Molecular Properties of the "Ideal" Inhaled Anesthetic: Studies of Fluorinated Methanes, Ethanes, Propanes, and Butanes

E. I Eger, II, MD*, J. Liu, MD*, D. D. Koblin, PhD, MD†, M. J. Laster, DVM*, S. Taheri, BS*, M. J. Halsey, DPhil*, P. Ionescu, MD*, B. S. Chortkoff, MD*, and T. Hudlicky, PhD‡

*Department of Anesthesia, University of California, San Francisco, †Veterans' Administration Hospital, San Francisco, California, and ‡Department of Chemistry, Virginia Polytechnic Institute, Blacksburg, Virginia

We examined 35 unfluorinated, partially fluorinated, and perfluorinated methanes, ethanes, propanes, and butanes to define those molecular properties that best correlated with optimum solubility (low) and potency (high). Limited additional data were obtained on longer-chained alkanes. Using standard techniques, we assessed anesthetic potency (minimum alveolar anesthetic concentration [MAC] in rats); vapor pressure; stability in soda lime; and solubility in saline, human blood, and oil. If nonflammability, stability, low solubility in blood, clinically useful vapor pressures, and potency permitting delivery of high concentrations of oxygen are essential components of an anesthetic that might supplant those presently available, our data indicate that such a drug would have three or four carbon atoms with single or dual hydrogenation of two carbons, especially terminal carbons. We conclude that: 1) smaller and larger molecules and lesser hydrogenation provide insufficient potency; 2) high vapor pressures of smaller molecules do not permit the use of variable bypass vaporizers; 3) greater hydrogenation enhances flammability, and complete hydrogenation decreases potency; 4) internal hydrogenation decreases stability; and 5) greater hydrogenation increases blood solubility.

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The search for a better inhaled anesthetic has proceeded largely by trial and error. For example, drugs such as enflurane, isoflurane, and desflurane were the consequence of synthesis of over 700 compounds. In the present study, we made use of the commercial availability of fluorinated alkanes to pursue a more systematic approach to identifying the molecular properties that might distinguish the ideal inhaled anesthetic. We chose alkanes halogenated solely with fluorine because the use of heavier halogens increases solubility (1–3) and a decreased solubility provides desirable kinetic characteristics. Therefore, we anticipate that future anesthetics will not be halogenated with chlorine or bromine. We define as "ideal" compounds having: 1) nonflammability; 2) stability in soda lime; 3) a boiling point above 35°C; 4) a potency that permits application of high partial pressures of oxygen; and 5) a low solubility in blood. Preliminary studies revealed that fluorinated alkanes might supplant those presently available, our data indicate that such a drug would have three or four carbon atoms with single or dual hydrogenation of two carbons, especially terminal carbons. We conclude that: 1) smaller and larger molecules and lesser hydrogenation provide insufficient potency; 2) high vapor pressures of smaller molecules do not permit the use of variable bypass vaporizers; 3) greater hydrogenation enhances flammability, and complete hydrogenation decreases potency; 4) internal hydrogenation decreases stability; and 5) greater hydrogenation increases blood solubility.

larger than four carbons have insufficient potency and that complete fluorination could eliminate any anesthetic effect (4).

Thus, we focused our attention on partially and completely fluorinated methanes, ethanes, propanes, and butanes, also obtaining limited data on longer-chained alkanes. The present paper assesses the effect of molecular size, and the degree and distribution of hydrogenation on solubility, potency, vapor pressure, and physical stability.

Methods

We obtained fluorinated and unhalogenated methanes, ethanes, propanes, and butanes from Aldrich Chemical Co. (Milwaukee, WI), PCR Inc. (Gainesville, FL), and TDC Research Inc. (Blacksburg, VA). Purities were known for all but two compounds. Where known, all purities were >97% with an average >98.2 ± 0.8% (mean ± SD). The same sources also were used to obtain longer-chained alkanes. Using standard techniques, we determined: 1) vapor pressure at room temperature [taking the manufacturer's value when available,

otherwise applying techniques described previously (5)]; 2) solubilities at 37°C in saline, olive oil, n-tetradecane, and (in a subset of compounds) blood, with all determinations in quadruplicate (3); 3) minimum alveolar anesthetic concentration (MAC) in rats for compounds stable in soda lime, using inspired rather than end-tidal concentrations of drug with concentrations determined by gas chromatography or by oxygen difference using a Beckman E2 analyzer (6); and 4) stability in soda lime using a previously described technique (7,8). Anesthesia was defined by absence of movement in response to tail clamp or electrical stimulation (6) and the inspired alkane concentrations just permitting and preventing movements were averaged to give an estimate of MAC. Temperature (rectal) was maintained between 36.5 and 39.5°C.

For the purposes of the present study, we arbitrarily defined instability as degradation of more than 3% of parent compound per hour at 60°C in a flask having a gas space of 580 mL minus the volume occupied by 100 g of moist soda lime. Degradation was defined by the disappearance of parent compound from the flask as determined by gas chromatography. All determinations of stability were obtained in quadruplicate. Potency data for perfluorinated compounds were taken from another report (4), as were potency and solubility data for unhalogenated n-alkanes (5,9). For perfluorinated alkanes and for $CF_3CF_2CFH_2$, $CF_3CF_2CH_3$, and $CF_2H(CF_2)_2CF_3$, anesthetic potency was determined by studies of additivity with desflurane. That is, we measured the decrease in desflurane MAC produced by the presence of the fluorinated compounds; in each rat, MAC of desflurane was tested approximately 1 wk before the test of additivity. The partial pressures of the test compounds applied in these studies equaled 0.5 atm of $CF_3CF_2CFH_2$, 0.5 atm of $CF_3CF_2CH_3$, and 0.77 atm of $CF_2H(CF_2)_2CF_3$.

In a subset of rats (two to four rats per compound), we compared the arrhythmogenicity of the test compounds with that of halothane (determined on a separate day in the same rats). All determinations were made at 1 atm. We defined arrhythmogenicity as the intravenously administered, bolus dose of epinephrine required to produce three or more premature ventricular contractions in 1 min (10).

All work in rats was approved by our institutional Committee on Animal Research. No rat was used for more than one study although rats were studied on two occasions for the determinations of arrhythmogenicity and additivity (see above). Similarly, the work with human blood was approved by our institutional Committee on Human Research. Blood (30 mL) was obtained from normal adult fasting patients before institution of anesthesia.

Results

Although all partially fluorinated or unfluorinated methanes, ethanes, propanes, and butanes produced anesthesia, some did so only under hyperbaric conditions (Table 1). In this series, greater chain length and partial hydrogenation provided greater potency and, as predicted by Meyer (11) and Overton (12), potency correlated with lipid solubility (Figure 1). Indeed, excluding three compounds [$CF_3CF_2CFH_2$, $CF_3CF_2CH_3$, and $CF_2H(CF_2)_2CF_3$], for the 24 partially hydrogenated fluorinated alkanes plus perfluoromethane for which MAC was determined, the product of MAC (for rats, in atmospheres) times the olive oil/gas partition coefficient equaled 2.01 ± 0.89 (mean ± SD), a value similar to that of 1.82 ± 0.56 obtained with conventional anesthetics (13). For the same group of compounds, the product of MAC and n-tetradecane (a solvent less polar than olive oil) equaled 1.12 ± 0.76, giving a variability not appreciably different from that obtained with olive oil.

In the studies requiring a determination of potency by additivity, the partial pressures of 0.5 atm of $CF_3CF_2CFH_2$ decreased desflurane MAC by 21%; 0.5 atm of $CF_3CF_2CH_3$ decreased desflurane MAC by 10%; and 0.77 atm of $CF_2H(CF_2)_2CF_3$ decreased desflurane MAC by 23%. The MAC values for the test compounds were derived by dividing the fractional percentage decrease into the applied partial pressure of the test compound. [E.g., 0.77/0.23 gave a MAC of 3.35 atm for $CF_2H(CF_2)_2CF_3$. The values thus obtained are given in Table 1.]

For the methane through butane series, partial hydrogenation, particularly hydrogenation spread over the entire molecule (Table 1), produced the greatest solubility in saline, blood (Table 2), and oil; the greatest potency (Figures 2 and 3); and the lowest vapor pressure (Table 1). The ranges of solubility in saline were considerable, the most soluble compound ($CFH_2CH_2CHF_2$) having a saline/gas partition coefficient (9.2) that was 70,600 times greater than the value (0.000136) for the least soluble compound [$CF_3(CF_2)_2CF_3$]. Determination of the solubilities of the least soluble compounds were most difficult and required great care. Even the slightest contamination with undissolved gas easily compromised the measurement.

Solubility in blood correlated more closely with solubility in saline than solubility in oil (Figure 4, Table 2). The importance of saline can be seen if we imagine that blood consists of a mixture of saline and oil. The results for solubility would indicate that saline contributed 97%–99% of the total composition.

Most compounds resisted degradation by soda lime. Table 3 lists decomposition rates for unstable compounds in the methane through butane series. These

Table 1. Solubilities, Potencies, and Vapor Pressures for Methanes, Ethanes, Propanes, and Butanes

No.	Alkane	Partition coefficients			MAC (atm)	VP (atm)
		Saline/gas	Tetradecane/gas	Oil/gas		
1	CF_4	0.0041 ± 0.0001	ND	0.052 ± 0.002	66.5 ± 13.4 (30)	★[a]
2	CF_3H	0.207 ± 0.003	ND	0.81 ± 0.02	1.6 ± 0.0 (5)	44.2†
3	CF_2H_2	1.08 ± 0.03	ND	2.24 ± 0.03	0.72 ± 0.05 (5)	13.6†
4	CFH_3	1.06 ± 0.02	ND	1.81 ± 0.03	1.03 ± 0.00 (5)	37.5†
5	CH_4	0.0244 ± 0.0001	ND	0.30 ± 0.00	9.90 ± 1.29 (5)	★[a]
6	CF_3CF_3	$135 \pm 6 \cdot 10^{-5}$	0.53 ± 0.01	0.146 ± 0.006	NA	31.6[b]
7	CF_3CF_2H	0.055 ± 0.001	0.96 ± 0.02	1.52 ± 0.01	1.51 ± 0.00 (5)	12.5[b]
8	CF_3CFH_2	0.230 ± 0.004	1.64 ± 0.02	3.02 ± 0.02	0.56 ± 0.06 (6)	9.85
9	CF_2HCF_2H	0.66 ± 0.04	1.97 ± 0.04	4.71 ± 0.18	0.239 ± 0.001 (4)	5.29
10	CF_2HCFH_2	2.49 ± 0.07	3.43 ± 0.08	8.55 ± 0.09	0.115 (2)	2.36
11	CF_3CH_3	0.0988 ± 0.0006	1.47 ± 0.02	1.59 ± 0.02	1.76 (2)	18.2[b]
12	CF_2HCH_3	0.781 ± 0.031	3.02 ± 0.07	4.34 ± 0.012	0.329 ± 0.000 (3)	5.96
13	CFH_2CH_3	0.93 ± 0.02	4.86 ± 0.07	4.91 ± 0.07	0.244 ± 0.000 (4)	6.45
14	CH_3CH_3	0.0254 ± 0.0006	1.66 ± 0.03	1.62 ± 0.04	1.46 ± 0.09 (5)	38.2
15	$CF_3CF_2CF_3$	$674 \pm 40 \cdot 10^{-6}$	0.633 ± 0.012	0.208 ± 0.005	NA	8.75
16	$CF_3CF_2CF_2H$	0.0144 ± 0.0005	ND	2.29 ± 0.04	1.84 ± 0.03 (3)	4.89
17	CF_3CFHCF_3	0.0215 ± 0.0005	ND	2.77 ± 0.14	0.95 ± 0.10 (5)	5.78[b]
18	$CF_2HCF_2CF_2H$	0.32 ± 0.02	4.41 ± 0.12	10.2 ± 0.4	0.146 ± 0.031 (3)	4.34
19	CF_3CFHCF_2H	0.230 ± 0.002	3.82 ± 0.15	8.79 ± 0.18	0.115 (2)	2.09
20	$CF_3CH_2CF_3$	0.070 ± 0.000	2.64 ± 0.13	5.09 ± 0.05	0.56 ± 0.03 (4)	2.91
21	$CF_3CF_2CFH_2$	0.0629 ± 0.0025	ND	4.20 ± 0.05	2.41 (2)	5.95[b]
22	$CF_3CF_2CH_3$	0.0216 ± 0.0007	ND	2.38 ± 0.05	5.55 (2)	ND
23	$CF_3CH_2CH_3$	4.64 ± 0.61	7.45 ± 0.12	15.4 ± 4.6	ND	1.82
24	$CH_3CF_2CH_3$	0.340 ± 0.004	7.69 ± 0.18	8.99 ± 0.012	0.30 ± 0.00 (4)	2.59
25	$CFH_2CH_2CFH_2$	9.20 ± 0.23	25.1 ± 0.5	47.3 ± 1.9	ND	0.462
26	CH_3CFHCH_3	0.70 ± 0.02	11.5 ± 0.3	11.3 ± 0.3	0.202 ± 0.000 (4)	2.63
27	$CH_3CH_2CH_3$	0.0221 ± 0.0010	ND	5.30 ± 0.15	0.94 ± 0.12 (5)	8.50
28	$CF_3(CF_2)_2CF_3$	$136 \pm 3 \cdot 10^{-6}$	1.25 ± 0.01	0.437 ± 0.007	NA	2.57
29	$CF_2H(CF_2)_2CF_3$	0.0052 ± 0.0003	3.34 ± 0.06	4.12 ± 0.09	3.36 ± 0.54 (6)	1.58
30	$CF_3(CFH)_2CF_3$	0.130 ± 0.005	7.05 ± 0.07	21.8 ± 0.4	ND	0.616
31	$CF_2H(CF_2)_2CF_2H$	0.158 ± 0.001	11.3 ± 0.2	30.4 ± 0.8	0.058 ± 0.016 (8)	0.418
32	$CF_3CF_2CFHCF_2H$	0.0594 ± 0.0005	6.18 ± 0.07	11.4 ± 0.2	ND	0.658
33	$CF_2H(CFH)_2CF_2H$	4.03 ± 0.18	24.3 ± 0.5	74.9 ± 3.4	0.013 ± 0.003 (4)	0.191
34	$CF_2HCH_2CFHCF_2H$	5.86 ± 0.33	32.2 ± 0.8	133 ± 8	0.0196 (2)	0.120
35	$CH_3(CH_2)_2CH_3$	0.0178 ± 0.0004	ND	19.3 ± 0.2	0.29 ± 0.03 (4)	2.12

Compounds are listed in four groups defined by carbon chain length. Within each group compounds are listed in order of increasing hydrogenation. Potency data for perfluorinated compounds were taken from another report (4), as were potency and solubility data for unhalogenated n-alkanes (5,9). Values are expressed as the mean $\pm$ SD.

MAC = minimum alveolar anesthetic concentration; VP = vapor pressure; ND = not determined; NA = not anesthetic. For MAC, numbers in parentheses indicate the number of rats studied.

[a] Above the critical temperature.

[b] Taken from commercial sources.

results also explain why the potencies of some of the compounds listed in Table 1 were not determined: they degraded too rapidly to study in a rebreathing circuit and were too expensive to use in a nonrebreathing circuit.

Arrhythmogenicity was studied for Compounds 6, 7, 9, 10, 12, 13, 15, 18, 19, 20, 28, 29, 33, and 34 (Table 1). All sensitized the heart at least to the same extent as did halothane. Compounds 7, 28, 33, and 34 produced greater sensitization. $CF_2H(CF_2)_2CF_3$ produced premature ventricular contractions in the absence of epinephrine injection. No obvious molecular pattern (Table 1) that would explain arrhythmogenicity emerges from an examination of these compounds.

Only a few compounds having chain lengths greater than four carbons were available to us. Most of these did not produce anesthesia at the partial pressures we were able to apply with the limited quantities of drug available to us. The physical and other properties that were found (Table 4) were consistent with those that might be predicted from the methane through butane series.

Discussion

Previous reports supply potency data for some of the fluorinated compounds examined in the present investigation. Using the righting reflex, Robbins (14) found

that CF_3CH_3 produced anesthesia at 0.5–0.6 atm, 30%–35% of our value of 1.7 atm. He also found that 0.11 atm of $CF_3CH_2CF_3$ was anesthetic, whereas we obtained a value fivefold greater. A modest portion of the difference between our results and those of Robbins probably is a consequence of the choice of different endpoints. A noxious stimulus usually requires a greater anesthetic partial pressure to provide anesthesia than does the righting reflex (15). Perhaps a greater portion results from the care we took in experimental design (e.g., ensuring that each animal's temperature was maintained at normal levels). Our results confirm those of Burns et al. (16) for $CF_2HCF_2CF_2H$ and $CF_2H(CF_2)_2CF_2H$. The same group failed to find an anesthetic effect of CF_3CF_2H, but limited their application to 0.93 atm (17). This group assessed anesthesia

in various ways, including "pinching the tail." Van Poznak and Artusio (18) did not obtain anesthesia with 0.8 atm CF_3H, but found that 0.50 atm CH_3CF_2H gave "light surgical anesthesia." Miller et al. (19) reference von Oettenger as finding anesthesia with 0.14 atm CFH_3 and 0.5 atm CF_2HCH_3 (Von Oettinger, WF. The halogenated hydrocarbons, toxicity and potential dangers. Public Health Service Publication 414. Washington DC: US Government Printing Office, 1955). The second but not the first value is similar to the value we obtained. Larsen (20) cites the preceding and other reports concerning these fluorinated alkanes.
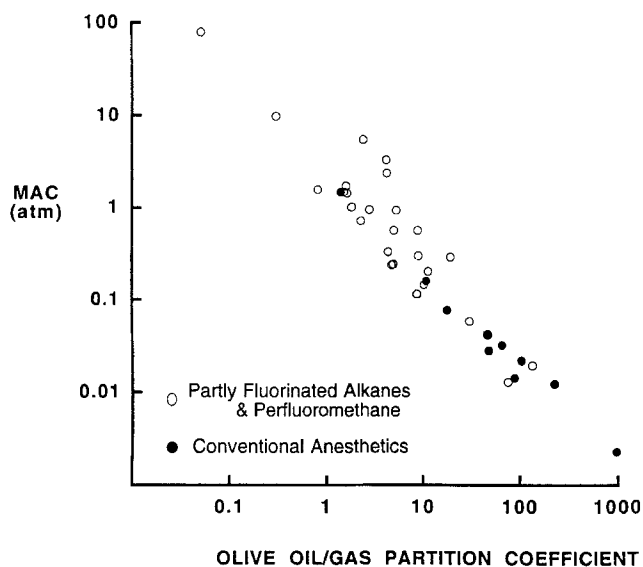

OLIVE OIL/GAS PARTITION COEFFICIENT

Figure 1. The anesthetic alkanes described in Table 1 had lipophilicities (oil/gas partition coefficient) that correlated with their potencies as defined by minimum alveolar anesthetic concentration (MAC) in atmospheres. This correlation (open circles) overlaps that for conventional anesthetics [closed circles; e.g., see Taheri et al. (13)].

NUMBER OF HYDROGENS

Figure 2. If hydrogenation is distributed evenly over the carbon skeleton, the addition of hydrogens to a perfluorinated alkane increases potency (as defined by minimum alveolar anesthetic concentration [MAC]) until the number of hydrogens exceeds the number of fluorines. Data are shown only for the one- and two-carbon series because insufficient data exist for the three- and four-carbon series. However, the less complete data available for the longer series are consistent with this portrayal.

Table 2. Blood/Gas Partition Coefficients

		Partition coefficients		
No.[a]	Alkane	Blood/gas	Saline/gas	Oil/gas
1	CF_3CF_2H	0.079 ± 0.002	0.0041 ± 0.0001	0.052 ± 0.002
8	CF_3CFH_2	0.56 ± 0.06	0.230 ± 0.004	3.02 ± 0.02
9	CF_2HCF_2H	0.76 ± 0.02	0.66 ± 0.04	4.71 ± 0.18
10	CF_2HCFH_2	2.61 ± 0.04	2.49 ± 0.07	8.55 ± 0.09
18	$CF_2HCF_2CF_2H$	0.330 ± 0.007	0.32 ± 0.02	10.2 ± 0.4
25	$CFH_2CH_2CFH_2$	9.31 ± 0.16	9.20 ± 0.23	47.3 ± 1.9
29	$CF_2H(CF_2)_2CF_3$	0.030 ± 0.002	0.0052 ± 0.0003	4.12 ± 0.09
30	$CF_3(CFH)_2CF_3$	0.26 ± 0.01	0.130 ± 0.005	21.8 ± 0.4
31	$CF_2H(CF_2)_2CF_2H$	0.44 ± 0.002	0.158 ± 0.001	30.4 ± 0.8
34	$CF_2HCH_2CFHCF_2H$	7.33 ± 0.39	5.86 ± 0.33	133 ± 8

Values are expressed as the mean ± SD. Values for saline/gas and oil/gas partition coefficients are the same as those in Table 1.
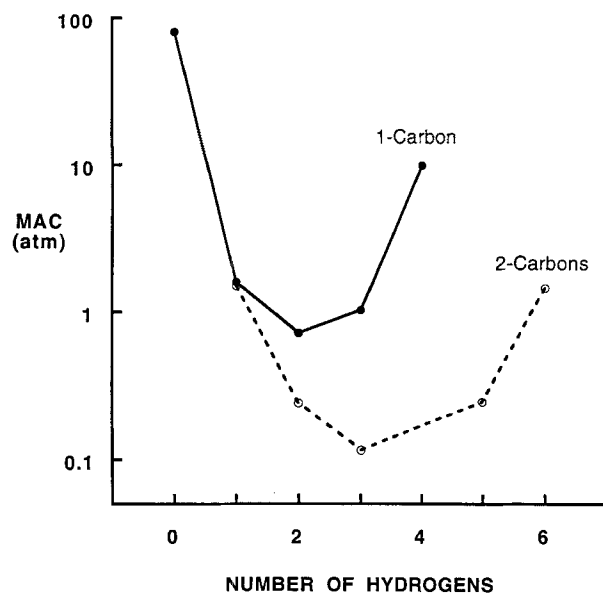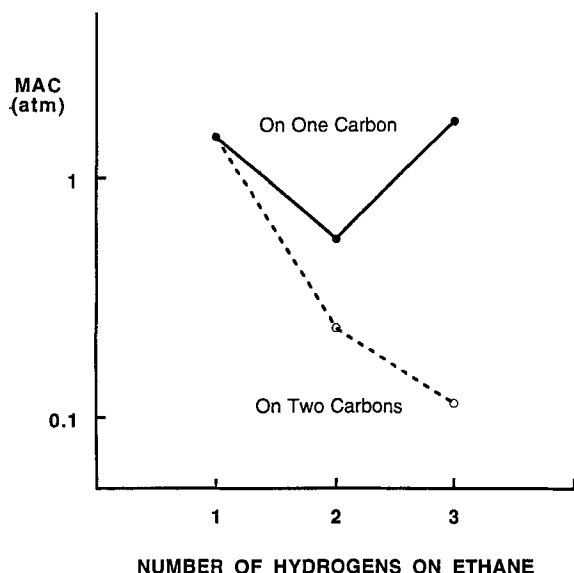[a] See Table 1 for association with other physical variables.

Figure 3. Increasing the number of hydrogen atoms on a single carbon is relatively ineffective in increasing potency (determined by minimum alveolar anesthetic concentration [MAC]). In contrast, the addition of hydrogens over the entire molecule may produce a 10-fold increase in potency as indicated in this figure.
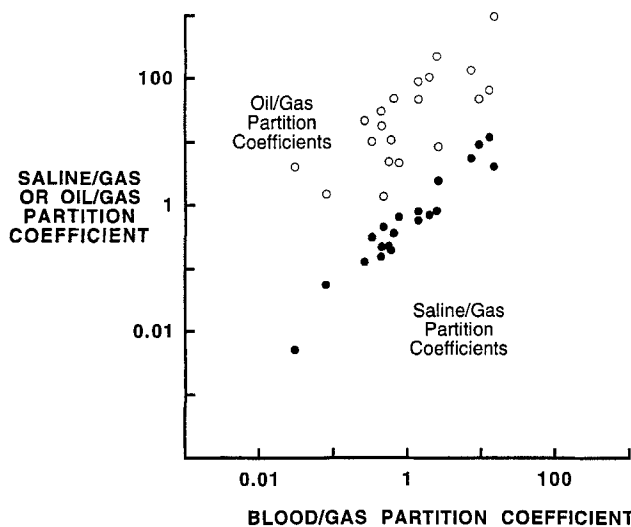

Figure 4. The saline/gas partition coefficient (●) correlates closely (adjusted r^2 = 0.961) with the blood/gas partition coefficient (least squares linear regression). The oil/gas partition coefficient (○) correlates less well (r^2 = 0.455).

Our results confirm most of the values given in the preceding paragraph, differences perhaps resulting from different end-points (e.g., some previous work assessed potency by the concentration required to abolish the righting reflex), from technical problems (some studies could not apply sufficient partial pressures because of the lack of hyperbaric facilities), or from differences in control of physiologic variables (e.g., other investigators often neither controlled nor measured body temperature). Some investigators estimated

Table 3. Fluorinated Alkanes Having a Degradation Rate in Soda Lime Greater Than 3%/Hour

Alkane	Degradation rate (%/h)
CF_3CFHCF_2H	21.9 ± 0.5
$CF_3CH_2CF_3$	29.1 ± 2.7
$CF_3CH_2CH_3$	Too rapid to measure
$CF_3(CFH)_2CF_3$	60.6 ± 0.8
$CF_3CF_2CFHCF_2H$	89.1 ± 1.2
$CF_2H(CFH)_2CF_2H$	15.5 ± 1.1
$CF_2HCH_2CFHCF_2H$	20.8 ± 0.6

Most of the fluorinated compounds in Table 1 resisted degradation by soda lime, having degradation rates of less than 3%/h at 60°C. Indeed, except for the compounds listed in this table the median degradation rate was less than 0.4%/h. Values are expressed as the mean ± SD.

rather than measured the partial pressures of anesthetic that was applied. One of the strengths of the present work is the use of a consistent end-point and the precision with which anesthetic concentrations were measured.

We did not have access to some compounds tested previously. Robbins (14) found that 0.05 atm of $CF_3CH_2CF_2CH_3$, 0.2 atm of $CH_3CF_2CF_2CH_3$, and 0.06 atm of $CH_3CF_2CH_2CH_3$ produced anesthesia in mice. He also found that 0.5 atm of $CF_3CH_2CH_3$ provided anesthesia in mice; we did not attempt to confirm this value because of the rapid destruction of $CF_3CH_2CH_3$ by soda lime (Table 3). Unfortunately, solubility data are not available for the other compounds studied by Robbins, and, as indicated above, the anesthetic potency reported by Robbins for other compounds differed from (was less than) that which we found by a factor of 3–5. Similarly, Bagnall et al. (21) found that $CF_2HCF_2CFH_2$ provided anesthesia in mice at 0.10 atm (lethal partial pressure 0.24 atm), and $CF_2HCF_2CH_3$ was anesthetic at 0.3–0.4 atm. In a separate study of fluorinated butanes, Bagnall et al. (22) found that $CH_3CF_2CH_2CH_3$ produced anesthesia at about 0.08 atm but also produced lung damage. $CF_3CFHCF_2CFH_2$ gave anesthesia at 0.045 atm.

Most of our results for methanes through butanes support the Meyer-Overton hypothesis (Figure 1) (11,12). Data from conventional anesthetics (Figure 1, closed circles) follow a similar relationship [e.g., see Taheri et al. (13)]. The Meyer-Overton hypothesis indicates the importance of lipophilicity (defined in the present study either by the olive oil/gas partition coefficient or the n-tetradecane/gas partition coefficient, Table 1) to anesthetic potency. The data in Table 1 suggest that several factors influence lipophilicity and potency. For a given number of hydrogens, increasing chain length increases lipophilicity (Table 1, Figure 5), a finding reported in other series of compounds such as the n-alkanes (5,23). However, increasing chain length does not clearly correlate with potency. CF_4 is

Table 4. Solubilities, Potencies, and Vapor Pressures for Pentanes, Hexanes, and Heptanes

No.	Alkane	Partition coefficients		MAC (atm)	VP (atm)
		Saline/gas	Oil/gas		
36	$CF_3(CF_2)_3CF_3$	$231 \pm 83\cdot10^{-7}$	0.662 ± 0.028	NA	0.80
37	$CF_2H(CF_2)_3CF_3$	0.207 ± 0.003	7.08 ± 0.38	>0.35 (2)	0.43
38	$(CF_3)_2CFHCF_2H$	0.018 ± 0.02	16.1 ± 0.7	ND	0.33
39	$CF_2H(CF_2)_3CFH_2$	0.203 ± 0.003	87.2 ± 3.7	>0.037 (1)	0.11
40	$CH_3(CH_2)_3CH_3$	0.0147 ± 0.0006	59.3 ± 2.1	0.127 ± 0.006 (5)	0.62
41	$CF_3(CF_2)_4CF_3$	ND^a	1.25 ± 0.04	NA	0.26
42	$CF_2H(CF_2)_4CF_3$	$157 \pm 7\cdot10^{-5}$	12.0 ± 0.4	>0.15 (2)	0.18
43	$CF_2H(CF_2)_3CF_2H$	0.0094 ± 0.0002	106 ± 6	NA	0.057
44	$CH_3(CH_2)_4CH_3$	0.0093 ± 0.0002	148 ± 7	0.0467 ± 0.0055 (4)	0.162
45	$CF_3(CF_2)_5CF_3$	ND^a	2.36 ± 0.13	NA	0.098
46	$CF_2H(CF_2)_5CF_3$	$363 \pm 84\cdot10^{-6}$	17.8 ± 0.2	NA	0.055
47	$CH_3(CH_2)_5CH_3$	0.0081 ± 0.0005	461 ± 8	0.0198 ± 0.0017 (4)	4.34

Compounds are listed in three groups defined by carbon chain length. Within each group compounds are listed in order of increasing hydrogenation. Potency data for perfluorinated compounds were taken from another report (4), as were potency and solubility data for unhalogenated n-alkanes (5,9). Values are expressed as the mean $\pm$ SD.

MAC = minimum alveolar anesthetic concentration; VP = vapor pressure; NA = not anesthetic; ND = not determined. For MAC, numbers in parentheses indicate the number of rats studied.

^{a} Not determined because the extremely low solubility precluded accurate results.
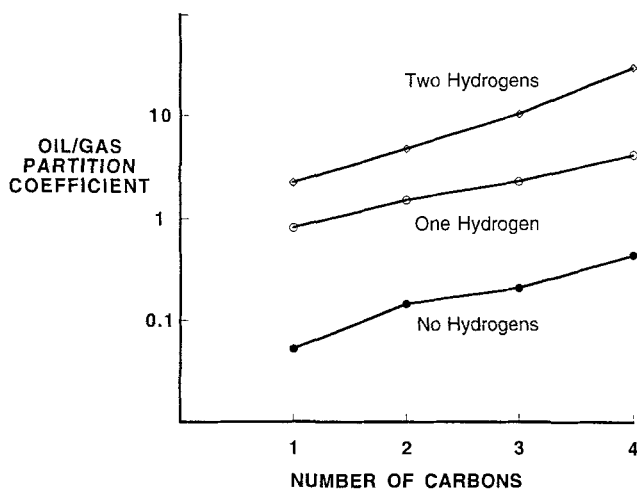

Figure 5. For a given number of hydrogens, an increase in alkane chain length correlates directly with the oil/gas partition coefficient.

Figure 6. The relationship between anesthetic potency (minimum alveolar anesthetic concentration [MAC]) and alkane chain length is complex. In the absence of hydrogenation (complete fluorination) an increase in chain length decreases potency, with no compound other than CF_4 having an anesthetic effect. With a single hydrogen, potency seems little affected by chain length. Further increases in chain length are associated with decreasing potency (data not shown). For methane through butane and dual hydrogenation, potency increases with increasing chain length. This trend, however, is not sustained, and at six carbons (data not shown) anesthetic effect is lost.

anesthetic (Figure 6), but larger perfluorinated compounds are not (4). For compounds having one hydrogen, increasing carbon chain length seems to have little effect on potency, at least for methane through butane, with a measurable *decrease* in potency for butane and perhaps propane (Figure 6, Table 1). Larger, singly hydrogenated compounds have little or no anesthetic effect (Table 4). For alkanes having two hydrogens on opposite terminal carbons, potency appears to increase progressively with increasing chain length (Figure 6, Table 1). However, 1H,6H-perfluorohexane appears to be devoid of an anesthetic effect (Table 4).

In the methane to butane series, partial hydrogenation maximizes potency, whereas total hydrogenation or total halogenation decreases potency (Figure 2, Table
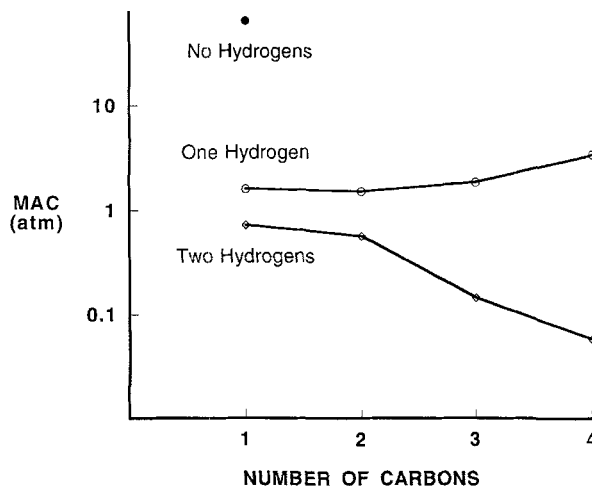
1). Increasing hydrogenation distributed over several carbons (rather than concentrated on one carbon) tends to increase potency until the number of hydrogens exceeds the number of fluorines (Table 1). The sequential addition of hydrogens to one carbon is less effective in increasing potency than distributing the hydrogens across several carbons (Figure 3, Table 1). Indeed, increasing the number of hydrogens on a single carbon may have no effect on potency (Figure 3) or may decrease potency (e.g., compare the potencies of
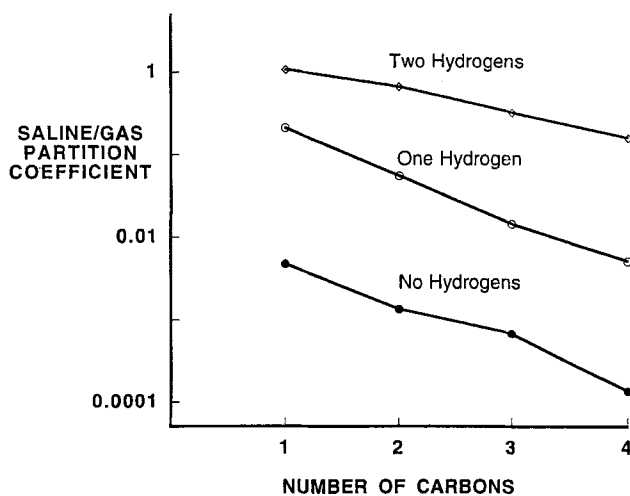
Figure 7. For a given number of hydrogens, an increase in alkane chain length correlates inversely with the saline/gas partition coefficient.

$CF_3CF_2CF_2H$, $CF_3CF_2CFH_2$, and $CF_3CF_2CH_3$; Table 1). Thus, from this and the preceding paragraph one may conclude that optimum (maximum) potency accrues to an even balance of fluorination and hydrogenation with hydrogenation balanced across carbons and to a chain length perhaps limited to three or four carbons. The point about hydrogenation and potency ignores the issue of solubility.

In contrast to potency, solubility in saline and thus in blood (Figure 4, Table 2) is lowest (optimal for more precise control over anesthetic maintenance and for rapidity of recovery from anesthesia) with complete halogenation or hydrogenation. However, the former produces impotent compounds and the latter produces flammable compounds, an unacceptable result for modern anesthetics. Increasing chain length correlates closely with decreasing solubility in saline (Figure 7, Table 1). Thus one may conclude that hydrogenation must be limited to two or three hydrogens spread across at least two carbons in order to achieve adequate potency while limiting the risk of flammability.

Compounds degraded by soda lime share certain characteristics (Table 3). All have hydrogens on internal carbons. Compounds lacking a fluorine on the carbon having a hydrogen and compounds having the hydrogens asymmetrically placed appear to be more susceptible to degradation.

Combining these observations with the observations on potency and solubility in the preceding paragraphs leads to the conclusion that the "best" anesthetic would have two or three hydrogens on two carbons with an otherwise fluorinated carbon skeleton having a chain length of three or four carbons. A longer chain length not only increases potency, it adds to the proportion of halogens and thereby decreases flammability. A still longer chain length may decrease potency. A chain

length of three or four carbons also is important to limit the vapor pressure (see Table 1) and allow the use of standard variable-bypass vaporizers. In addition, it appears that all alkanes promote arrhythmogenicity, and a new and more ideal anesthetic may require an ether linkage or some other alteration to avoid this problem. Consonant with these premises, the structures of two new anesthetics, sevoflurane and desflurane, consist of three or four carbons with two or three hydrogens on no more than two carbons, and an ether linkage.

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