[Chem. Pharm. Bull. 27(8)1820—1823(1979)]

UDC 615.31'298.1.011.5.014.2.074 : 543.252.061

Applications of a Carbon Dioxide Selective Electrode. I. Determination of Meprobamate by Decomposition with Alkali

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(Received January 5, 1979)

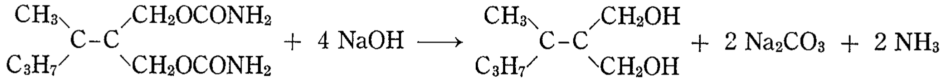
Meprobamate decomposes into NH_3, Na_2CO_3, and a diol compound on heating in 1 N NaOH, and CO_2 evolved at pH 4.8 can be determined by the use of a CO_2 selective electrode without separation from the decomposition solution. A linear calibration curve was obtained within the concentration range of 1×10^{-4}—2.5×10^{-2} M meprobamate. Carbon dioxide in water does significantly influence the potential response, so that this method requires the use of distilled water pre-treated by boiling.

Keywords——meprobamate; carbon dioxide; potentiometry; ion selective electrode; gas permeable membrane

During the past few years, the use of ion-selective membrane electrodes for analysis has attracted much attention, because these electrodes have considerable advantages in terms of simplicity as well as accuracy in assay, speed in operation, and lower cost compared with conventional methods.

An ion-selective membrane electrode characterized by high selectivity for CO_2 has recently been reported.[2] Also, there have been many reports[3] published on the application of enzyme electrodes for quantitative determination of amino acids. However, applications to drug analysis have not yet been reported in the literature. In this paper, we describe the use of the CO_2 selective electrode and its possible application for the determination of drugs.

As an example, we developed an assay method for meprobamate. In Japanese Pharmacopoeia VIII, the method for its identification is described as follows: Meprobamate decomposes into NH_3, Na_2CO_3, and a diol compound on heating with 1 N NaOH, and the evolved NH_3 gas changes the color of a litmus paper from red to blue.



$$\begin{matrix} CH_3 & & CH_2OCONH_2 \\ & C\text{-}C & \\ C_3H_7 & & CH_2OCONH_2 \end{matrix} + 4\,NaOH \longrightarrow \begin{matrix} CH_3 & & CH_2OH \\ & C\text{-}C & \\ C_3H_7 & & CH_2OH \end{matrix} + 2\,Na_2CO_3 + 2\,NH_3$$

Therefore, it may be possible to use the CO_2 selective electrode to determine CO_2 derived from Na_2CO_3 in the decomposition solution.

Experimental

Apparatus——The CO_2 selective electrode used was an Orion model 95-02 electrode. Potential measurements were carried out with a Hitachi-Horiba F-7ss pH/mV meter with a Toa Electronic EPR-22A polyrecorder providing 10 mV full scale.

All measurements were made in a thermostated vessel which could be made gas-tight to prevent any take-up of CO_2 from the ambient air.

Reagents——Meprobamate (Daiichi Seiyaku Co., Tokyo) used was purified twice by recrystallization from H_2O, and then dried *in vacuo* at 60° for 3 hr. Other chemicals used in the present study were of reagent grade.

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1) Location: *Sugitani, Toyama, 930-01, Japan.*

2) H.B. Herman and G.A. Rechnitz, *Anal. Chim. Acta*, **76**, 155 (1975).

3) T. Kawashima and G.A. Rechnitz, *Anal. Chim. Acta*, **83**, 9 (1976); S.L. Tong and G.A. Rechnitz, *Anal. Lett.*, **9**, 1 (1976); N.R. Larsen, E.H. Hansen, and G.G. Guilbault, *Anal. Chem. Acta*, **79**, 9 (1975); G.G. Guilbault and F.R. Shu, *Anal. Chem.*, **44**, 2161 (1972).

A stock solution of 0.1 M $NaHCO_3$ was prepared for testing the CO_2 response of the electrode, and a citrate buffer solution (pH 4.5) was used to adjust the pH of the solution within the operating range of the electrode.

The internal filling solution supplied with the CO_2 electrode from Orion Instrumentation Laboratory (Cat. No. 95-02-02) was used.

Standard Meprobamate Solution——A mixture of 545.7 mg of meprobamate and 15 ml of carbonate-free 1 N NaOH was placed in a 50-ml round-bottomed flask. A reflux condenser equipped with a soda lime tube to prevent the entrance of CO_2 from the air was attached and the mixture was boiled gently in an oil bath for 90 min. The flask was then cooled, and the solution poured into a 250-ml beaker, then diluted with *ca.* 180 ml of H_2O. The solution was made slightly alkaline (pH 8.5) by adding 3 N H_2SO_4. pH measurement with a pH-meter was carried out in the beaker, which could be made gas-tight to prevent contamination from the air. The solution was then poured into a 250-ml volumetric flask, and diluted to this volume with H_2O. The concentration of the final meprobamate solution was 1×10^{-2} M, corresponding to 2×10^{-2} M CO_2. Standard solutions for preparation of the calibration curve were obtained by diluting this stock solution with H_2O.

Assay Procedure——A mixture of about 200 mg of the sample (accurately weighed) and 10 ml of 1 N NaOH was boiled for 90 min. As described above, the resulting solution was made slightly alkaline and diluted to 250 ml in a volumetric flask.

A portion of 50 ml of the sample solution was transferred into a *ca.* 85-ml vial (3.5 × 9 cm), then 5 ml of 0.1 M citrate buffer (pH 4.5) was added and the mixture was incubated for 30 min at 20°. Finally, potential measurement with the CO_2 electrode was carried out. Because of the temperature dependence of the CO_2 electrode, the sample solution was thermostated at 20° ± 0.1°, and was stirred during the measurement. The CO_2 concentration in the sample solution was determined from the calibration curve previously established using the standard $NaHCO_3$ solutions.

Results and Discussion

Potential Measurement

CO_2 diffusing through the membrane during one measurement may be retained in the internal solution of the electrode, and this would lead to an error in subsequent potential measurements, so the electrode was soaked in 0.1 M NaCl solution with stirring before subsequent use. As a result of this treatment, CO_2 contamination of the internal filling solution in the electrode was avoided.

Reproducibilities and response times of the electrode in test solutions prepared by the decomposition of known concentrations of meprobamate are presented in Table I and Fig. 1, respectively. The electrode potentials reached maxima in about 7 to 10 min in high concentrations of meprobamate, but in a low concentration (0.5×10^{-4} M), the response curve slowly reached a plateau in about 30 min.

Change in temperature causes the potential response to shift. Fig. 2 shows the variation of the potential response with temperature. A change of 10° in temperature gave rise to a 6 mV potential shift. The response of the electrode was also slower at lower solution temperatures.

TABLE I. Reproducibility of the CO_2 Selective Electrode at 20° in the Assay of Meprobamate by Decomposition with Alkali

Meprobamate concentration		0.5×10^{-4}M	1×10^{-4}M	2.5×10^{-4}M	0.5×10^{-3}M	1×10^{-3}M	2.5×10^{-3}M	0.5×10^{-2}M	1×10^{-2}M	2.5×10^{-2}M
Response (mV)	1	−83.0	−72.0	−52.0	−35.0	−19.5	+3.2	+20.2	+38.0	+58.2
	2	−84.0	−73.8	−51.8	−35.2	−18.8	+3.0	+21.0	+36.9	+58.0
	3	−82.8	−73.0	−52.5	−36.0	−19.0	+3.5	+21.0	+37.5	+58.0
	4	−83.7	−73.5	−52.0	−35.3	−19.2	+2.9	+20.8	+38.7	+58.3
	5	−83.5	−73.7	−52.2	−35.0	−18.7	+3.5	+20.7	+37.0	+57.8
	Average	−83.4	−73.2	−52.1	−35.3	−19.0	+3.2	+20.7	+37.6	+58.1
	Std. dev.	±0.5	±0.7	±0.3	±0.4	±0.3	±0.3	±0.3	±0.8	±0.2

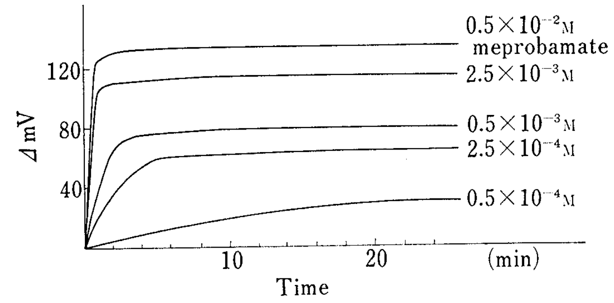

Fig. 1. Dynamic Response Curves of the CO_2 Selective Electrode to Various Concentrations of Meprobamate at 20°

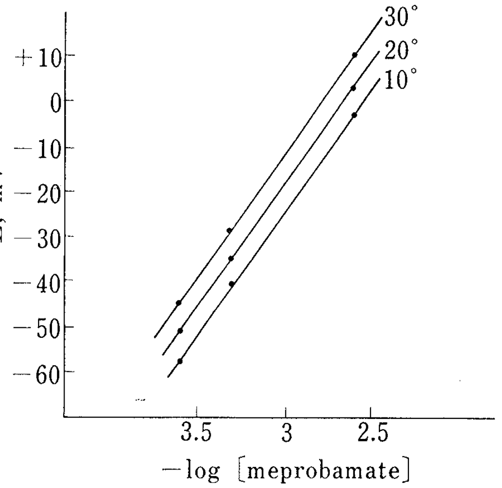

Fig. 2. Effect of Temperature on the CO_2 Selective Electrode

On the other hand, the higher the temperature, the more CO_2 was lost from the solution. Therefore, the optimal temperature was selected as 20°.

Adjustment of pH

If sample solutions prepared by the decomposition of meprobamate were to be stored, they were made slightly alkaline (pH 8—9) by adding 3 N H_2SO_4 and stored in a tightly capped vessel to prevent take-up of CO_2 from the air. Just before measurement, the stored sample solutions were acidified to pH 4.8 with 0.1 M citrate buffer, because all the carbon dioxide in the solution at this pH is in the form of gas species.

Decomposition of Meprobamate

A mixture of 2.5×10^{-3} mol of meprobamate and 10 ml of 1 N NaOH was boiled gently and the resulting CO_2 in the decomposition solution was determined at various boiling times. The electrode potential reached the maximum at a boiling time of 80 min and remained unchanged with longer boiling time. If the maximum electrode potential developed was taken as 100%, the potentials obtained after boiling for 5, 20, 40, and 60 min corresponded to 50%, 65%, 80%, and 95%, respectively. Further, when a mixture of 2.5×10^{-3} mol of meprobamate and 20 ml of 1 N NaOH was boiled, the electrode potential reached 100% within the shorter boiling time of 60 min and remained unchanged thereafter.

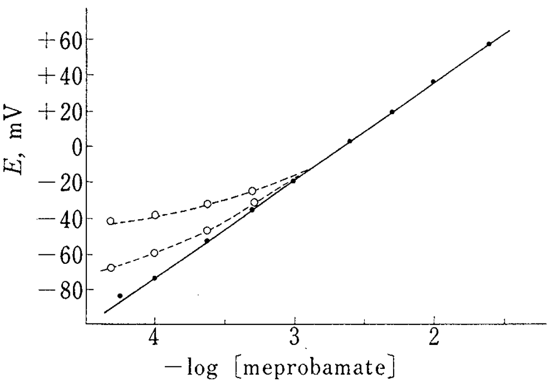

Fig. 3. Calibration Plots of Potential *vs.* −log [meprobamate] for the CO_2 Selective Electrode

—●—: doubly distilled water pre-treated by boiling was used.

---○---: distilled water was used without being boiled.

Calibration Curve

When the potential was plotted *vs.* the logarithm of meprobamate concentration, as shown in Fig. 3, a linear calibration curve was obtained in the concentration range of 1×10^{-4} to 2.5×10^{-2} M meprobamate with a slope of 56 mV/decade.

If distilled water was used without being boiled in potential measurements, a nonlinear relationship was observed at concentrations below 1×10^{3} M of sample solution. The results are illustrated by dotted curves in Fig. 3. In an attemt to overcome this, we used doubly distilled water pre-treated by boiling. Above

3×10^{-2} M meprobamate, corresponding to 6×10^{-2} M CO_2, the partial pressure of CO_2 in solution is greater than the normal atmospheric partial pressure[4] of CO_2, resulting in the loss of CO_2 into the air.

Conclusion

In the literature, many methods for the assay of meprobamate have been reported. These can be classified into (1) the Kjeldahl method, (2) the U. S. P. method, (3) the *p*-dimethylaminobenzaldehyde method,[5] and (4) the non-aqueous titration method.[6] The Kjedahl method adopted in Japanese Pharmacopeia VIII is nonspecific, the assay method is not convenient, and the separation of NH_3 gas from the decomposition solution is difficult. On the other hand, the accuracies of methods (2) and (3) depend on the experimental conditions, while in method (4) the normality factor is unstable.

The present method using the CO_2 selective electrode has high specificity, and CO_2 can be easily determined without separation from the decomposition solution. Because of the gas-permeable membrane of the CO_2 selective electrode, only 6.2×10^{-3} M acetic acid[7] among common chemical reagents at pH 5 causes a 10% error at 10^{-3} M carbon dioxide. Thus, no serious interference with the potential measurements may result unless a fairly high level of acetic acid coexists in the sample solution. The major drawback of this method is that CO_2 in water used for the analysis does significantly influence the potential response, so that this method essentially requires the use of distilled water pre-treated by boiling.

Acknowledgement The author is grateful to Professor Takenori Tanimura for his unfailing guidance throughout the course of this work.

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[4] W.F. Linke, "Solubilities, Inorganic and Metal-Organic Compounds," 4th ed., Vol. 1, D. Van Nostrand, New York, 1958.

[5] S. Sakai, H. Mori, and S. Ichimura, *Yakugaku Zasshi*, **78**, 1185 (1958).

[6] O. Cerri and A. Spialtini, *Bull. Chim. Farm.*, **97**, 259 (1958).

[7] "Instruction Manual," Orion Research, Inc., Cambridge, 1977, p. 14.