ANESTHESIA. XIV. A STUDY OF CERTAIN PHYSICAL PROPERTIES OF ISOPROPENYL VINYL ETHER

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Isopropenyl vinyl ether (propylene) has been shown to possess desirable anesthetic properties when administered to various species of laboratory animals (1). Likewise, in man, propylene has been employed successfully as a general anesthetic (2). It was shown that in the blood of the monkey and the dog, this anesthetic agent, after long periods of time, was hydrolyzed partially into acetic aldehyde and acetone. The purpose of this present investigation is to study further the conditions of stability and hydrolysis of propylene ether. In addition, certain other physical studies relating to the anesthetic properties of propylene were investigated further.

Quantitative Determination of Propylene: Propylene may be determined quantitatively in blood by hydrolysis to acetic aldehyde and acetone (1) and determining the acetone formed by the colorimetric method of Behr and Benedict (3). This method was studied critically and certain refinements instituted. The method depends upon the reaction of acetone with salicylic aldehyde to form dihydroxydibenzal acetone in alkaline solution. To meet our conditions we found it advantageous to use potassium hydroxide instead of sodium hydroxide, to measure accurately the salicylic aldehyde instead of using a few drops and conduct the reaction in a boiling water bath.

Saturated aliphatic ethers, such as ethyl ether, are remarkably stable organic compounds. They are refractory to hydrolysis by acids, alkalies and biological metabolic processes. The introduction of a double bond into the molecule greatly increases the reactivity of the ether, and hydrolysis readily proceeds in acid medium. Thus, with propylene the following equation expresses the decomposition in the presence of a preponderance of hydrogen ions.

\[
\text{CH}_3\text{COH} + (\text{CH}_3)_2\text{CO} + [\text{H}^+] \rightarrow \text{CH}_3\text{COH} + (\text{CH}_3)_2\text{CO}
\]

The procedure ultimately adopted by us is outlined as follows. Standard solutions of propylene in distilled water were prepared,

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50 mg. per cent. These were diluted to prepare lesser concentrations of the standard specimen. The solution was hydrolyzed by the addition of diluted sulfuric acid. The acetone was estimated by comparison with standard acetone solutions. The comparisons were carried out after dilution to 50 cc. volumes in a Fisher Nesslerimeter. Theoretically, 100 mg. of propylene yields 69 mg. of acetone on a stoichiometric basis. Our findings over a limited range of concentrations confirmed this yield of acetone.

**Analytical Method:** To 5 cc. of the standard acetone solution or anesthetic solution, 5 cc. of 3 per cent potassium hydroxide and 0.2 cc. of salicylic aldehyde are added. The flask is placed in a boiling water bath for exactly five minutes under a reflux condenser. It is then removed and cooled to room temperature, and within five to ten minutes diluted with 30 cc. distilled water, filtered through a pledget of cotton and the cotton washed with sufficient distilled water to make 50 cc. After dilution, the colors were found to be stable for a period of twelve hours. The undiluted solution must not be permitted to stand as the color intensity continues to develop.

Using standard acetone solutions as a basis for the analytical procedure, a series of propylene solutions were analyzed and the following results obtained.

**Table 1**

<table>
<thead>
<tr>
<th>No.</th>
<th>Present mg. per cent</th>
<th>Found mg. per cent</th>
<th>Difference at 10%</th>
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<tbody>
<tr>
<td>1</td>
<td>0.75</td>
<td>0.73</td>
<td>0.02</td>
</tr>
<tr>
<td>2</td>
<td>1.00</td>
<td>1.10</td>
<td>0.10</td>
</tr>
<tr>
<td>3</td>
<td>1.50</td>
<td>1.62</td>
<td>0.12</td>
</tr>
<tr>
<td>4</td>
<td>2.00</td>
<td>1.82</td>
<td>0.18</td>
</tr>
<tr>
<td>5</td>
<td>2.50</td>
<td>2.20</td>
<td>0.30</td>
</tr>
<tr>
<td>6</td>
<td>3.00</td>
<td>2.80</td>
<td>0.20</td>
</tr>
</tbody>
</table>

**Speed of Hydrolysis and Hydrogen-ion Concentration:** Having established a method by which propylene could be determined quantitatively, its speed of hydrolysis was then determined under various degrees of hydrogen-ion concentration. The determinations were made at 25± 0.5 C. The solutions in the acid range of hydrogen-ion concentration were solutions of hydrochloric acid of various normalities. A phosphate buffer was used for pH 7.4, and water from which carbon dioxide was expelled by boiling was employed for aqueous solutions. The solutions on the alkaline side of the hydrogen-ion concentration range were those of sodium hydroxide of various normalities. The degree of hydrolysis was determined by the amount of acetone formed by hydrolytic cleavage in various time periods. In general, the following results were obtained. At pH 1 to 3 the hydrolysis was complete within one to ten minutes. Between pH 3 and 5 the hydrolytic rate was re-
tarded. In carbon dioxide-free distilled water and in phosphate buffer pH 7.4 there was no detectable hydrolysis within a three-hour observation period. Alkaline solutions pH 8 to 13 did not cause hydrolysis within the three-hour period.

**Oil/Water Coefficient of Propylene:** In our studies with various new anesthetic agents, we have been eager to detect correlations between physical properties of the anesthetic agent and its anesthetic potency. Previously (4), we have shown that the insolubility of the volatile anes-

![Chart 1. Solubility in water and oil/water coefficient.](chart.png)

**Chart 1.**

Solubility in water and oil/water coefficient.

<table>
<thead>
<tr>
<th>No.</th>
<th>Compound</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Diethyl Ether</td>
</tr>
<tr>
<td>2</td>
<td>Cyclopropyl Methyl Ether</td>
</tr>
<tr>
<td>3</td>
<td>Cyclopropyl Ethyl Ether</td>
</tr>
<tr>
<td>4</td>
<td>Divinyl Ether</td>
</tr>
<tr>
<td>5</td>
<td>Cyclopropyl Vinyl Ether</td>
</tr>
<tr>
<td>6</td>
<td>Isopropenyl Vinyl Ether</td>
</tr>
</tbody>
</table>

thetic in water was a function of its anesthetic potency, and in some respects a more reliable criterion than the classical oil/water coefficient. The water solubility of propylene is exceedingly small, namely, 0.4 cc. per 100 cc. at 25 C. The solubility of ethyl ether is 8.6 cc. in 100 cc. of water. To complete our data on this series of compounds we endeavored to determine the oil/water coefficient of propylene.

Using corn oil as the oil phase, we learned that, when agitated briskly with the two phase system, propylene rapidly hydrolyzed, thus frus-
trating the reliability of the measurement. All of our efforts to check the hydrolysis under the conditions of the experiment were thwarted. The use of mineral oil, the addition of dilute alkali and the inclusion of a small percentage of phenyl alpha naphthylamine, all failed to prevent hydrolysis. Agitation of the ether in water did not catalyze the hydrolysis, but the two phase system immediately initiated hydrolysis. We are at loss to explain this phenomenon, unless it is associated with the electronic charge on the colloidal oil particles, which possibly catalyze the hydrolysis.

Experimentally, the results in the oil/water distribution experiments were vitiated by hydrolysis. We had, however, data on other volatile anesthetics that were cogent to this problem. In chart 1 the oil/water coefficients of several volatile anesthetics are plotted as abscissae against the water solubilities as ordinates. It will be noted that a smooth type of an exponential curve is obtained.
In chart 2, the values in chart 1 are plotted as logarithms and the curve shows a linear relationship between its x and y axis. The equation for the slope of the curve is \( x + y = 10.61 \) and, picking from it the log of the oil/water coefficient of propylene, we find it to be 8.677 and the natural number 86.

We hold the view that this datum obtained in this manner is likely more reliable than that obtained experimentally, as one cannot over-emphasize the sources of error inherent to this ostensibly simple procedure. As the determination of water solubility is so simple and amenable to a high degree of precision and is shown here to be definitely a function of the oil/water coefficient, we strongly commend it as a criterion of anesthetic potency.

**Conclusions**

1. A method has been described for the analysis of solutions of propylene. It is applicable to blood and body fluids.
2. Speeds of hydrolysis of propylene at various hydrogen-ion concentrations have been determined. In general, propylene is stable in neutral and alkaline solutions, but instantly decomposed by solutions of strongly dissociated acids.
3. The oil/water coefficient of propylene, calculated from its water solubility, is 86. The significance of water solubility among the general anesthetics, as a criterion of potency, is discussed.

**References**


**Election of Officers of the Section on Anesthesiology of the American Medical Association 1945-46**

During the Scientific Session held in Chicago June 12 to 16, 1944, the following were elected: Chairman, Ansel M. Caine, M.D., New Orleans, La. (1 year); Vice Chairman, Harold C. Kelley, M.D., New York City (1 year); Secretary, John S. Lundy, M.D., Rochester, Minn. (2 years); Delegate to the House of Delegates, Henry S. Ruth, M.D., Philadelphia, Pa. (2 years); and Alternate Delegate, H. Boyd Stewart, M.D., Tulsa, Okla. (2 years).