

The Lack of Hydrate Formation at a Temperature of 0 C of Methoxyflurane, Halothane, Diethyl Ether and Fluoroxene

Edmond I. Eger, II, M.D.,* and Richard O. Shargel, A.A.S.†

Hydrates of methoxyflurane, halothane, diethyl ether or fluoroxene were not found at 0 C at vapor pressures of 5.5, 93.8, 116.3 and 179.4 mm Hg, respectively, which suggests that the correlation of anesthetic potency and hydrate dissociation pressure at 0 C is not as close as originally suggested by values for other gases.

THE HYDRATE THEORY of anesthesia is supported by the correlation of the partial pressure of anesthetic required for anesthesia and the hydrate dissociation pressure of that anesthetic at 0 C.^{1,2} With two exceptions, the correlation has not been tested for the more potent anesthetics. Both ether¹ and halothane (Fluothane)³ are reported not to form hydrates, except that halothane forms a hydrate in the presence of an additional stabilizing agent, hydrogen sulfide. Pauling suggested that ether acts as an anesthetic through some mechanism other than hydrate formation.¹ The present report describes experiments designed to show hydrate formation (or lack thereof) at 0 C and to measure the anesthetic partial pressure overlying (within) the aqueous phase. We were unable to produce hydrates with either ether or halothane at this temperature. In addition, we found that methoxyflurane (Penthurane) and fluoroxene (Fluoromar) do not form hydrates at 0 C.

Methods

100 ml each of methoxyflurane, halothane, diethyl ether or fluoroxene and twice-glass-distilled water together were brought to 0 C

in an apparatus modified from that described by Ramsay and Young.⁴ The mixture was stirred constantly with a magnetic Teflon®-coated stirring bar. The pressure above the mixture was reduced until slight boiling occurred. A constant pressure was reached in less than ten minutes and a further 45 minutes were allowed for temperature equilibration and thorough evacuation of dissolved air. Care was taken not to permit the temperature to fall below -0.1 C. A tendency to fall below zero existed because of the evaporative heat loss. In early experiments with methoxyflurane, when the temperature fell below zero, ice did form but melted with return to zero. Pressure above the mixture was determined with a mercury manometer and recorded at 15-minute intervals. Each mixture was then observed for crystal formation for the next two hours. After this the connection to the vacuum pump was sealed. The pressure overlying the mixture was observed and found to remain constant for ten minutes or more. The anesthetic partial pressure was calculated as barometric pressure minus the sum of the height of mercury in the U-manometer and the vapor pressure of water at 0 C. The vapor pressure of water was corrected for the mole fraction of anesthetic dissolved in the aqueous phase. Each thermometer was an A.S.T.M. 33C graduated in 0.2-degree divisions readable to 0.1 degrees. The calibration of each at 0 C was confirmed with an ice-water slush.

An additional experiment was performed to answer two possible criticisms of the above experiment. First, since these studies were conducted with commercially available material, small amounts of impurities, including stabilizers, were present. Second, hydrate formation might require more than two hours.

* Professor.

† Chemist.

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Fluroxene, halothane and methoxyflurane without stabilizers were obtained from their respective manufacturers. Each agent was at least 99.99 per cent pure. Reagent-grade ether (99.994 per cent pure) was used. Equal aliquots of agent and twice-glass-distilled water were sealed in glass bottles, shaken and placed in a Dewar flask for five weeks. The temperature within the flask was maintained at 0 C with an ice slush. The water phase in each bottle was intermittently inspected without removal from the Dewar flask by means of a periscope.

A third experiment was done to eliminate the possibility that lack of hydrate formation resulted from incomplete mixing of water and agent despite the prolonged period (five weeks) for equilibration. The anesthetics were vaporized with a bubble-through vaporizer cooled to 0 C. For 48 hours the resulting vapor was directed through a 27-gauge needle into twice-glass-distilled water at 0 C. This was repeated with cyclopropane, which is known to form hydrates.⁶

Results and Discussion

The vapor pressures of the anesthetics above the mixture are given in table I. The pressures in the table are the means of the values taken during the final 80 minutes of equilibration when overt boiling was not present. At 0 C, mixtures of water with halothane, methoxyflurane, fluroxene or ether remained liquid for both the two-hour and the five-week periods. No hydrate formation was observed for these agents during the 48-hour period of equilibration with bubbling. When this was repeated with cyclopropane two hydrates appeared to form: one lighter and the other denser than water. These were present between 0 and 0.5 C.

Since we found no hydrate formation for methoxyflurane, halothane, ether or fluroxene (i.e., no solid or "ice" formed in the water) at the observed partial pressure, we assume

TABLE I

	Number of Readings	Vapor Pressure of Water Saturated with Anesthetic at 0°C (mm Hg)	Vapor Pressure of Anesthetic, Mean, 0°C (mm Hg) \pm 1 Standard Deviation
Methoxyflurane	7	4.6	5.5 \pm 0.1
Halothane	4	4.6	93.8 \pm 0.2
Fluroxene	6	4.6	116.3 \pm 0.5
Ether	6	4.5	179.4 \pm 1.0

that any formation that might occur would require still higher pressures (unobtainable—since the pressures we found were close to the vapor pressure of the pure anesthetics) or additional stabilization from other sources.

As noted in a separate paper⁷ these data show that the correlation of potency and hydrate dissociation pressure at 0 C is not as close as originally suggested by Pauling and by Miller.

The methoxyflurane for these experiments was contributed by Abbott Laboratories, the halothane by Ayerst Laboratories, and the fluroxene by the Ohio Medical Products, Division of Air Reduction, Inc.

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