[Chem. Pharm. Bull. 28(9)2642—2646(1980)]

Application of the Ammonia Selective Electrode: Determination of Meprobamate by Decomposition with Acid

Shoichiro Tagami

Toyama Medical and Pharmaceutical University[1)]

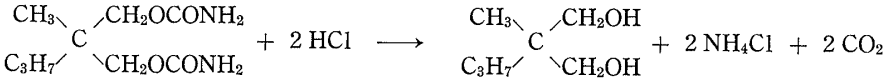
(Received March 13, 1980)

Meprobamate decomposes into NH_4Cl, CO_2, and a diol compound on heating in 20% HCl, and the NH_3 evolved at pH above 11 can be determined using the NH_3 selective electrode without separation from the decomposition solution. A linear calibration plot was obtained within the concentration range of 1×10^{-5}—1×10^{-2} M meprobamate. Volatile amines and the Hg ion, which forms a metal complex with NH_3, are known to interfere with the electrode measurements.

Keywords——meprobamate; ammonia; potentiometry; ion selective electrode; gas-permeable membrane

Gas-permeable membrane electrode offer considerable advantages in terms of simplicity as well as accuracy of assay, speed of operation, and lower cost compared to the conventional methods. We previously attempted therefore to determine meprobamate using a CO_2 selective electrode.[2)] The method has high specificity, and CO_2 can be readily determined without separation from the alkali decomposition solution. However, the major drawback is that the CO_2 in the water used for the analysis significantly influences the potential response.

In the present paper, we describe the use of the NH_3 selective electrode[3)] to overcome the drawbacks of the CO_2 electrode. In the Japanese Pharmacopoeia VIII, the method of identification is described as follows: meprobamate decomposes into NH_4Cl, CO_2, and a diol compound on heating with hydrochloric acid.



$$\begin{matrix}CH_3\\ C_3H_7\end{matrix}\!\!\diagdown\!\!\begin{matrix}C\\ C\end{matrix}\!\!\diagup\!\!\begin{matrix}CH_2OCONH_2\\ CH_2OCONH_2\end{matrix} + 2\,HCl \longrightarrow \begin{matrix}CH_3\\ C_3H_7\end{matrix}\!\!\diagdown\!\!\begin{matrix}C\\ C\end{matrix}\!\!\diagup\!\!\begin{matrix}CH_2OH\\ CH_2OH\end{matrix} + 2\,NH_4Cl + 2\,CO_2$$

It may thus be possible to utilize the NH_3 electrode to determine the NH_3 derived from NH_4Cl in the decomposition solution.

Experimental

Apparatus——The NH_3 electrodes used were the Horiba model 5002-05T NH_3 electrode and the Orion model 95—10 NH_3 electrode. Potential measurements were carried out with a Hitachi-Horiba F-7ss pH/mV meter using a Toa Electronic EPR-22A polyrecorder providing 10 mV full scale.

All measurements were performed in a thermostated vessel.

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

A stock solution of 0.1 M NH_4Cl was prepared for testing the NH_3 response of the electrode, and 10 M NaOH was employed to adjust the pH of the solution to within the operating range of the electrode.

The internal filling solutions supplied with the NH_3 electrode by Horiba Ltd., Kyoto, and by Orion Research Inc., Cambridge, Mass. (Cat. No. 95-10-02), were used.

Standard Meprobamate Solution——A mixture of 545.65 mg of meprobamate and 50 ml of 20% HCl was placed in a 100 ml round-bottomed flask and the mixture was boiled gently in an oil bath for 2 hr. The flask was then cooled, then the solution poured into a 250 ml beaker and diluted with *ca.* 150 ml of H_2O. A

1) Location: *Sugitani, Toyama.*
2) S. Tagami, *Chem. Pharm. Bull.*, **27**, 1820 (1979).
3) R.F. Thomas and R.L. Booth, *Environ. Sci. Technol.*, **7**, 523 (1973); T.R. Gilbert and A.M. Clay, *Anal. Chem.*, **45**, 1757 (1973); A.F. Attili, D. Autizi, and L. Capocassia, *Biochem. Med.*, **14**, 109 (1975).

drop of methyl orange was added and, while cooling the beaker continuously, the acid was cautiously neutralized with 6 N NaOH solution until the indicator began to change color. The solution was then adjusted to pH 6.5 with dil. NaOH solution using a pH meter. The solution was 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 NH_3. Standard solutions for calibration were obtained by diluting this stock solution with H_2O.

Assay Procedure——A mixture of about 200 mg of the sample (accurately weighed) and 20 ml of 20% HCl was boiled for 2 hr. As described above, the resultant solution was adjusted to pH 6.5, and diluted to 100 ml in a volumetric flask, then 2 ml of this solution was diluted to 100 ml with H_2O. A 50 ml portion of the sample was transferred to a *ca.* 85 ml vial (3.5×9 cm), 1 ml of 10 M NaOH or 2 ml of 5 M NaOH was added, and the mixture was incubated for 30 min at 20°. Finally the NH_3 electrode was immersed in the solution and potential measurements were carried out. The vessel should be stoppered to inhibit loss of NH_3 and to prevent evaporation of H_2O. The NH_3 concentration in the sample solution was determined from the calibration curve previously prepared.

In view of the temperature dependence of the NH_3 electrode, the sample solution was thermostated at 20 ± 0.1°, and was stirred during the measurement. Since the potential may vary as a result of changes in the internal filling solution, the solution was replaced with fresh internal filling solution before subsequent use. It is also advisable to check two points on the standard curve before beginning the actual determination.

Results and Discussion

Potential Measurements

The response times of the two electrodes in test solutions prepared by decomposition of known concentrations of meprobamate are presented in Fig. 1 and 2. The hydrophobic gas-permeable membrane of the Orion electrode is very thin and the working area of the membrane is larger than that of the Horiba electrode, so that NH_3 can move more rapidly across the membrane. In 1×10^{-3} M meprobamate, the electrode potential reached the maximum in about 1 min, whereas with the Horiba electrode the response curve slowly reached a plateau in about 30 min. Both electrode responses were a function of meprobamate concentration, with faster responses at higher meprobamate levels. However, in the case of the Orion electrode, the potential reached the maximum in about 2.5 min in 1×10^{-2} M meprobamate and decreased subsequently. The electrode potentials were particularly unstable at high concentrations and the reproducibility of the potentials was inadequate. In the Horiba electrode, the gas-permeable membrane is comparatively thick and the working area of the membrane is small. The response time was thus slow and no potential drift occurred in

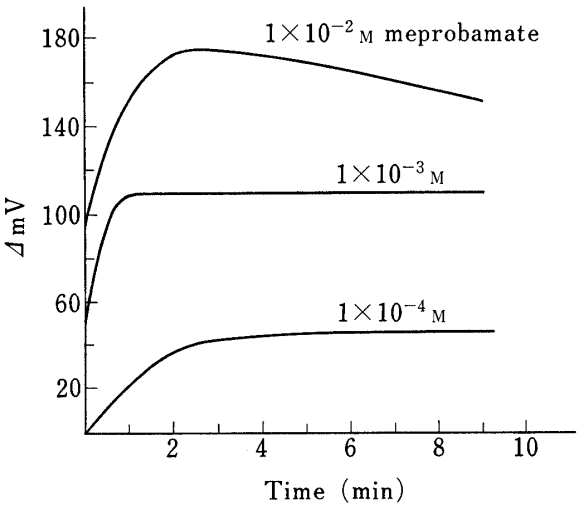


Fig. 1. Dynamic Response Curves of the Orion NH_3 Selective Electrode to Various Concentrations of Meprobamate at 20°

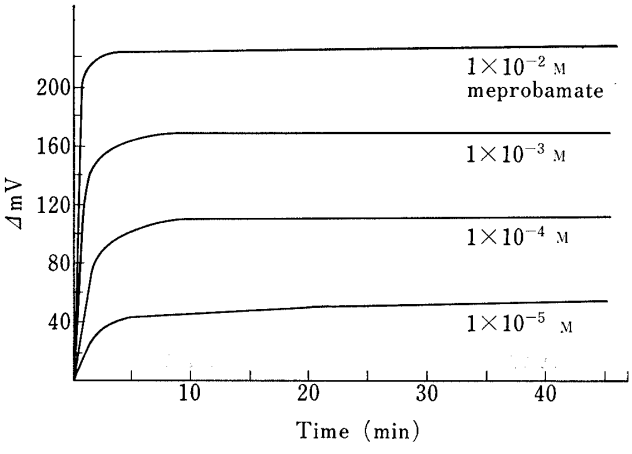


Fig. 2. Dynamic Response Curves of the Horiba NH_3 Selective Electrode to Various Concentrations of Meprobamate at 20°

Table I. Reproducibility of the Horiba NH_3 Selective Electrode at 20° in the Assay of Meprobamate by Decomposition with 20% HCl

Meprobamate concentration		1.0×10^{-5} M	2.0×10^{-5} M	1.0×10^{-4} M	1.0×10^{-3} M	1.0×10^{-2} M
Response (mV)	1	−62.6	−78.0	−121.0	−179.5	−236.7
	2	−62.3	−78.5	−121.1	−179.5	−236.8
	3	−62.5	−78.3	−121.0	−179.4	−237.0
	4	−63.0	−79.2	−121.0	−179.5	−236.6
	5	−63.5	−79.5	−121.2	−179.4	−236.8
	Average	−62.8	−78.7	−121.1	−179.5	−236.8
	Std. dev.	±0.53	±0.63	±0.10	±0.07	±0.15

1×10^{-2} M meprobamate. The reproducibility of the potentials was good, as shown in Table I. Subsequent measurements were therefore carried out with the Horiba electrode.

Effect of Dissolved NaCl

With the Orion electrode, potential drift occurred in 1×10^{-2} M meprobamate. The total level of dissolved species in this solution (osmotic strength) is not equal to that of the internal filling solution. Water vapor as well as NH_3 can move across the hydrophobic gas-permeable membrane, modifying the concentration of the internal filling solution. Such changes appear as electrode drift and lead to errors in subsequent potential measurements. We therefore examined the effect of dissolved NaCl using the Horiba electrode. The results are given in Fig. 3. In 1×10^{-3} M NH_4Cl with 0—1 M NaCl, the potential reached the maximum value in about 30—40 min and remained unchanged for a further 30 min. In 2 M NaCl, the potential reached the maximum in about 20 min, was stable for 10 min and then drifted slowly lower. In 3 M NaCl, the potential reached the maximum in about 17 min, and a large downward electrode drift followed. The maximum potential was lower than in the former cases. Experiments were carried out in the same manner for 0.5×10^{-3} M meprobamate solution containing NaCl (0.06 M) formed during the neutralization of 20% HCl with 6 N NaOH solution. The results were similar to those with NH_4Cl. Based on these results, it was clear that the potential responses and reproducibility were affected by the structure of the gas-permeable membrane and by the concentration of salt. In the Horiba NH_3 electrode, H_2O vapor transport across the membrane was not a problem if the level of dissolved NaCl in the meprobamate solution was below *ca.* 2 M. The potential measurements are thus not influenced by the dissolved NaCl in meprobamate solution decomposed with 20% HCl. To eliminate errors caused by electrode drift, the electrode should be soaked in NH_4Cl solution of ionic concentration equal to that of the fresh internal filling solution before subsequent use, or the contaminated internal filling solution should be replaced by fresh internal filling solution.

Temperature changes cause the potential response to shift. In 1×10^{-3} M meprobamate solution, a change in temperature from 10 to 20° gave rise to a 12 mV potential shift. Samples and standards should be maintained at the same temperature. The response of the electrode was also slower at a lower solution temperature. On the other hand, the higher the temperature, the faster was the loss of NH_3 from the solution. An optimal temperature of 20° was therefore selected.

Decomposition of Meprobamate

A mixture of meprobamate and 10% HCl or 20% HCl was gently boiled and the resultant NH_3 in the decomposition solution was determined at various boiling times. In the case of decomposition with 10% HCl, the electrode potential reached the maximum at a boiling time of 6 hr. However, the potential reached the maximum at a short boiling time of 1.5 hr on decomposition with 20% HCl and was unchanged with longer boiling time. The results are shown in Fig. 4.

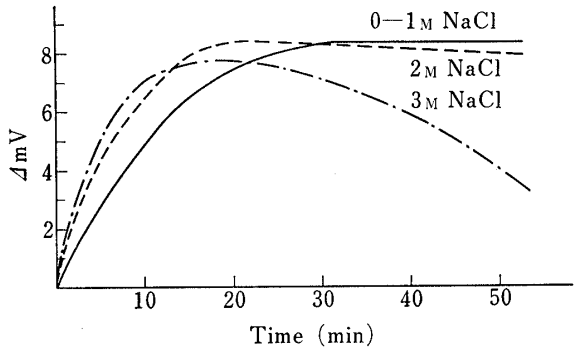


Fig. 3. Effect of Dissolved NaCl in 1×10^{-3} M Meprobamate as estimated with the Horiba NH_3 Selective Electrode

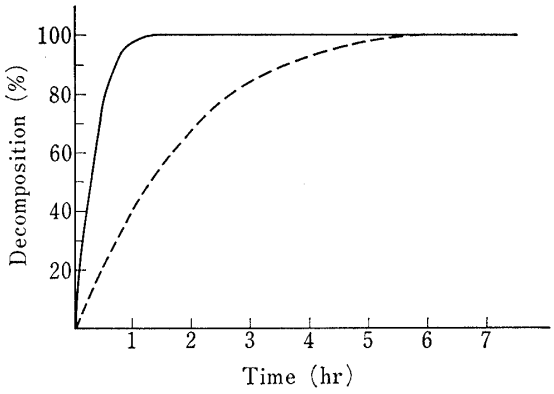


Fig. 4. Effect of HCl Concentration on Meprobamate Decomposition

—: 20% HCl, ------: 10% HCl.

Calibration Curve

When the potential was plotted against the logarithm of the meprobamate concentration, a linear calibration plot was obtained in the concentration range of 1×10^{-5} to 1×10^{-2} M meprobamate. The electrode potential responded slowly at low concentrations, as shown in Fig. 2. In 1×10^{-5} M meprobamate, the potential did not reach the maximum within 1 hr. The reason is that the ΔP_{NH_3} is small and the concentration of dissolved species in the filling solution is higher than that in the meprobamate solution; consequently, the H_2O vapor pressure in the meprobamate solution, in contrast to the case of dissolved NaCl (3 M) in meprobamate solution, is higher than that in the filling solution. The potential results in a continuous upward electrode drift. The potential values after 30 min were therefore adopted to draw the calibration curve. A nonlinear relationship was observed at concentrations above 1×10^{-1} M meprobamate due to the influence of dissolved NaCl. From the calibration curve, the amount of meprobamate was determined in samples of pure meprobamate powder. According to the Japanese Pharmacopoeia VIII, meprobamate determined on a dry weight basis should be over 97% pure. The determination was performed on four 200 mg samples of meprobamate powder (see "Experimental"). The recoveries of meprobamate were 99.5%, 99.8%, 98.8%, and 99.8%, respectively, and the standard deviation was 0.77.

Conclusion

Many methods have been described for the analysis of meprobamate. They can be classified into the following types: (1) the Kjeldahl method, (2) the U.S.P. method, (3) the colorimetric method,[4] (4) the non-aqueous titration method,[5] and (5) the CO_2 electrode method.[2] The Kjeldahl method adopted in the Japanese Pharmacopoeia VIII is nonspecific, the assay method is not convenient, and separation of the NH_3 gas from the decomposition solution is difficult. The accuracy of the U.S.P. method is governed by the experimental conditions, and this tends to give rise to error. The colorimetric method using *p*-dimethylaminobenzaldehyde provides sufficient precision, but is again dependent on the experimental conditions. In the non-aqueous titration method, the normality factor is unstable. The CO_2 electrode method has high specificity and a linear calibration plot is obtained over a wide concentration range (1×10^{-4}—2.5×10^{-2} M). However, the CO_2 in the water significantly influences the potential, so that the use of distilled water pre-treated by boiling is required.

4) S. Sakai, H. Mori, and S. Ichimura, *Yakugaku Zasshi*, **78**, 1185 (1958).
5) O. Cerri and A. Spialtini, *Bull. Chem. Farm.*, **97**, 259 (1958).

The present method using the NH_3 selective electrode has high specificity, as in the case of the CO_2 electrode; further, NH_3 can easily be determined without separation from the decomposition solution, and the potential is not influenced by CO_2 in the air. The drawback of the method is that volatile amines and a number of metal ions, such as Hg, Ag, Au, Ni, Co, Cd, and Zn, which form metal complexes with NH_3, interfere with the electrode measurements. Most of these metals are removed in the form of hydroxide complexes in basic solution. When hydroxide is present at the 0.1 M level and the NH_3 concentration is below 10^{-3} M,[6] only Hg is able to undergo appreciable complexation with NH_3.

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

6) Orion Research Incorporated, "Instruction Manual," 1978, p. 23.