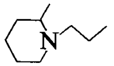
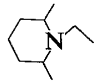
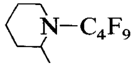
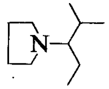
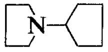
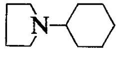
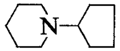
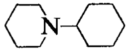
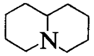
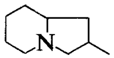
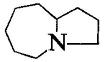
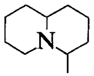
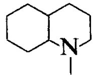
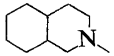
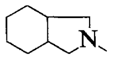
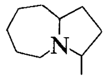
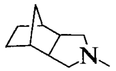
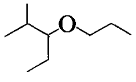
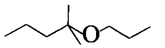
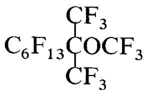
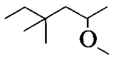
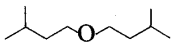
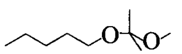
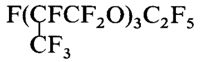
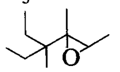
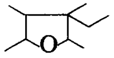
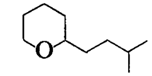
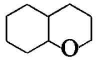
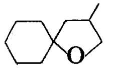
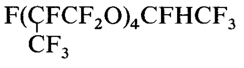
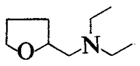
14 (K)		$C_9F_{19}N$	307.6	6.02	1.2245	33.79	483.10	262.55	1.58	2.38	5.02	4.288	1.4761	1.2409 (0.235)	1.2821 (0.194)
15 (M)		$C_{10}F_{21}N$	318.2	6.10	0.9389	36.71	533.12	287.70	1.69	2.62	5.55	4.881	1.7312	1.8622 (0.131)	1.6401 (0.091)
16 (M)		$C_{10}F_{19}N$	309.5	5.91	1.1665	36.20	495.12	265.05	1.51	2.43	5.12	4.309	0.9536	1.3545 (0.401)	1.1314 (0.178)
17 (C)		$C_9F_{19}N$	307.6	6.05	1.4336	33.86	483.10	262.55	1.58	2.38	5.02	4.342	1.4761	1.1716 (0.305)	1.2821 (0.194)
18 (C)		$C_9F_{19}N$	305.6	6.06	1.3756	34.00	483.10	260.71	1.57	2.38	5.02	4.253	1.0785	1.0914 (0.013)	1.2821 (0.204)
19 (C)		$C_{10}F_{21}N$	316.1	6.08	0.9906	36.42	533.12	285.40	1.69	2.62	5.55	4.253	1.7770	1.7408 (0.036)	1.6401 (0.137)
20 (A)		$C_{10}F_{21}N$	313.5	6.01	0.9771	35.69	533.12	277.81	1.67	2.62	5.55	4.753	1.4462	1.6160 (0.167)	1.6401 (0.194)
21 (G)		$C_9F_{17}N$	303.8	6.13	1.2936	34.14	445.10	239.43	1.47	2.18	4.64	3.966	1.1782	1.0292 (0.149)	0.7735 (0.405)
22 (G)		$C_{10}F_{19}N$	303.3	6.21	0.9339	36.45	495.12	259.91	1.61	2.43	5.18	4.466	1.1753	1.1235 (0.052)	1.1314 (0.044)
23 (G)		$C_{10}F_{19}N$	306.0	6.21	0.9771	36.78	495.12	258.41	1.61	2.43	5.18	4.466	1.1606	1.2434 (0.083)	1.1314 (0.029)
24 (G)		$C_{11}F_{21}N$	309.1	6.27	0.7071	39.44	545.13	281.72	1.77	2.67	5.71	4.966	1.7947	1.4869 (0.308)	1.4894 (0.305)
25 (I)		$C_9F_{17}N$	295.8	6.40	1.2397	34.00	445.10	231.94	1.48	2.18	4.64	3.966	0.6716	0.6495 (0.022)	0.7735 (0.102)
26 (M)		$C_9F_{17}N$	294.6	6.26	1.3775	33.31	445.10	235.13	1.47	2.18	4.64	3.860	0.6985	0.5443 (0.154)	0.7735 (0.075)
27 (B)		$C_9F_{17}N$	294.0	6.36	1.3151	33.79	445.10	234.26	1.49	2.18	4.64	3.966	0.3008	0.5351 (0.234)	0.7735 (0.4726)
28 (I)		$C_{10}F_{19}N$	300.2	6.39	1.0287	36.86	495.12	251.08	1.60	2.43	5.18	4.337	0.8267	0.9381 (0.075)	1.1314 (0.269)

TABLE I. (continued)

Compound													$\log t_{1/2}$		
No. (Source[a])	Structure[b]	Molecular formula	CST (K)	δ	$\log P_v$	ΔS	M_r	M_v	F[c]	V_w	A_w	$^1\chi$	Obsvd.	Calcd[d] (|Δ|)	Calcd[e] (|Δ|)
29 (H)		$C_{10}F_{19}N$	305.5	6.36	0.9079	37.45	495.12	253.78	1.61	2.43	5.18	4.377	0.9771	1.2415 (0.264)	1.1314 (0.154)
30 (H)		$C_{10}F_{19}N$	304.8	6.39	0.9725	37.45	495.12	251.08	1.60	2.43	5.18	4.362	0.9438	1.1853 (0.241)	1.1314 (0.188)
31 (M)		$C_{10}F_{19}N$	300.9	6.52	1.0821	36.01	495.12	257.25	1.60	2.43	5.18	4.398	1.0122	0.9552 (0.057)	1.1314 (0.119)
32 (B)		$C_{10}F_{19}N$	299.4	6.34	1.0367	36.56	495.12	255.88	1.62	2.43	5.18	4.377	0.8859	0.8957 (0.010)	1.1314 (0.246)
33 (M)		$C_{10}F_{17}N$	304.1	6.33	1.0327	36.27	457.12	234.91	1.49	2.23	4.80	4.010	0.9438	1.1305 (0.084)	0.6228 (0.321)
34 (A)		$C_9F_{20}O$	313.4	5.79	1.4674	32.91	504.09	276.97	1.60	2.49	5.28	4.719	1.543	1.4486 (0.094)	1.5364 (0.007)
35 (A)		$C_9F_{20}O$	315.0	5.83	1.4819	32.94	504.05	275.44	1.61	2.49	5.28	4.621	1.543	1.5233 (0.020)	1.5364 (0.007)
36 (A)	$C_7F_{15}OC_3F_7$	$C_{10}F_{22}O$	319.1	5.69	1.2447	35.01	554.11	313.06	1.78	2.74	5.81	5.414	1.9809	1.8156 (0.165)	1.8945 (0.087)
37 (J)	 $C_6F_{13}C(CF_3)_2OCF_3$	$C_{10}F_{22}O$	320.5	5.89	1.0163	35.76	554.11	293.18	1.72	2.74	5.81	5.121	1.8117	1.9508 (0.139)	1.8945 (0.083)
38 (A)		$C_{10}F_{22}O$	320.5	5.92	0.9536	36.27	554.11	289.05	1.71	2.74	5.81	5.076	1.9854	1.9716 (0.014)	1.8945 (0.091)
39 (C)		$C_{10}F_{22}O$	321.7	5.77	1.0712	35.69	554.11	303.12	1.75	2.74	5.81	5.126	2.2656	1.9923 (0.273)	1.8944 (0.371)
40 (K)	$C_6F_{13}OC_6F_{13}$	$C_{12}F_{26}O$	320.9	6.26	0.3008	40.30	654.13	323.03	1.87	3.23	6.87	6.414	2.7224	2.7048 (0.018)	2.6103 (0.112)
41 (A)		$C_9F_{20}O_2$	318.0	5.69	1.3847	33.18	520.09	288.94	1.64	2.57	5.40	5.121	1.9986	1.7046 (0.294)	1.5364 (0.462)

42 (D)	 $F(CF(CF_3)CF_2O)_3C_2F_5$	$C_{11}F_{24}O$	328.8	5.46	1.0407	35.91	636.12	365.59	1.99	3.15	6.56	6.702	2.1478	2.3552 (0.207)	2.5233 (0.105)
43 (B)		$C_{10}F_{20}$	314.1	6.21	0.9816	36.49	516.11	267.28	1.66	2.54	5.44	3.999	1.4005	1.6443 (0.244)	1.3857 (0.015)
44 (A)		$C_{10}F_{20}O$	298.7	6.01	1.0675	36.05	516.11	271.07	1.63	2.54	5.44	4.231	1.5175	0.8507 (0.667)	1.3857 (0.132)
45 (C)		$C_{10}F_{20}O$	315.0	6.02	0.9950	35.70	516.11	277.48	1.67	2.54	5.44	4.788	1.6010	1.6846 (0.084)	1.3857 (0.215)
46 (D)		$C_9F_{16}O$	296.2	6.32	1.4056	32.44	428.09	231.65	1.46	2.10	4.53	3.966	0.5437	0.6144 (0.071)	0.5192 (0.025)
47 (D)		$C_{10}F_{18}O$	303.5	6.23	1.1665	34.21	478.11	252.83	1.57	2.35	5.06	4.308	1.0784	1.0564 (0.022)	0.8771 (0.201)
48 (E)	$C_4F_9CH=CHC_4F_9$	$C_{10}F_{18}H_2$	295.3	6.18	1.0996	35.47	464.13	277.92	1.72	2.43	5.36	4.914	0.8686	0.6711 (0.198)	0.8771 (0.009)
49 (E)	$C_4F_9CH=CHC_6F_{13}$	$C_{12}F_{21}H_2$	307.4	6.20	0.1139	39.83	545.15	316.76	1.96	2.82	6.24	5.914	1.6978	1.5989 (0.099)	1.3388 (0.359)
50 (E)	$C_6F_{13}CH=CHC_6F_{13}$	$C_{14}F_{26}H_2$	318.9	6.12	−0.5225	44.94	664.17	367.15	2.25	3.41	7.49	6.914	2.6003	2.3812 (0.219)	2.3090 (0.291)
51 (F)	 $F(CF(CF_3)CF_2O)_4CFHCF_3$	$C_{14}F_{29}HO_4$	328.3	5.37	0.1760	43.91	784.16	445.55	2.39	3.92	8.24	8.596	2.5155	2.6169 (0.101)	3.0719 (0.556)
52 (M)		$C_9F_{19}NO$	N.A.	5.96	1.2592	34.08	499.10	269.20	1.60	2.46	5.14	4.455	1.3001	N.A.	1.2821 (0.018)

a) Source: A, K. V. Scherer, Jr., Univ. So. Calif., U.S.A. and ref. 19*a*; B, Industrial Smelting Co., UK; C, Dainippon Ink & Chem. Ltd., Jpn; D. H. Muramatsu, T. Abe, and S. Nagase, Government Industrial Res. Inst., Nagoya, Jpn; E, J. G. Riess, Univ. Nice, France; F, E. I. du Pont de Numours, Ltd., U.S.A.; G, ref. 19*c*; H, ref. 19*b*; I, ref. 19*d*; J, refs. 19*a* and 19*e*; K. Offered by NHLBI, U.S.A. (supplied by Air Products & Chem., U.S.A.); L, offered by NHLBI, U.S.A. (supplied by Suntech, Inc., U.S.A.). *b*) All unmarked bonds are to fluorine. *c*) Expressed as 10^{-3} values. *d*) Calculated from Eq. 5. Values in parentheses are residuals. *e*) Calculated from Eq. 7. Values in parentheses are residuals. N.A., not available; *CST*, critical solution temperature; δ, solubility parameter; P_v, vapor pressure; ΔS, entropy of vaporization; M_r, molecular weight; M_v, molar volume; *F*, molar attraction constant ($F=\sqrt{EV}$); V_w, van der Waals volume ($\times 10^2$ Å^3); A_w, van der Waals area ($\times 10^2$ Å^2); $^1\chi$, molecular connectivity.

the rate constants (K) and vapor pressure (P_v) data reported therein, this situation can be formulated by Eq. 1.

$$\log K = 1.59(\pm 0.83) \log P_v - 4.62(\pm 0.75) \tag{1}$$

$$(r = 0.937,\ s = 0.278,\ n = 6,\ F_0 = 28.64)$$

In Eq. 1, the numbers in parentheses are 95% confidence intervals, r is the correlation coefficient, s is the standard deviation, and n is the number of data points used in deriving the equation. F_0 denotes the F-test showing 99% statistical confidence.

The expiratory excretion rate thus appeared to be governed by evaporation through the cell membrane of the lung largely owing to the vapor pressure. We have also found that *cis-F*-decalin has a slightly greater excretion rate than the *trans*-isomer, despite a slightly lower vapor pressure and the same molecular weight.[9] These findings indicate that the excretion of PFCs is not governed solely by the vapor pressure. Moore and Clark proposed one physical property, critical solution temperature (*CST*), as the rate determining factor.[10] They found a good correlation between the transpiration rate and *CST* for eight PFCs which they synthesized, and suggested that the *CST* is a measure of relative lipid solubility. However, there has remained to be determined whether the *CST* values can be an exact measure to explain the excretion rate in case of intravenous injection of PFC in an emulsified form, since Clark's transpiration rates were obtained by intraperitoneal injection of $100\,\mu$l of neat PFC liquid.[10]

On the basis of the preceding work, we decided to study the empirical parameters–*in vivo* half-life relationships for 52 kinds of PFCs, in the hope of identifying the best influential factor(s) to the excretion rate of PFCs. At this stage as many independent indices as possible were primarily considered. Table I shows the empirical parameters for PFCs.

The *in vivo* half-life ($t_{1/2}$) was obtained from the elimination profiles of PFC derived from organ retention data (see the experimental section for details). In the strict sense, the $t_{1/2}$ used here may represent the disappearance rate of PFC from the organs, but it can also be regarded as a representative excretion rate from the whole body, because there has been reported a good correlation between the expiratory excretion rate and the excretion rate obtained from organ retention data, although values of the former are usually smaller than the those of the latter.[11] The parameters *CST* and δ (solubility parameter) refer to the lipid solubility of PFCs and $\log P_v$ and ΔS (entropy of vaporization) represent thermodynamic properties which have been thought to be important in the expiratory excretion system. The M_r (molecular weight), M_v (molar volume), V_w (van der Waals volume), A_w (van der Waals area) and F (molar attraction constant)[12] are physicochemical parameters which indicate the steric bulk. The ${}^1\chi$ (molecular connectivity) denotes the molecular branching. The *NOF* (number of fluorines), *NOC* (number of carbons) and *NOR* (number of rings) are also considered indicators of topological features of the molecules. A dummy variable used is HA (hetero atom), which takes a value of 0 or 1 according to the absence or presence of nitrogen and/or oxygen in the molecule.

The logarithm of Clark's transpiration rate has been shown to correlate linearly with the *CST*.[10] A similar effect may be observed for $t_{1/2}$, because the excretion of PFC from the body apparently follows a first-order process, and consequently $t_{1/2} = 0.693/\mathrm{K}$. In fact, the preliminary calculations for single-parameter Eqs., $t_{1/2}$ *versus* empirical parameters, showed that the logarithm of the $t_{1/2}$ can be best correlated with the present parameters (X) except for the P_v, according to Eq. 2,

$$\log t_{1/2} = aX + \text{constant} \tag{2}$$

thus allowing that the *CST* was best correlated with the $t_{1/2}$ to give Eq. 3. As to P_v, the logarithm of P_v was found to give much better correlation than P_v itself ($r=0.394$), as exemplified by Eq. 4.

$$\log t_{1/2}=0.055(\pm 0.007)CST-15.51(\pm 2.12) \tag{3}$$

$$(r=0.917,\ s=0.247,\ n=51,\ F_0=258.4)$$

$$\log t_{1/2}=-0.079(\pm 0.350)\log P_v+2.20(\pm 0.37) \tag{4}$$

$$(r=0.535,\ s=0.517,\ n=52,\ F_0=20.03)$$

In the case of δ, we could not find a good correlation with $t_{1/2}$ for our compounds ($r=0.745$), although Moore and Clark demonstrated that δ correlates well with the transpiration rate.[10]

An attempt to analyze individual groups, which were classified according to structural features, was also made, but no significant advantage over the following treatments could be found. Therefore, the 52 compounds are treated as a single group in this paper.

Then two-parameter equations were considered; Eq. 5 seemed to be the most interesting and meaningful, though Eq. 6 gave the best correlation.

$$\log t_{1/2}=0.050(\pm 0.006)CST-0.331(\pm 0.155)\log P_v-13.64(\pm 1.97)$$

$$(r=0.941,\ s=0.212,\ n=51,^{13)}\ F_0=184.7) \tag{5}$$

$$\log t_{1/2}=0.032(\pm 0.011)CST+0.102(\pm 0.041)NOF-10.57(\pm 3.41)$$

$$(r=0.946,\ s=0.202,\ n=51,^{13)}\ F_0=205.7) \tag{6}$$

Equation 5 resulted from the addition of log P_v over Eq. 3 is significant at better than 0.99 level of significance ($F_{1,48}=18.51$, $F_{1,48,0.01}=7.20$ for P_v). This probably reflects an important role of the vapor pressure of the PFC that is not accounted for by the *CST*, and also suggests that the P_v be a parameter independent of the *CST*. It may probably be regarded as a correction factor for *CST*. Although the *NOF* shows the highest correlation coefficient together with the *CST* in the two-parameter equations, and Eq. 6 is significant at better than 0.99 level of significance ($F_{1,48}=25.12$ for *NOF*), the contribution of *NOF* in Eq. 6 may not be as meaningful as the correlation in Eq. 5. The reason for this is that *CST* is mostly determined by *NOF*, as discussed later.

Correlations between representative parameters used are shown in Table II.

As indicated by these results, $t_{1/2}$ seems likely to be predominantly determined by the *CST*. This situation means that multi-parameter equations, which produce only little improvement, may not be important. We thus believe that Eq. 5 is an important and useful equations for predicting the $t_{1/2}$ of PFCs. Calculated $t_{1/2}$ obtained by using Eq. 5 are shown in Table I.

TABLE II. Correlation Matrix for the Representative Parameters

	NOC	*NOF*	M_r	$\log P_v$	*CST*	δ	ΔS	$^1\chi$	$t_{1/2}$
NOC	1.00	0.72	0.79	−0.94	0.38	−0.58	0.96	0.75	0.51
NOF		1.00	0.98	−0.70	0.86	−0.60	0.69	0.90	0.91
M_r			1.00	−0.73	0.81	−0.58	0.74	0.94	0.86
$\log P_v$				1.00	−0.39	−0.01	−0.95	−0.65	−0.54[a]
CST					1.00	−0.75	0.35	0.71	0.92[b]
δ						1.00	0.03	−0.62	−0.70
ΔS							1.00	0.95	0.48
$^1\chi$								1.00	0.78

a) Equation 4. *b*) Equation 3.

In order to predict $t_{1/2}$ of a PFC from only structural information, *e.g.*, formula weight and chemical structure, Eqs. 7 and 8 may be useful.

$$\log t_{1/2}=0.254(\pm 0.035)NOF-0.151(\pm 0.077)NOC-2.19(\pm 1.06)$$

$$(r=0.927,\ s=0.232,\ n=52,\ F_0=149.8) \qquad (7)$$

$$\log t_{1/2}=0.166(\pm 0.031)NOF-0.169(\pm 0.083)NOR-1.75(\pm 0.64)$$

$$(r=0.929,\ s=0.229,\ n=52,\ F_0=153.6) \qquad (8)$$

Equations 7 and 8 give a good approximation of $t_{1/2}$, by which a rough $t_{1/2}$ can be simply obtained without determining physical constants. Calculated $t_{1/2}$ obtained by using Eq. 7 are shown in Table I. Addition of the HA dummy variable over Eqs. 7 and 8 does not improve the correlations, suggesting that the presence of hetero atom(s) such as nitrogen in the PFC molecule is not a major factor influencing the $t_{1/2}$. However, the introduction of a nitrogen into the PFC, for instance, means an increase of one fluorine atom,$^{14)}$ by which the $t_{1/2}$ may be correspondingly increased. Addition of $^1\chi$ over Eq. 6 or substitution of M_r for NOC also does not produce much better correlations.

The reason why the combination of NOF and NOC is significant may simply be attributed to the good correlation with the CST in Eq. 9, by which the CST can be predicted.

$$CST=4.669(\pm 0.597)NOF-4.409(\pm 1.322)NOC+259.9(\pm 18.2)$$

$$(r=0.926,\ s=3.95,\ n=51,^{13)}\ F_0=144.4) \qquad (9)$$

We, therefore, believe that Eq. 7 is more general than Eq. 8 in representing the $t_{1/2}$ of PFCs.

Discussion

The object of this study was to obtain reliable equations which would be applicable to all types of PFCs without classification according to chemical structure (such as amines or ethers) in order to permit the design of better PFCs. Therefore, it is of particular interest to find the most meaningful variables which reflect precisely the *in vivo* half-life of PFC.

As represented by Eq. 5, the $t_{1/2}$ of PFC can be described by the use of CST and P_v. The contribution of this combination to the excretion may be rationalized by the following hypothesis for the excretion mechanism: after intravenous administration of a PFC emulsion into mammals, the PFC particles gradually disappear from the blood stream while being exhaled in part through the lung and accumulated in the reticuloendothelial system (RES) organs. Since the PFC is expelled from the body even after being taken up into the RES organs,$^{7)}$ one might be led to propose that there is a critical pathway of PFC from the cell membrane of the organs into the blood stream then to the lung. In fact, a recent morphological study indicates that monocytes and macrophages might phagocytose PFC particles retained in the RES organs and move into the blood stream, then to the lung, and PFC leaves the body through the alveoli.$^{15)}$ On this hypothesis, the ease of the phagocytosis across the cell membrane of the monocytes or macrophages is probably the rate-determining step of the excretion. Therefore, the CST, which indicates the lipid solubility, is considered to be the predominant factor in the excretion.

On the other hand, the vapor pressure apparently plays an important role in the excretion system. Its negative sign in Eq. 5 indicates that a greater P_v is preferred to shorten the $t_{1/2}$ (within an acceptable limit so as not to cause lung damage).$^{16)}$ It is likely that P_v contributes to the movement of PFCs from the blood stream to the alveolar ridge and to evaporation *via* the lung into expired air. Thus, P_v may play a critical part in the expiratory excretion, especially when PFC particles exist abundantly in the blood stream, since there will be more active vaporization of PFC in the lung. When the blood level of the PFC particles decreases due to accumulation of the particles in the RES organs, the role of vapor pressure probably becomes minimized. Therefore, the P_v can be considered a correction factor in Eq. 6.

Then we wish to know what factors have influence on the *CST*. The parameter which best correlates with *CST* is *NOF*, even though it is a simple factor. The M_r ranked second (see Table II). The amount of fluorine of PFC and the M_r are thought to reflect simply the bulkiness of PFC. Consequently, the *CST* may be best predicted by the combination of *NOF* and *NOC* (Eq. 9).

The unexpectedly modest correlation of $^1\chi$ to $t_{1/2}$ and *CST* may possibly be explained by the following hypothesis: a saturated perfluorocarbon structure around a carbon chain or ring system may be present without significant overcrowding. Recent spectral studies on F-alkanes revealed that planar zig-zag conformations, in which carbon chains twist to relieve repulsions between fluorines on alternate carbons, are most stable.[17] An analogous situation could be possible with the PFCs being discussed, and might provide quite similar molecular geometry for each PFC. Thus, it is likely that $t_{1/2}$ is quite insensitive to conventional connectivity indices for a class of PFCs.

The presence of hetero atom(s) in a PFC molecule seems likely to be fairly less important in relation to $t_{1/2}$. If F-ether and F-tertiary amines actually underwent some sort of chemical binding in tissue, as discussed in an earlier paper,[18] the effect of hetero atom(s) on the $t_{1/2}$ might be significant and then the HA dummy variable could serve as an important parameter. However, the addition of HA over Eq. 7, for instance, does not improve the correlation, indicating that the hetero atom(s) of PFCs is not a key factor influencing the $t_{1/2}$.

Furthermore, since there is an increase of one fluorine with each incorporation of nitrogen into a PFC molecule, variation of the *NOF* will become of importance rather than the presence of nitrogen. In other words, variation of the *NOF* seems more likely to be influential in relation to the excretion. If this is the case, it will be of particular interest to discuss electric features of PFCs such as the dipole moment, although data are not fully available at present. In Eqs. 7 and 8, *NOF* was also shown to be the key factor: the smaller the *NOF* is, the shorter the $t_{1/2}$ is. Thus, cyclic structures containing less fluorine are favored.

It can be concluded from these results that the $t_{1/2}$ of PFC may be delineated by two physicochemical parameters, *CST* and P_v, and ultimately a topological parameter, *NOF*. Taking account of the excellent emulsifiability of hetero atom-containing PFCs,[2c] it thus appears that a cyclic F-ether or cyclic F-tertiary amine with fused ring(s), which contains fewer fluorines than acyclic analogues, may be the best PFC for use as an oxygen transporter. This further suggests that a PFC having, for instance, one or two hydrogens instead of fluorine (although such a compound would no longer be a PFC) might be a potential candidate compound as an oxygen transporter, if it is biologically inert.

Experimental

Perfluorochemical is abbreviated as PFC and F- stands for perfluoro- throughout this article.

Materials——The PFCs indicated alphabetically under source in Table I were mostly gifts, the sources of which are given in the footnotes. All other PFCs were prepared by conventional electrochemical fluorination method, the details of which were reported elsewhere,[19] or will be reported separately. Chemical structures given in Table I are expressed without showing the fluorine symbol, *i.e.*, all unmarked bonds are to fluorine unless otherwise stated.

Preparation of Test Emulsion[7]——A mixture of a PFC and an aqueous yolk phospholipid suspension was emulsified using a Manton Gaulin high-pressure homogenizer. The emulsion used for animal experiments consisted of 10% (w/v) PFC, 2% (w/v) yolk phospholipid and 0.9% (w/v) sodium chloride. The average particle sizes of all PFC emulsions ranged from 0.09 to 0.15 μm in diameter.

Determination of *in Vivo* Half-Life——Forty ml of PFC emulsion per kg body weight (4 g/kg as PFC) was intravenously administered into each of ten Wistar strain male rats weighing 100—110 g, and the PFC contents in the liver, spleen, lung and kidney were determined by gas chromatography[20] 3, 7, 14 and 28 d after injection. The *in vivo* half-life ($t_{1/2}$) of PFC was calculated from the excretion rate estimated from the change of total PFC content in the above organs. Since the PFC injected into rats is mostly retained in the RES organs,[2a] the sum of the PFC in those organs may be regarded as the PFC content in the whole body. Thus, the total PFC contents in the four organs were plotted against time on a log 10 scale; linear plots were obtained, showing that the process is first order. The slopes of the lines for each PFC injection were obtained by linear regression analyses of the data and give the excretion rate constants for each PFC. With the use of the rate constants, *in vivo* half-lives were calculated representing the required period (days) for a decrease of the body load to 2 g of PFC after injection of 4 g of PFC. The accuracy of the *in vivo* half-life values thus obtained was better than 15% when 10 rats were used for each PFC.

Determination of *CST*——Liquid–liquid solubilities were measured in a sealed tube (*ca.* 3 cm long, 3 mm i.d.): PFC and *n*-hexane, 50 μl each, were placed in the tube, which was then sealed under cooling at around −60 °C. A typical procedure for determining liquid–liquid miscibility was to raise or lower the bath temperature slowly, and when two phases appeared (or disappeared), the temperature was recorded. The average values obtained from three determinations showed a standard deviation within 0.2% and the coefficient of variation was less than 0.4%. All *CST* values are expressed in K.

Calculations——Molecular connectivity indices ($^1\chi$) were calculated throughout this paper according to the method of Randić.[21] The influence of fluorine atoms was disregarded for calculating $^1\chi$, *i.e.*, only carbon skeletons of PFCs are considered in obtaining an index of molecular branching. Entropies of vaporization (ΔS) were obtained by using the equation developed by Sato: $\Delta S = H_v/T$.[22] Calculations of H_v were carried out according to the method of Lawson *et al.*[23]: $H_v^{298} = 0.0724Tb^2 - 17.17Tb + 5309$. Solubility parameters (δ) were given by the equation: $\delta = [(H_v - RT)/V]^{1/2}$[24] Molar attraction constants (F) were given by the equation: $\delta = (E/MV)^{1/2} = F/MV$.[12] Calculations of van der Waals volume (V_w) and area (A_w) were carried out according to the method of Moriguchi *et al.*[25] Molar volume (M_v) was given by the equation: $M_v = M_r/d$ (d; density).[25b] Regression analyses were carried out on an NEC PC8801 computer and an OKI if800 model 50 computer.

References and Notes

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5) For example, see *a)* R. P. Geyer, "Proc. 5th Int. Symposium on Perfluorochemical Blood Substitutes," ed. by R. Frey, H. Beisbarth, and K. Stosseck, Mainz, March 1981, W. Zuckschverdt Verlag, Munich, 1982, pp. 19—29; *b)* R. Dagani, *Chem. Eng. News*, **60** (18), 31 (1982).

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7) K. Yokoyama, K. Yamanouchi, and R. Murashima, *Chem. Pharm. Bull.*, **23**, 1368 (1975).

8) The expiratory excretion rate was calculated from the amounts of PFC expelled into expired air over various intervals.

9) K. Yokoyama, K. Yamanouchi, and R. Murashima, "Proc. 4th Int. Symposium on Perfluorochemical Blood Substitutes," Kyoto, August 1975, Medical Publisher, Osaka, 1975, pp. 103—111.

10) R. Moore and L. C. Clark, Jr., "Proc. 5th Int. Symposium on Perfluorochemical Blood Substitutes," March 1981, W. Zuckschverdt Verlag, Munich, 1982, pp. 50—60.

11) C. Heldebrant and K. Yokoyama, Phase I Report, Vol. I to NHLBI, U.S.A. Contract number NOI-HB-9-2927, RFP-NHLBI-HB-79-15.

12) *a)* J. A. Ostrenga, *J. Med. Chem.*, **12**, 349 (1969); *b)* A. F. M. Barton, *Chem. Rev.*, **75**, 731 (1975).

13) Compound 52 was omitted from the correlation, because its *CST* value was not available.

14) For example, if a nitrogen atom is introduced into compound **3** to give a representative compound such as PFC **28**, total fluorines will change to **19** from **18**, *viz.*, $C_{10}F_{18} \rightarrow C_{10}F_{19}N$.

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16) Too high a vapor pressure will result in a bloated lung. An appropriate vapor pressure range of PFCs is considered to be 10—20 mmHg at 37 °C. See ref. 2*a*.

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