

Theoretical Aspects of Narcosis

Preparation of a Solid Hydrate of Halothane

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The molecular theory of anesthesia, as formulated by Pauling, relates anesthesia to formation of gas hydrates in the brain. It would imply that all anesthetic agents can form gas hydrates. While many kinds of gas hydrates have been prepared in artificial environments, preparation of the hydrates of some important anesthetic agents has not yet been reported.

Preparation of a solid halothane hydrate is described in this paper. The hydrate was obtained as a white precipitate, slightly heavier than water. It had a melting point of 7° C.

GAS HYDRATES are solid compounds that consist primarily of water. The water molecules in a gas hydrate are attached to each other without binding with the molecules of the hydrating agent.¹ Water molecules form a skeleton somewhat similar to, but less dense than ice because this structure contains many cavities of molecular size. These cavities are dispersed through the water skeleton in a regular pattern. The skeleton can exist only if a fraction of the cavities is filled with molecules of a hydrating agent. When it exists, the thermal stability is often higher than that of ice; that is, the skeleton will melt at a temperature higher than 0° C.

When hydrate formation occurs, the number of cavities that become filled with an agent molecule depends not only on concentration of the agent, but also on size and other characteristics of the molecules. Thus a mixture of hydrating agents, with different molecular sizes, often fills a larger fraction of cavities than a single agent. This results in a higher thermal stability of the mixed hydrate. Mixed hydrates that melt between 15 and 20° C. (atmospheric pressure) have been reported.²

Note of a hydrate melting point as high as 37° C. has not been found in the literature. However, the molecular theory of anesthesia as formulated by Pauling,³ assumes the presence of hydrating agents in the brain, which could form mixed hydrates with this order of stability. But these hydrates would be formed only when an anesthetic agent also is present.

During anesthesia, the anesthetic agent is transported to the brain and dissolved in the cerebral fluid. According to the theory, the agent immediately forms very small mixed hydrate crystals. These crystals would interfere with electrical processes responsible for short-range memory and consciousness: The interference would cause narcosis.

This paper describes an attempt to prepare *in vitro* a simple hydrate from halothane (CF_3CHClBr) and water. When the initial experiment proved unsuccessful, it was repeated with an additional stabilizing hydrating agent. Hydrogen sulfide (H_2S) was chosen because it is described as an extremely effective stabilizer.⁴ Under those circumstances it was possible to prepare a hydrate; its thermal stability was determined. A comparison was made with two similar hydrates prepared from chloroform (CHCl_3) and H_2S , and from trichloromethane (CFCl_3) and H_2S .

Procedure

Formation. A glass beaker containing 300 ml. of water was cooled to 0° C. Forty grams of liquid halothane and ice were added. Ice facilitates hydrate crystallization as well as temperature control. Hydrate formation always is accompanied by evolution of heat. When ice is present, some of it melts and the temperature remains at 0° C. A few drops of an emulsifier* were added to facilitate intro-

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Accepted for publication July 20, 1965.

* Triton X-100 (Rohm and Haas).

mate contact between the two liquid phases. The mixture was agitated vigorously with a magnetic stirrer. After stirring for one hour, no solid material had formed. Therefore, hydrate formation did not occur.

When H_2S was introduced at a rate of a few bubbles per second, a flocculent white compound began to precipitate after approximately 20 min. After another half hour, more precipitate formed. A viscous milky slurry was obtained. Heating this white material transformed it into liquid halothane and water. Thermal stability of the white precipitate was higher than that of simple hydrogen sulfide hydrate, which melts very close to $0^\circ C$. Therefore, it was concluded that the product was a mixed hydrate of halothane and H_2S .

Decomposition. To obtain a better equilibrium, the hydrate slurry was stirred for a few more hours without introduction of additional H_2S . The slurry was transferred into a 500-ml. Dewar flask provided with a magnetic stirrer and a small submerged electric heating element. The flask was covered, and the temperature was read at fifteen second intervals. Heat was regulated with a variable transformer to raise the temperature at a rate of 0.5 to $1^\circ C$. per minute.

Heating a homogeneous liquid causes temperature to change linearly with time, but if the liquid contains material which melts, increase in temperature will be interrupted at this material's melting point. Temperature will not rise as long as melting material is present but will rise after all material becomes molten. When several materials of different melting points are present in the slurry, a period of constant temperature can be observed at the melting point of each substance.

In the experiment described herein, an interruption in temperature rise was observed for approximately ten minutes when the temperature reached $7^\circ C$. A slow temperature change of $0.5^\circ C$. was observed during this period, indicating that the decomposing hy-

drate was not completely uniform in composition.

Results

Halothane hydrate stabilized with H_2S melted at approximately $7^\circ C$. It is a voluminous white precipitate somewhat heavier than water. Hydrate prepared in a similar manner from chloroform and H_2S melted at $13^\circ C$. A hydrate obtained from fluorotrichloromethane and H_2S melted at $14.5^\circ C$.

Conclusions

Experimental results show that halothane has the proper chemical and physical characteristics to form hydrates when effective stabilizers are present.

Thermal stabilities of $CHCl_3$ hydrate and $CFCl_3$ hydrate (both stabilized with H_2S) are rather similar. $CFCl_3$ has much weaker anesthetic properties than $CHCl_3$.⁵ Therefore, it seems unlikely that the thermal stability of a mixed hydrate, prepared in the laboratory from an anesthetic agent and H_2S , is indicative of the anesthetic potency of that agent.

The author acknowledges the assistance of N. Evkovich, who developed details of the experimental procedures followed and who performed the reported experiments.

Halothane (Fluothane) for this study was supplied by Ayerst Laboratories.

References

1. van der Waals, J. H., and Platteeuw, J. C.: Clathrate solutions, *Adv. Chem. Phys.* 2: 1, 1959.
2. von Stackelberg, M., and Meinhold, W.: Mischhydrate, *Z. Electrochem.* 58: 40, 1954.
3. Pauling, L.: A molecular theory of anesthesia, *Science* 134: 15, 1961.
4. von Stackelberg, M., and Fruehbusch, H.: Doppelhydrate, *Z. Electrochem.* 58: 99, 1954.
5. Threshold Limit Values 1964, as accepted at the 26th Annual Meeting of American Conference of Governmental Industrial Hygienists, April 25-28, 1964, Philadelphia.

