

Polyhalogenated Methyl Ethyl Ethers: Solubilities and Anesthetic Properties

Donald D. Koblin, PhD, MD*, Michael J. Laster, DVM†, Pompiliu Ionescu, MD‡, Diane Gong, BS†, Edmond I Eger II, MD‡, Michael J. Halsey, D Phil‡, and Tomas Hudlicky, PhD§

Departments of Anesthesia, *Veteran's Administration Hospital, San Francisco, California, and †University of California, San Francisco, California; ‡Nuffield Department of Anaesthetics, Oxford, England; and §Department of Chemistry, University of Florida, Gainesville, Florida

The several potent inhaled anesthetics released for clinical use in the past four decades have been halogenated ethers, and, with one exception, methyl ethyl ethers. In the present report, we detail some structural and physical properties associated with anesthetic potency in 27 polyhalogenated methyl ethyl ethers. We obtained new data for 22 compounds. We used response/nonresponse of rats to electrical stimulation of the tail as the anesthetic end point (i.e., we measured the minimum alveolar anesthetic concentration [MAC]). For compounds that did not produce anesthesia when given alone (they only produced excitation/convulsions), we studied MAC by additivity studies with desflurane. We obtained MAC values for 20 of 22 of the studied ethers, which gave products of $\text{MAC} \times \text{oil/gas partition coefficient}$ ranging from 1.27 to 18.8 atm, compared with a product of 1.82 ± 0.56 atm for conventional inhaled anesthetics. Despite solubilities in olive oil and application of partial pressures predicted by

the Meyer-Overton hypothesis to provide anesthesia, 2 of 22 ethers ($\text{CCIF}_2\text{OCCIFCF}_3$ and $\text{CCIF}_2\text{OCF}_2\text{CCIF}_2$) had no anesthetic (immobilizing) effect when given alone, did not decrease the anesthetic requirement for desflurane, and had excitatory properties when administered alone. As with other inhaled anesthetics, anesthetic potency seemed to correlate with both polar and nonpolar properties. These ethers, representing structural analogs of currently used clinical volatile anesthetics, may be useful in identifying and understanding the mechanisms by which inhaled anesthetics act. **Implications:** The several potent, inhaled, polyhalogenated methyl ethyl ether anesthetics released for clinical use in the past four decades seem to have specific useful characteristics that set them apart from other methyl ethyl ethers. Properties of this class of compounds have implications for the future development of anesthetics and the mechanisms by which they act.

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Of the five volatile anesthetics used in clinical practice, three are halogenated methyl ethyl ethers (enflurane [$\text{CF}_2\text{HOCCF}_2\text{CCIFH}$], isoflurane [$\text{CF}_2\text{HOCCIHCF}_3$], desflurane [$\text{CF}_2\text{HOCFHCF}_3$]), the fourth is a methyl isopropyl ether sevoflurane ($\text{CFH}_2\text{OCH}[\text{CF}_3]_2$), and the fifth, halothane (CF_3CHBrCl), is an alkane. These inhaled anesthetics reached the clinical arena after initial qualitative screening studies in mice showed favorable anesthetic properties (1,2) and follow-up quantitative studies in larger animals and clinical trials demonstrated favorable outcomes. Other halogenated methyl ethyl ethers (1,2) were set aside because they displayed apparently

unfavorable characteristics (e.g., they were only weakly anesthetic, produced excitation/convulsions, were flammable, degraded in the presence of strong base, and/or were difficult or dangerous to produce). Only a limited effort was made to define the physical and structural characteristics that produced the most useful compounds.

In the present study, we quantify the anesthetic potencies and solubilities of structural analogs of the clinically used methyl ethyl ethers to define properties that influence the anesthetic and excitatory effects of these anesthetics. We also sought structural analogs of clinically used volatile anesthetics that could be used as tools to test for putative sites of anesthetic action. We previously described lipid-soluble nonanesthetic (now nonimmobilizing) alkanes (3,4) that do not cause anesthesia (i.e., they do not produce immobility in an animal challenged with a noxious stimulus) when administered alone, and they do not decrease the required minimum alveolar anesthetic concentration

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Address correspondence to Edmond I Eger II, MD, Department of Anesthesia, University of California, San Francisco, CA 94143-0464.

Table 1. Source of Polyhalogenated Methyl Ethyl Ethers

Structural formula	Compound	Purity (%)	Source
C ₃ Cl ₂ F ₆ O	CClF ₂ OCClFCF ₃	>99	RCT
C ₃ Cl ₂ F ₆ O	CClF ₂ OCF ₂ CClF ₂	>98	TH
C ₃ Cl ₃ F ₅ O	CClF ₂ OCCl ₂ CF ₃	99.9	RCT
C ₃ Cl ₃ F ₅ O	CClF ₂ OCF ₂ CCl ₂ F	100	RCT
C ₃ Cl ₃ F ₅ O	CCl ₂ FOCF ₂ CClF ₂	99.6	TH
C ₃ ClF ₆ HO	CClF ₂ OCFHCFC ₃	>99	RCT
C ₃ ClF ₆ HO	CF ₂ HOCClFCF ₃	>99.8	RCT
C ₃ ClF ₆ HO	CF ₂ HOFC ₂ CClF ₂	>99	TH
C ₃ ClF ₅ H ₂ O	CClF ₂ OCH ₂ CF ₃	99.99	RCT
C ₃ ClF ₅ H ₂ O	CF ₂ HOCClHCF ₃	>99	Isoflurane
C ₃ ClF ₅ H ₂ O	CF ₂ HOFC ₂ CClFH	>99	Enflurane
C ₃ Cl ₂ F ₅ HO	CClF ₂ OCClHCF ₃	99.4	RCT
C ₃ Cl ₂ F ₅ HO	CF ₂ HOCCl ₂ CF ₃	99.5	RCT
C ₃ Cl ₂ F ₅ HO	CClF ₂ OCF ₂ CClFH	98.5	RCT
C ₃ Cl ₂ F ₅ HO	CF ₂ HOFC ₂ CFCl ₂	99.9	TH
C ₃ Cl ₂ F ₂ H ₄ O	CH ₃ OCF ₂ CHCl ₂	>99	Methoxyflurane
C ₃ F ₇ HO	CF ₂ HOFC ₂ CF ₃	>99	TH
C ₃ F ₇ HO	CF ₃ OCFHCFC ₃	>99	SynQuest
C ₃ F ₆ H ₂ O	CF ₂ HOFCFHCFC ₃	>99	Desflurane
C ₃ F ₅ H ₃ O	CF ₂ HOCH ₂ CF ₃	>97	PCR
C ₃ F ₅ H ₃ O	CFH ₂ OCFHCFC ₃	>99	Hoechst
C ₃ F ₅ H ₃ O	CFH ₂ OCF ₂ CF ₂ H	99.7	Anaquest
C ₃ ClF ₃ H ₄ O	CH ₂ OCF ₂ CClFH	97	PCR
C ₃ BrClF ₅ HO	CF ₂ HOFCBrClFC ₃	99.5	RCT
C ₃ BrClF ₅ HO	CF ₂ HOFC ₂ CBrcClF	>97	Anaquest
C ₃ BrF ₅ H ₂ O	CF ₂ HOFCBrHCF ₃	>99	I-537 (9)
C ₃ BrF ₃ H ₄ O	CH ₃ OCF ₂ CBrcFH	>98	RCT

RCT = synthesized by Dr. Ross C. Terrell, TH = synthesized by Dr. Tomas Hudlicky.

SynQuest Laboratories, Alachua, FL; PCR Incorporated, Gainesville, FL; Hoechst, Frankfurt, Germany; Anaquest, Liberty Corner, NJ.

(MAC) for conventional anesthetics. Our present results demonstrate that certain halogenated methyl ethyl ethers also lack anesthetic effects and disobey the Meyer-Overton hypothesis. Such nonimmobilizing methyl ethyl ethers should not produce the same effect as their clinical analogs at physiological/biochemical sites important for the production of anesthesia as defined by immobility.

Methods

With approval from the University of California San Francisco Committee on Animal Research, we studied the anesthetic properties of 22 polyhalogenated methyl ethyl ethers in adult specific pathogen-free Sprague-Dawley male rats (300–420 g). Each animal was caged individually and had continuous access to standard rat chow and tap water until studied. The sources and purities of the compounds are listed in Table 1.

Animals were prepared as in previous studies (4). Each rat had three pairs of subcutaneous stimulating electrodes secured to its tail, had a rectal temperature probe inserted, and was placed into an individual plastic cylinder. The plastic cylinders containing the

rats were placed into a closed system that allowed the administration of oxygen (typically maintained at 0.5–1.0 atm), administration and sampling of the test drug, circulation of gases with a fan to allow for removal of carbon dioxide (typically <0.01 atm) with soda lime, and monitoring of temperature (36.5–39.5°C). The closed system was either a 3.4-L clear plastic cylinder (4) capable of holding two rats, which was used when limited amounts of compound were available, or a closed system (3) that allowed concurrent testing of four rats and was used when there was less concern about the availability and/or expense of the drug.

Each methyl ethyl ether was tested alone (in the presence of 0.5–1.0 atm O₂) over a range of partial pressures. If the compound alone did not produce anesthesia [defined by an absence of motor response to electrical stimulation of the tail (5)], we performed additivity studies to define the ability of the anesthetic to decrease the MAC for desflurane. Control MAC values for desflurane were determined approximately 1 wk before additivity studies using a standard approach (4,5). MAC values for desflurane were then redetermined approximately 1 wk later in the presence of a constant concentration (predicted to be approximately 1 MAC by the Meyer-Overton rule) of the test methyl ethyl ether, allowing 20- to 30-min equilibrations for each change in desflurane concentration. Initially, desflurane was added to approximately 0.6 MAC (0.04–0.055 atm desflurane) and allowed to equilibrate 20–30 min before introduction of the experimental methyl ethyl ether. This background concentration of desflurane prevented the excitable/convulsive activity associated with the experimental methyl ethyl ethers of limited anesthetic potency. The anesthetic end point was the presence versus absence of purposeful movement of the rat in response to a 15-volt electrical stimulus (5). Chamber gas samples of desflurane and the concomitantly administered methyl ethyl ether were separated and quantified by gas chromatography (4).

MAC values for desflurane and the methyl ethyl ethers that produced anesthesia when administered alone were calculated for each animal as the average of the partial pressures that just permitted and just prevented movement. In the additivity studies, anesthetic potency was estimated by taking the ratio: (average desflurane MAC in the presence of the methyl ethyl ether)/(average control desflurane MAC in absence of the methyl ethyl ether), abbreviated as (MAC_{des + mee})/(MAC_{des}). A value of (MAC_{des + mee})/(MAC_{des}) ≥ 1 indicated an absence of any anesthetic effect of the polyhalogenated compound (i.e., such a compound was deemed to be a nonimmobilizer). If this ratio was <1, the MAC of the methyl ethyl ether (MAC_{mee}) was calculated by dividing 1 minus this ratio into the

Table 2. Anesthetic Potencies (MAC Values) of Methyl Ethyl Ethers

Structural formula	Compound	<i>n</i>	Control desflurane MAC _{des} (atm)	Experimental desflurane MAC _{des+mee} (atm)	PP _{mee} (atm)	MAC _{mee} (atm)
C ₃ Cl ₂ F ₆ O	CCIF ₂ OCCIFCF ₃	4	0.084 ± 0.000	0.082 ± 0.011	0.253 ± 0.004	No anesthesia
C ₃ Cl ₂ F ₆ O	CCIF ₂ OCF ₂ CCIF ₂	6	0.0752 ± 0.000	0.0707 ± 0.0076	0.181 ± 0.029	No anesthesia
C ₃ Cl ₃ F ₅ O	CCIF ₂ OCCl ₂ CF ₃	7	0.0799 ± 0.0056	0.0677 ± 0.0063	0.0202 ± 0.0016	0.132 ± 0.0413
C ₃ Cl ₃ F ₅ O	CCIF ₂ OCF ₂ CCl ₂ F	8	0.0718 ± 0.0042	0.0641 ± 0.0034	0.020 ± 0.0052	0.186 ± 0.0515
C ₃ Cl ₃ F ₅ O	CCl ₂ FOCF ₂ CCIF ₂	6	0.0785 ± 0.0045	0.0652 ± 0.0079	0.0308 ± 0.0033	0.182 ± 0.0315
C ₃ CIF ₆ HO	CCIF ₂ OCFHCF ₃	3				0.291 ± 0.024
C ₃ CIF ₆ HO	CF ₂ HOCCIFCF ₃	8	0.0758 ± 0.0031	0.0459 ± 0.0088	0.127 ± 0.0025	0.322 ± 0.0895
C ₃ CIF ₆ HO	CF ₂ HOCF ₂ CCIF ₂	2	0.0717 ± 0.0000	0.0550 ± 0.0000	0.140	0.604 ± 0.000
C ₃ CIF ₅ H ₂ O	CCIF ₂ OCH ₂ CF ₃	12	0.0726 ± 0.0063	0.0592 ± 0.0077	0.0542 ± 0.0060	0.287 ± 0.049
C ₃ CIF ₅ H ₂ O ^a	CF ₂ HOCCIHCF ₃					0.0145
C ₃ CIF ₅ H ₂ O ^a	CF ₂ HOCF ₂ CCIFH					0.022
C ₃ Cl ₂ F ₅ HO	CCIF ₂ OCCIHCF ₃	4				0.0486 ± 0.216
C ₃ Cl ₂ F ₅ HO	CF ₂ HOCCl ₂ CF ₃	2	0.0800 ± 0.0000	0.0527 ± 0.0000	0.0335 ± 0.0000	0.0982 ± 0.0000
C ₃ Cl ₂ F ₅ HO	CCIF ₂ OCF ₂ CCIFH	4				0.0300 ± 0.0038
C ₃ Cl ₂ F ₅ HO	CF ₂ HOCF ₂ CFCl ₂	4	0.0788 ± 0.0000	0.0565 ± 0.0084	0.0255 ± 0.0031	0.0901 ± 0.0134
C ₃ Cl ₂ F ₂ H ₄ O ^a	CH ₃ OCF ₂ CHCl ₂					0.0027
C ₃ F ₇ HO	CF ₂ HOCF ₂ CF ₃	2	0.0746 ± 0.0066	0.0701 ± 0.0000	0.319 ± 0.000	5.64 ± 8.31
C ₃ F ₇ HO	CF ₃ OCFHCF ₃	2				1.96 ± 0.00
C ₃ F ₆ H ₂ O ^b	CF ₂ HOCFHCF ₃					0.072–0.084
C ₃ F ₅ H ₃ O	CF ₂ HOCH ₂ CF ₃	4				0.1102 ± 0.0076
C ₃ F ₅ H ₃ O	CFH ₂ OCFHCF ₃	4				0.0464 ± 0.0055
C ₃ F ₅ H ₃ O	CFH ₂ OCF ₂ CF ₂ H	4				0.0421 ± 0.0000
C ₃ CIF ₃ H ₄ O	CH ₃ OCF ₂ CCIFH	4				0.0159 ± 0.0041
C ₃ BrCIF ₃ HO	CF ₂ HOCBrClCF ₃	4	0.0800 ± 0.0038	0.0369 ± 0.0000	0.0081 ± 0.0000	0.0151 ± 0.0006
C ₃ BrCIF ₃ HO	CF ₂ HOCF ₂ CBrCIF	3				0.0150 ± 0.0009
C ₃ BrF ₅ H ₂ O ^a	CF ₂ HOCBrHCF ₃					0.0052
C ₃ BrF ₃ H ₄ O	CH ₃ OCF ₂ CBrFH	4				0.0069 ± 0.0016

Experimental values are expressed as means ± SD.

MAC = minimum alveolar anesthetic concentration, MAC_{des} = MAC value desflurane, MAC_{des+mee} = MAC value for desflurane with the methyl ethyl ether, PP_{mee} = partial pressure of the methyl ethyl ether during the additivity studies, MAC_{mee} = estimated MAC of the methyl ethyl ether assuming additivity with desflurane.

^aLiterature MAC values for isoflurane (CF₂HOCCIHCF₃) and enflurane (CF₂HOCF₂CCIFH) are taken from Reference 5; for methoxyflurane (CH₃OCF₂CHCl₂), from Reference 13; and for compound I-537 (CF₂HOCBrHCF₃), from Reference 9.

^bDesflurane MAC values are from the current study.

average partial pressure of the methyl ethyl ether (PP_{mee}) present during the additivity studies:

$$\text{MAC}_{\text{mee}} = \text{PP}_{\text{mee}} / (1 - [\text{MAC}_{\text{des}} + \text{mee}] / [\text{MAC}_{\text{des}}]).$$

The standard deviation associated with MAC_{mee} was estimated by multiplying MAC_{mee} by the square root of the sum of the squares of the ratios of the standard deviations of MAC_{des}, MAC_{des+mee}, and PP_{mee} divided by their respective mean values.

Partition coefficients of methyl ethyl ethers at 37°C in saline and olive oil, and vapor pressures at room temperature, were determined as described previously (3,4,6,7).

Results

We present data for 27 compounds: 22 are newly examined and the remaining 5 are known anesthetics with previously reported properties. Of the 22 newly examined compounds, 10 produced anesthesia when administered alone and 12 did not (Table 2). The 12 compounds that did not produce anesthesia when

administered alone caused excitation/convulsions when given at partial pressures near those predicted to be anesthetic by the Meyer-Overton rule. The quantitative excitatory effects of these methyl ethyl ethers are reported in a separate article (8), along with the convulsant properties of other inhaled anesthetics. Of the 10 new methyl ethyl ethers that were anesthetic when given alone, the most potent was CH₃OCF₂CBrFH (MAC 0.0069 atm), and the least potent was CF₃OCFHCF₃ (MAC 1.96 atm) (Table 2).

Control desflurane MAC values ranged from 0.072 to 0.084 atm (Table 2). Two completely halogenated compounds containing six fluorine atoms and two chlorine atoms (CCIF₂OCCIFCF₃, CCIF₂OCF₂CCIF₂) did not significantly lower the requirement for desflurane (Table 2) and are considered to be nonimmobilizers (3). Three other completely halogenated methyl ethyl ethers containing five fluorine atoms and three chlorine atoms (CCIF₂OCCl₂CF₃, CCIF₂OCF₂CCl₂F, and CCl₂FOCF₂CCIF₂) marginally decreased the desflurane requirement, as did an ether perfluorinated except for a

Table 3. Physical Properties of Methyl Ethyl Ethers

Structural formula	Compound	Vapor Pres (atm)	Agent MAC (atm)	Pred MAC (atm) ^a	Saline/Gas Part Coeff (37°C)	Oil/Gas Part Coeff (37°C)	MAC×O/G Part Coeff (atm)
C ₃ Cl ₂ F ₆ O	CClF ₂ OCClF ₂ CF ₃	0.42	NA	0.168	0.0023	10.8	NI
C ₃ Cl ₂ F ₆ O	CClF ₂ OCF ₂ CClF ₂	ND	NA	0.125	0.00212	14.6	NI
C ₃ Cl ₃ F ₅ O	CClF ₂ OCCl ₂ CF ₃	0.13	0.132	0.0221	0.0067	82.3	10.9
C ₃ Cl ₃ F ₅ O	CClF ₂ OCF ₂ CCl ₂ F	0.12	0.186	0.0183	0.00694	99.6	18.5
C ₃ Cl ₃ F ₅ O	CCl ₂ FOCF ₂ CClF ₂	0.412	0.182	0.018	0.0067	103	18.8
C ₃ ClF ₆ HO	CClF ₂ OCFHCF ₃	0.74	0.291	0.131	0.022	13.9	4.04
C ₃ ClF ₆ HO	CF ₂ HOCclF ₂ CF ₃	0.73	0.322	0.125	0.0253	14.6	4.70
C ₃ ClF ₆ HO	CF ₂ HOCF ₂ CClF ₂	ND	0.604	0.100	0.0241	18.3	11.1
C ₃ ClF ₅ H ₂ O	CClF ₂ OCH ₂ CF ₃	0.52	0.287	0.070	0.043	25.8	7.90
C ₃ ClF ₅ H ₂ O	CF ₂ HOCclHCF ₃	0.32	0.0145	0.021	0.544	88.2	1.28
C ₃ ClF ₅ H ₂ O	CF ₂ HOCF ₂ CClFH	0.23	0.022	0.018	0.738	103	2.27
C ₃ Cl ₂ F ₅ HO	CClF ₂ OCClHCF ₃	0.29	0.0486	0.0238	0.0519	76.5	3.72
C ₃ Cl ₂ F ₅ HO	CF ₂ HOCcl ₂ CF ₃	0.197	0.0982	0.0209	0.0754	87	8.54
C ₃ Cl ₂ F ₅ HO	CClF ₂ OCF ₂ CClFH	0.174	0.0300	0.0160	0.0734	114	3.42
C ₃ Cl ₂ F ₅ HO	CF ₂ HOCF ₂ CFCl ₂	0.19	0.0901	0.017	0.0851	110	9.88
C ₃ Cl ₂ F ₄ H ₂ O	CH ₃ OCF ₂ CHCl ₂	0.039	0.0027	0.0021	4.2	850	2.30
C ₃ F ₇ HO	CF ₂ HOCF ₂ CF ₃	ND	5.64	0.672	0.0072	2.71	15.5
C ₃ F ₇ HO	CF ₃ OCFHCF ₃	ND	1.96	1.02	0.0073	1.78	3.49
C ₃ F ₆ H ₂ O	CF ₂ HOCFHCF ₃	0.88	0.078	0.10	0.225	17.9	1.40
C ₃ F ₅ H ₃ O	CF ₂ HOCCH ₂ CF ₃	0.57	0.1102	0.0973	0.518	18.7	2.06
C ₃ F ₅ H ₃ O	CFH ₂ OCFHCF ₃	0.52	0.0464	0.066	0.99	27.6	1.28
C ₃ F ₅ H ₃ O	CFH ₂ OCF ₂ CF ₂ H	0.355	0.0421	0.048	1.46	37.7	1.59
C ₃ ClF ₃ H ₄ O	CH ₃ OCF ₂ CClFH	ND	0.0159	0.0102	1.771	178	2.83
C ₃ BrClF ₅ HO	CF ₂ HOCBrClCF ₃	0.109	0.0151	0.0074	0.137	245	3.70
C ₃ BrClF ₅ HO	CF ₂ HOCF ₂ CBrClF	0.164	0.0150	0.0048	0.137	378	5.67
C ₃ BrF ₅ H ₂ O	CF ₂ HOCBrHCF ₃	ND	0.0052	0.0074	ND	245	1.27
C ₃ BrF ₃ H ₄ O	CH ₃ OCF ₂ CBrFH	ND	0.0069	0.0050	2.44	363	2.51

For clarity, standard deviations of the partition coefficients (part coeff) are not included. Partition coefficients were typically obtained from four separate measurements and had coefficients of variation <5%.

NA = no anesthesia, NI = nonimmobilizer, ND = not determined, pres = pressure, pred = predicted.

^a Based on the assumption that minimum alveolar anesthetic concentration (MAC) × oil/gas (O/G) partition coefficient = 1.82 atm (6).

single hydrogen (CF₂HOCF₂CF₃) (Table 2). Although these ethers seemed to have an anesthetic effect, their potencies were at least 3.5 times less than that predicted by their oil/gas partition coefficients. Such anesthetics are called transitional compounds. Four other compounds (CF₃OCH₂CClF₂, CF₂HOCcl₂CF₃, CF₂HOCF₂CF₂Cl, and CF₂HOCF₂CFCl₂) are also transitional compounds. The remaining compounds contained at least one hydrogen atom and exhibited anesthetic properties predicted from their oil/gas partition coefficients (Tables 2 and 3). The MAC values for 17 of the 27 methyl ethyl ethers that remain after exclusion of the nonimmobilizer and transitional compounds correlated ($r^2 = 0.99$) with their oil/gas partition coefficients (Fig. 1).

CF₂HOCcl₂CF₃ was the only compound tested by additivity studies that demonstrated an acute toxicity: two of four animals died during the desflurane MAC determinations in the presence of 0.0335 atm CF₂HOCcl₂CF₃. When administered alone, CF₂HOCcl₂CF₃ did not induce convulsions or anesthesia but was lethal at partial pressures >0.06 atm. With rare exceptions, rats examined in the additivity studies

survived for 24 h after exposure to the test drug and desflurane.

Solubilities in oil and saline increased with substitution of Cl or Br for F atoms (Br > Cl) (Table 3). Oil/gas partition coefficients for the 22 methyl ethyl ethers varied over a range of approximately 200-fold, whereas saline/gas partition coefficients varied by nearly 1000-fold. Of the 22 test compounds, the non-immobilizers (CClF₂OCClF₂CF₃, CClF₂OCF₂CClF₂) were the least soluble in saline (Table 3). For 24 compounds (data for the saline/gas partition coefficient not available for one compound), the Meyer-Overton constant (the product of MAC and the oil/gas partition coefficient) correlated ($r^2 = 0.45$) inversely with their polarity, as reflected in the saline/gas partition coefficient (Fig. 2).

Discussion

As in our previous studies with completely halogenated alkanes (3), we found five completely halogenated methyl ethyl ethers to have no anesthetic effect

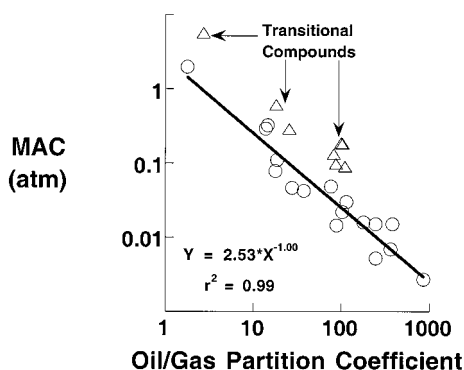


Figure 1. For 17 (O) of the 27 methyl ethyl ethers studied, anesthetic potency (minimum alveolar anesthetic concentration [MAC]) correlates ($r^2 = 0.99$) with the olive oil/gas partition coefficient (i.e., with nonpolarity). The correlation indicates that the product of MAC and the oil/gas partition coefficient varies little (the exponent for X in the equation is close to -1.00) for these compounds. A deviation occurs for 10 of the 27 compounds. Two of these do not produce anesthesia (are nonimmobilizers), whereas eight others (transitional compounds; Δ) produce anesthesia at partial pressures higher than would be predicted from their lipophilicity.

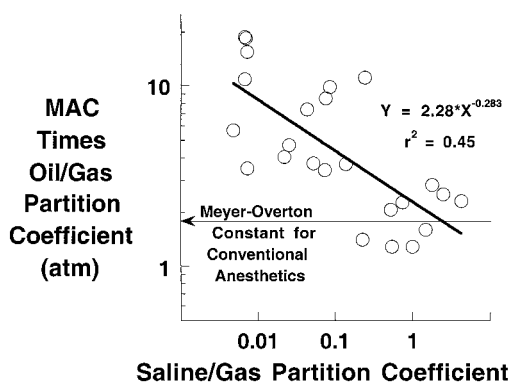


Figure 2. The Meyer-Overton constant (the product of the minimum alveolar anesthetic concentration [MAC] and the oil/gas partition coefficient) is, in fact, not constant. This is explained, in part, by an effect of polarity. Compounds with a lesser polarity (as suggested by a smaller saline/gas partition coefficient) are less potent than would be predicted by the Meyer-Overton hypothesis. These results support the notion that anesthetic potency as defined by MAC is a function of both the polar and nonpolar characteristics of a molecule.

when given by themselves, despite the administration of these compounds at partial pressures predicted to be anesthetic by the Meyer-Overton hypothesis (Tables 2 and 3) (4,6). Two of these, $\text{CClF}_2\text{OCClFCF}_3$ and $\text{CClF}_2\text{OCF}_2\text{CClF}_2$, produced no detectable decrease in the desflurane requirement (Table 2) at partial pressures of 0.253 atm and 0.181 atm, respectively. The products of the partial pressure at which these nonimmobilizers were tested and their oil/gas partition coefficients were 2.7 atm for $\text{CClF}_2\text{OCClFCF}_3$ and 2.6 atm for $\text{CClF}_2\text{OCF}_2\text{CClF}_2$. These values can be compared with the products of MAC (in rats) \times oil/gas partition coefficient for conventional anesthetics that obey the Meyer-Overton hypothesis. The products for conventional anesthetics provide a constant

(the Meyer-Overton constant) of 1.82 ± 0.56 atm (6). When $\text{CClF}_2\text{OCClFCF}_3$ and $\text{CClF}_2\text{OCF}_2\text{CClF}_2$ were given at partial pressures predicted to be approximately 1.5 MAC by the Meyer-Overton hypothesis (Table 3), there was no decrease in the MAC of desflurane (Table 2).

Substitution of a chlorine atom for a fluorine atom increased anesthetic potency. For example, although $\text{CClF}_2\text{OCClFCF}_3$ and $\text{CClF}_2\text{OCF}_2\text{CClF}_2$ did not measurably lower desflurane requirements, $\text{CClF}_2\text{OCCl}_2\text{CF}_3$, $\text{CClF}_2\text{OCF}_2\text{CCl}_2\text{F}$, and $\text{CCl}_2\text{FOCF}_2\text{CClF}_2$ decreased desflurane MAC by approximately 10%–15% (Table 2). Although these three perhalogenated compounds have anesthetic properties, they still markedly deviated from the Meyer-Overton hypothesis (Table 3). $\text{CClF}_2\text{OCCl}_2\text{CF}_3$, $\text{CClF}_2\text{OCF}_2\text{CCl}_2\text{F}$, and $\text{CCl}_2\text{FOCF}_2\text{CClF}_2$ have oil/gas partition coefficients between 82.3 and 103.2, similar to those of isoflurane and enflurane (7), yet the presence of 0.02–0.03 atm of these test drugs only marginally decreased the desflurane requirement (Table 2). Substitution of a hydrogen or a bromine atom for a chlorine atom further increased potency. Thus, $\text{CClF}_2\text{OCClHCF}_3$ is an anesthetic when given alone, but $\text{CClF}_2\text{OCClFCF}_3$ is a nonimmobilizer. The MAC of $\text{CHF}_2\text{OCCl}_2\text{CF}_3$ is 0.098 atm, whereas the MAC of $\text{CHF}_2\text{OCBrClCF}_3$ is 0.015 atm. These progressions in potency with the substitution of bromine or hydrogen for chlorine, and chlorine for fluorine, have been noted previously (9).

Most of the experimental methyl ethyl ethers that contain at least one hydrogen atom in their molecular structures have potencies and oil/gas partition coefficients consistent with the Meyer-Overton hypothesis. The products of MAC \times oil/gas partition coefficient lay within a threefold range of the predicted value of 1.82 atm (Table 3). That is, potency (MAC) correlated inversely with the oil/gas partition coefficient (Fig. 1), which suggests that an attraction to a nonpolar phase is a determinant of the potencies of these compounds.

However, several compounds provided exceptions to the correlation of potency and lipophilicity. These included $\text{CF}_2\text{HOCCl}_2\text{CF}_3$, $\text{CF}_2\text{HOCCl}_2\text{CF}_3$, $\text{CF}_2\text{HOCCl}_2\text{CF}_3$, and $\text{CF}_2\text{ClOCH}_2\text{CF}_3$ (the 485th compound in the series of >700 compounds synthesized by Ross Terrell in a search for a better anesthetic) (Table 3). For eight of the methyl ethyl ethers, including four that contained one or more hydrogen atoms, the Meyer-Overton constants were >3.5 times the predicted value of 1.82 atm (Fig. 1, Table 3). These deviations may be explained, in part, by the lower affinity of these compounds to an aqueous phase (a lower saline/gas partition coefficient). That is, it seems that an element of polarity, as well as nonpolarity, is an important determinant of the potency of methyl ethyl ethers (Fig. 2). These results are consistent with the argument that anesthesia, as defined by MAC, results from an action of molecules at a polar-nonpolar interface, such as a membrane surface (10–12).

Table 4. Previous Examinations of Polyhalogenated Methyl Ethyl Ethers

Structural formula	Compound	Behavioral effects	Species	Reference
C ₃ Cl ₂ F ₆ O	CCIF ₂ OCCIFCF ₃	No known previous testing		
C ₃ Cl ₂ F ₆ O	CCIF ₂ OCF ₂ CCIF ₂	Convulsions at 0.175 atm, toxic	Mouse	1
C ₃ Cl ₃ F ₅ O	CCIF ₂ OCCl ₂ CF ₃	Convulsions at 0.05 atm	Mouse	14
C ₃ Cl ₃ F ₅ O	CCIF ₂ OCF ₂ CCl ₂ F	Convulsions at 0.1 atm, toxic	Mouse	1
C ₃ CIF ₆ HO	CCIF ₂ OCFHCF ₃	No known previous testing		
C ₃ CIF ₆ HO	CF ₂ HOCCIFCF ₃	No known previous testing		
C ₃ CIF ₆ HO	CF ₂ HOCHF ₂ CCIF ₂	No known previous testing		
C ₃ CIF ₅ H ₂ O	CF ₃ OCH ₂ CCIF ₂	Convulsions at 0.06 atm Anesthetic (MAC) at 0.125 atm	Dog	7
C ₃ CIF ₅ H ₂ O	CF ₂ HOCCIHCFC ₃	Isoflurane		
C ₃ CIF ₅ H ₂ O	CF ₂ HOCHF ₂ CCIFH	Enflurane		
C ₃ Cl ₂ F ₅ HO	CCIF ₂ OCCIHCF ₃	Weak anesthetic at 0.05 atm	Mouse	1
C ₃ Cl ₂ F ₅ HO	CF ₂ HOCCl ₂ CF ₃	Anesthesia, twitching (concentration not stated)	Mouse	14
C ₃ Cl ₂ F ₅ HO	CCIF ₂ OCF ₂ CCIFH	Anesthetic with convulsions at 0.05 atm Rigidity, twitching, shivering (atm not stated)	Mouse Dog	1,15
C ₃ Cl ₂ F ₅ HO	CF ₂ HOCHF ₂ CFCl ₂	Anesthetic at 0.025 atm; convulsions at 0.05 atm	Mouse	1
C ₃ Cl ₂ F ₂ H ₄ O	CH ₃ OCF ₂ CHCl ₂	Methoxyflurane		
C ₃ F ₇ HO	CF ₃ OCFHCF ₃	No known previous testing		
C ₃ F ₇ HO	CF ₂ HCF ₂ CF ₃	No known previous testing		
C ₃ F ₆ H ₂ O	CF ₂ HOCHF ₂ CF ₃	Desflurane		
C ₃ F ₅ H ₃ O	CF ₂ HOCH ₂ CF ₃	Very weak anesthetic at 0.1 atm	Mouse	1
C ₃ F ₅ H ₃ O	CFH ₂ OCFHCF ₃	No known previous testing		
C ₃ F ₅ H ₃ O	CFH ₂ OCF ₂ CF ₂ H	Anesthetic at 0.08 atm	Mouse	1
C ₃ CIF ₃ H ₄ O	CH ₃ OCF ₂ CCIFH	Good surgical anesthesia (concentration not stated)	Dog	15
C ₃ BrCIF ₅ HO	CF ₂ HOCCBrCICF ₃	No known previous testing		
C ₃ BrCIF ₅ HO	CF ₂ HOCHF ₂ CBrCIF	No known previous testing		
C ₃ BrF ₅ H ₂ O	CF ₂ HOCCBrHCF ₃	I-537; anesthetic at 0.005 atm	Mouse	9
C ₃ BrF ₃ H ₄ O	CH ₃ OCF ₂ CBrFH	Excellent anesthetic at 0.025 atm	Mouse	15

MAC = minimum alveolar anesthetic concentration.

Using crude measurements of behavioral end points in either mice or dogs, previous investigations have examined 13 of the compounds tested in the present study (Table 4). We found that CCIF₂OCCl₂CF₃, CCIF₂OCF₂CCl₂F, CCIF₂OCF₂CCIF₂, and CCl₂FOCF₂CCIF₂ produced convulsions in rats, a result that agrees with previous results for mice (Table 4). For CCIF₂OCF₂CCIFH, we observed excitatory but not convulsive effects in rats, a finding that was consistent with previous observations in dogs but not in mice (Table 4). In previous studies, CCIF₂OCCIHCF₃, CF₂HOCH₂CF₃, CH₃OCF₂CCIFH, CFH₂OCF₂CF₂H, and CH₃OCF₂CBrFH were found to be anesthetic under nonequilibrated conditions (Table 4), and we found that these compounds, when administered alone, could produce anesthesia as defined by MAC (Table 2).

The determination of MAC for compounds that did not produce anesthesia by themselves required the assumption that the anesthetic effects of desflurane and the experimental methyl ethyl ether are additive. Although additivity is typical for conventional

inhaled anesthetics, our previous studies in dogs suggested that compound 485 (CF₂ClOCH₂CF₃), a structural isomer of isoflurane and enflurane, produced a non-linear decrease in the fraction of isoflurane MAC required to produce anesthesia in dogs (i.e., an antagonistic effect) (7). An antagonism between compound 485 and conventional anesthetics such as desflurane may explain, at least in part, the different MAC values listed for compound 485 in dogs and rats. In the current study in rats, a MAC of 0.287 atm was calculated from additivity studies with desflurane. In previous studies in dogs, endotracheal intubation and mechanical ventilation allowed for a gradual replacement of isoflurane with compound 485, and a MAC of 0.125 atm for compound 485 alone was measured (7). However, examination of the nonadditive effects of compound 485 with isoflurane (7) reveals that a 50% reduction in isoflurane MAC occurs with 0.1 atm compound 485, a finding consistent with the combined effects of compound 485 and desflurane in the current study (Table 2). As with our previous studies with

nonimmobilizer halogenated alkanes (4), the compounds labeled as nonimmobilizers in Table 2 might exhibit anesthetic effects, but the anesthetic properties of such drugs were too small to be detected by the sensitivity of our measurements.

In summary, we examined the anesthetic properties, as defined by MAC in rats, of 22 polyhalogenated methyl ethyl ethers that have structural similarities to clinically used volatile anesthetics. Two compounds were nonimmobilizers at partial pressures predicted to produce an anesthetic effect by the Meyer-Overton hypothesis. Other compounds had anesthetic potencies much less than those predicted by their lipid solubilities. These structural analogs of clinical anesthetics should be useful in studies of anesthetic mechanisms. For *in vitro* models in which a single or a limited number of sites are thought to be important in the production of the anesthetic end point, the lipid- and tissue-soluble nonimmobilizer methyl ethyl ethers should not produce the same physiological/molecular changes as isoflurane, enflurane, and desflurane.

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