REFERENCES

1. Richard B.M. and John H.r., "Determination of Intercellular pH by ^{31}P Magnetic Resonance", J. Bio. Chem., volume 248 (20), 7276-7278, 1973.

2. Hoult D.I., Busby S.J.W., Gadian D.G., Radda G.K., Richards R.E., and Seeley P.J., "Observation of tissue metabolites using ^{31}P Nuclear Magnetic Resonance", Nature, 252, 285-287, 1974.

3. Labotka R.J., Glonek T., Hruby M.A. and Honig G.R., "Phosphorus-31 spectroscopic determinations of the phosphorus metabolite profiles of blood components: Erythrocytes, reticulocytes and platelets", Biochem.Med., 15, 311-329, 1976.

4. Gadian D.G., Hoult D.I., Radda G.K., Seeley P.J., Chance B. and Barlow C., "Phosphorus Nuclear Magnetic Resonance studies on normoxic and ischemic cardiac tissue", Proc.Natl.Acad.Sci. U.S.A., 73, 4446-4448, 1976.

5. Yashizaki K., "Phosphorus Nuclear Magnetic Resonance studies of phosphorus metabolites in frog muscle", J. Biochem., 84, 11-18, 1978.

6. Casey R.P., Njus D., Radda G.K. and Sehr P.A., "Active proton uptake by chromaffin granules: Observation by amine distribution and phosphorus-31 nuclear magnetic resonance techniques", Biochemistry, 16, 972-977, 1977.

7. Burt C.T., Glonek T. and Barany M., "Analysis of phosphate metabolites, the intracellular pH and the state of adenosine triphosphate in intact muscle by phosphorus nuclear magnetic resonance", J.Biol.Chem., 251, 2584-2591, 1976.

8. Busby S.J.W., Gadian D.G., Radda G.K., Richard R.E. and Seeley P.J., "Phosphorus Nuclear Magnetic Resonance studies of compartmentation in muscle", Biochem.J., 170, 103-114, 1978.

9. Seeley, P.J. Busby, S.J.W., Gadian, D.G., Radda, G.K., and Richards, R.E. A new approach to metabolite compartmentation in muscle. Biochem. Soc. Trans., 4: 62-64, 1976.

10. Dawson, M.J. Gadian, D.G., and Wilkle, D.R. Contraction and recovery of living muscles studies by ^{31}P Nuclear magnetic resonance, J. Physiol. (Lond.), 267: 703-735, 1977.

11. Yoshizaki, K. Phosphosrus nuclear magnetic resonance studies of phosphorus metabolites in frog muscle. J. Biochem., 84: 11-18, 1978.

12. Gupta V.D. and Ghanekar A.G., "Quantitative determinations of codeine phosphate, guaifenesin, pheniramine maleate, phenylpropanolamine HCl and pyrilamine maleate in an expectorant by High Pressure Liquid Chromatography", J.Pharm.Sci., volume 66(6), 895-898, 1977.

13. Yoshizaki K., Nishikawa H., Yamada S., Morimoto T. and Watari H., "Intracellular pH measurement in frog muscle by means of ^{31}P Nuclear Magnetic Resonance", Japanese Journal of Physiology, 29, 211-225, 1979.

14. Monti J.P., Gallice P., Baas M., Murisasco A., Crevat A., "Modification of intra-erythrocytic homeostasis in uremic patients, as studied with ^{31}P NMR", Clin.Chem., 33(1), 76-80, 1987.

15. Muller R.N., Petersen S.B. and Rinck P.A., "Nuclear Magnetic Resonance Basis", 1-22.

16. James T., "Individual Tablet analysis for Codeine and Caffeine in Codeine - Aspirin - Phenacetin - Caffeine Tablets", J. Pharm. Sci., Volume 62, 9, 1500-1502, 1973.

17. Yoshioka T., "Phosphorus -31 NMR study of living tissues", Jeol News, Volume 16A, 2, 2-8, 1980.

18. The National Formulary XIII, 178-180, 1970.

19. George C.V., Robert L.L., Gordon L.N., "Carbon -13 Nuclear Magnetic Resonance Spectroscopy, 3-7, 1980.

20. The Pharmaceutical Codex, 215-217, 1979.

21. British Pharmacopoeia Volume II, 678-679, 735-736, 1980.

22. British Pharmaceutical Codex, 123, 722, 799, 1973.

23. Alfred G.G., Louis S.G., Alfred G., "Goodman and Gilman's The Pharmacological Basis of Therapeutics"., 424-521, 1975.

24. U.S.P. XXI, 243-244, 1985.

25. Rothwell W.P., Waugh J.S., Yesinowski J.P., "High Resolution Variable-Temperature ^{31}P NMR of solid calcium phosphates", J. of the American Chemical Society., 102(8), 2637-2643, 1980.

26. Seo Y., Murakami M., Watari H., Imai Y., Yoshizaki K., Nishikawa H., Morimoto T., "Intracellular pH Determination by a ^{31}P NMR Technique. The second dissociation constant of phosphoric acid in a biological system", J.Biochem., 94, 729-734, 1983.

Appendix

Linear regression method

The basic premise of linear regression is that the best straight line is the straight line for which the sum of the squares of the difference between the predicted value and the measured value is a minimum.

The line of regression for the measured data (x_1, y_1), (x_2, y_2), ..., (x_n, y_n).

Let $f(x) = mx + b$ The predicted value at x_i is $f(x_i) = mx_i + b$. The measured value is y_i. Thus we wish to minimize

$$F(m, b) = \sum_{i=1}^{n} (mx_i + b - y_i)^2$$

$$= \sum_{i=1}^{n} [m^2(x_i)^2 + b^2 + (y_i)^2 + 2mbx_i - 2by_i - 2mx_iy_i]$$

or

(1) $$F(m, b) = m^2 \sum_{i=1}^{n} (x_i)^2 + \sum_{i=1}^{n} b^2 + \sum_{i=1}^{n} (y_i)^2 + 2mb \sum_{i=1}^{n} x_i - 2b \sum_{i=1}^{n} y_i - 2m \sum_{i=1}^{n} x_iy_i$$

We note that $\sum_{i=1}^{n} b^2 = \underbrace{b^2 + b^2 + \cdots + b^2}_{n \text{ times}} = nb^2$.

To simplify the notation we let

(2) $$\begin{cases} P = \sum_{i=1}^{n} (x_i)^2 \quad Q = \sum_{i=1}^{n} (y_i)^2 \quad R = \sum_{i=1}^{n} x_i \\ S = \sum_{i=1}^{n} y_i \quad \text{and} \quad T = \sum_{i=1}^{n} x_iy_i \end{cases}$$

These numbers are all determined by the measured data. Thus, substituting these equations into Equation (1), we have $F(m, b) = m^2P + nb^2 + Q + 2mbR - 2bS - 2mT$

We wish to minimize F. The critical points are given by

$$F_m = 2mP + 2bR - 2T = 0$$

and $F_b = 2nb + 2mR - 2S = 0$

You will show that the solution of this pair of equations is

$$m = \frac{nT - RS}{nP - R^2} \qquad b = \frac{PS - RT}{nP - R^2} \tag{3}$$

Geometrically it is clear that F has a global minimum. Since the domain of F is all paris (m, b), the minimum must be at the critical point found. Note that the use Equation (3) it is not necessary to compute Q.

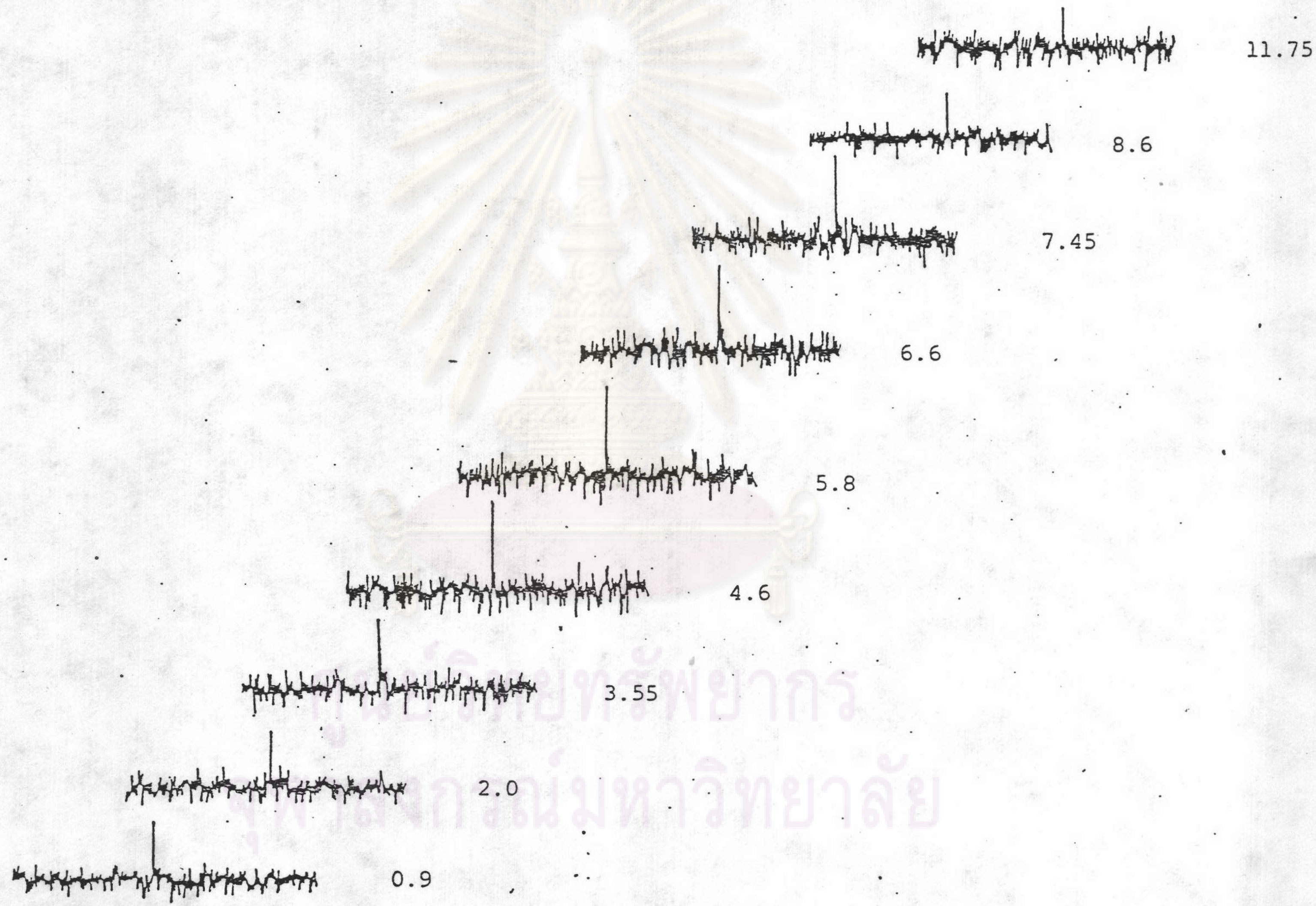


Figure 1: Effect of pH

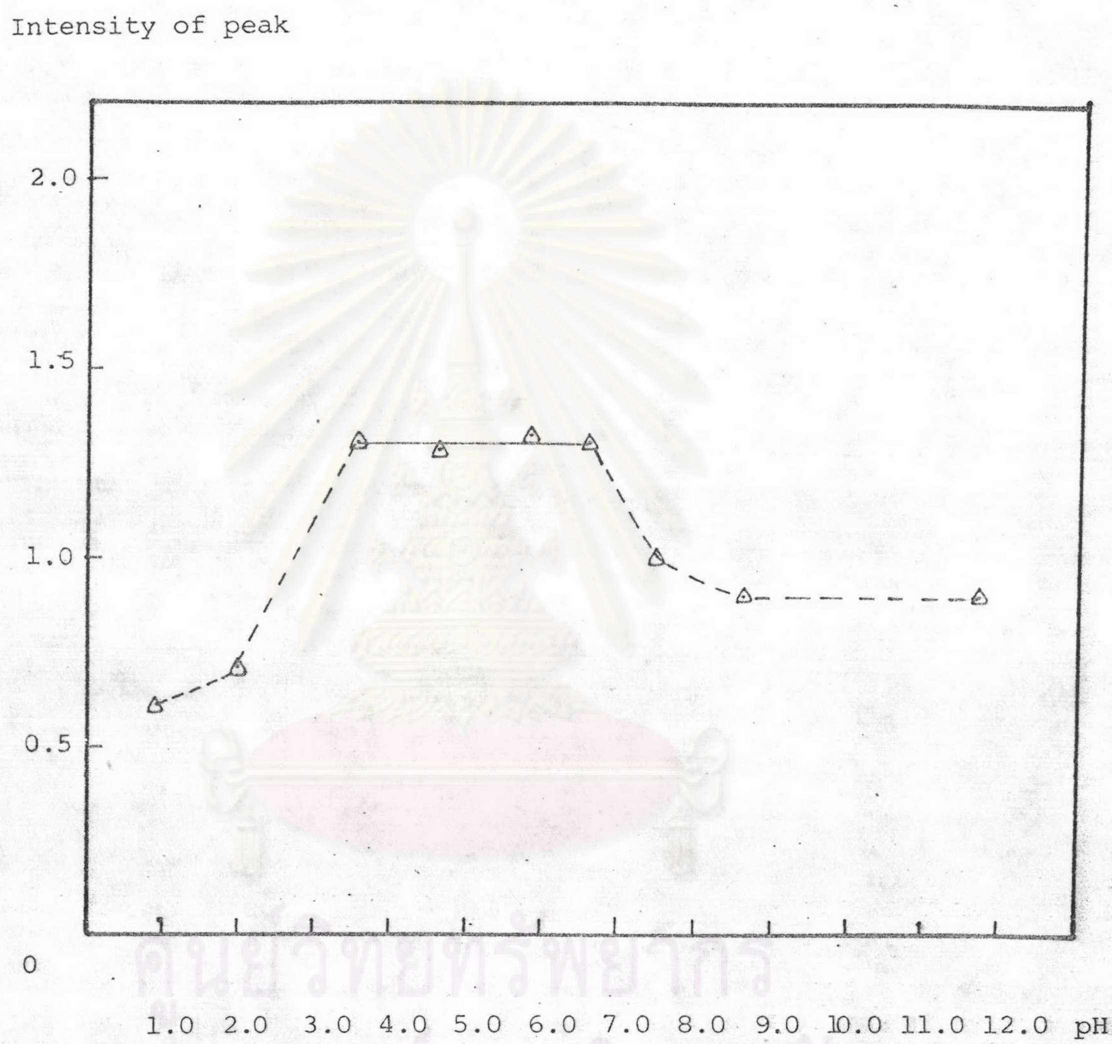
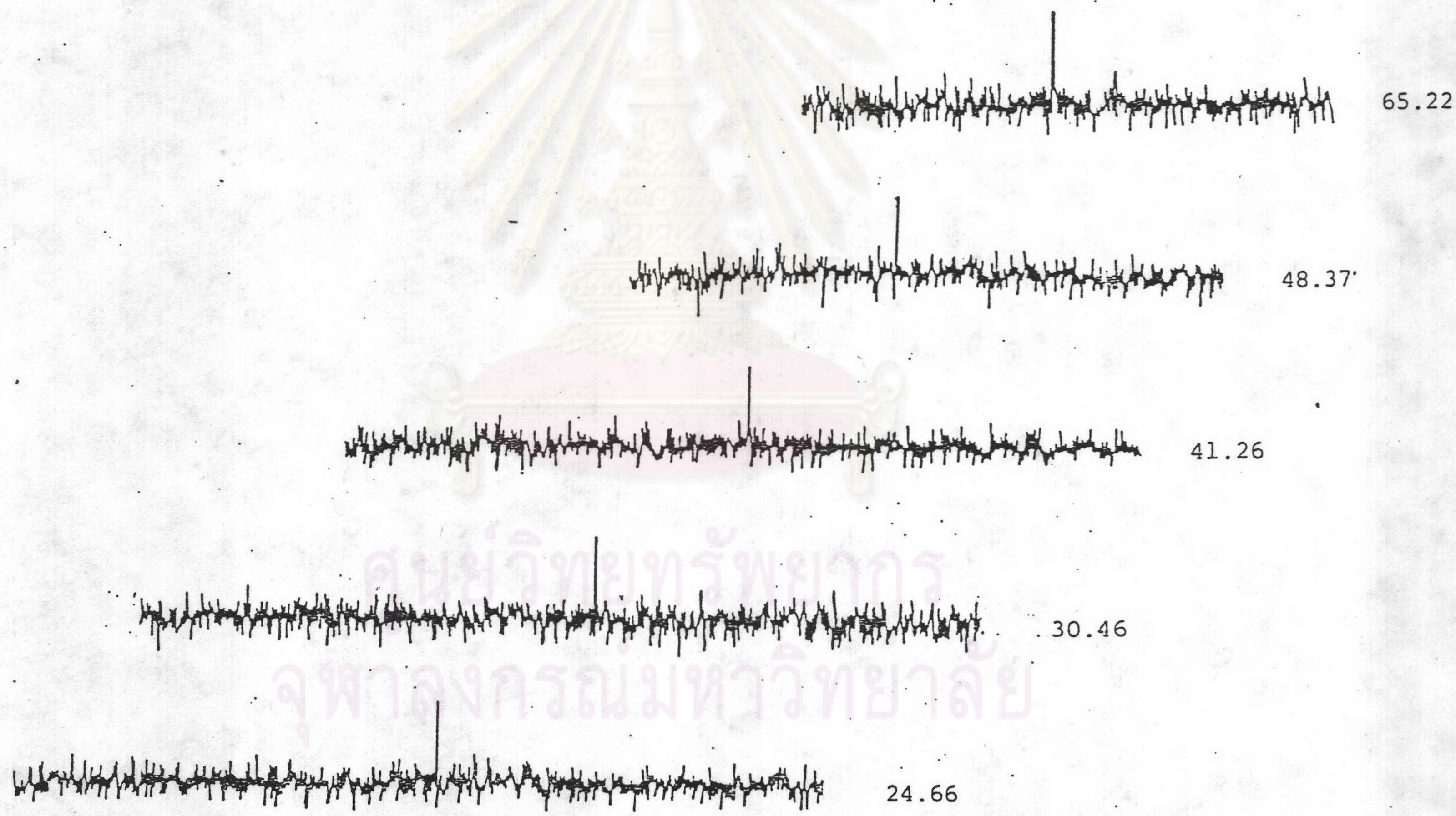


Figure 2: Effect of pH

Figure 3: Effect of viscosity (centipoise)



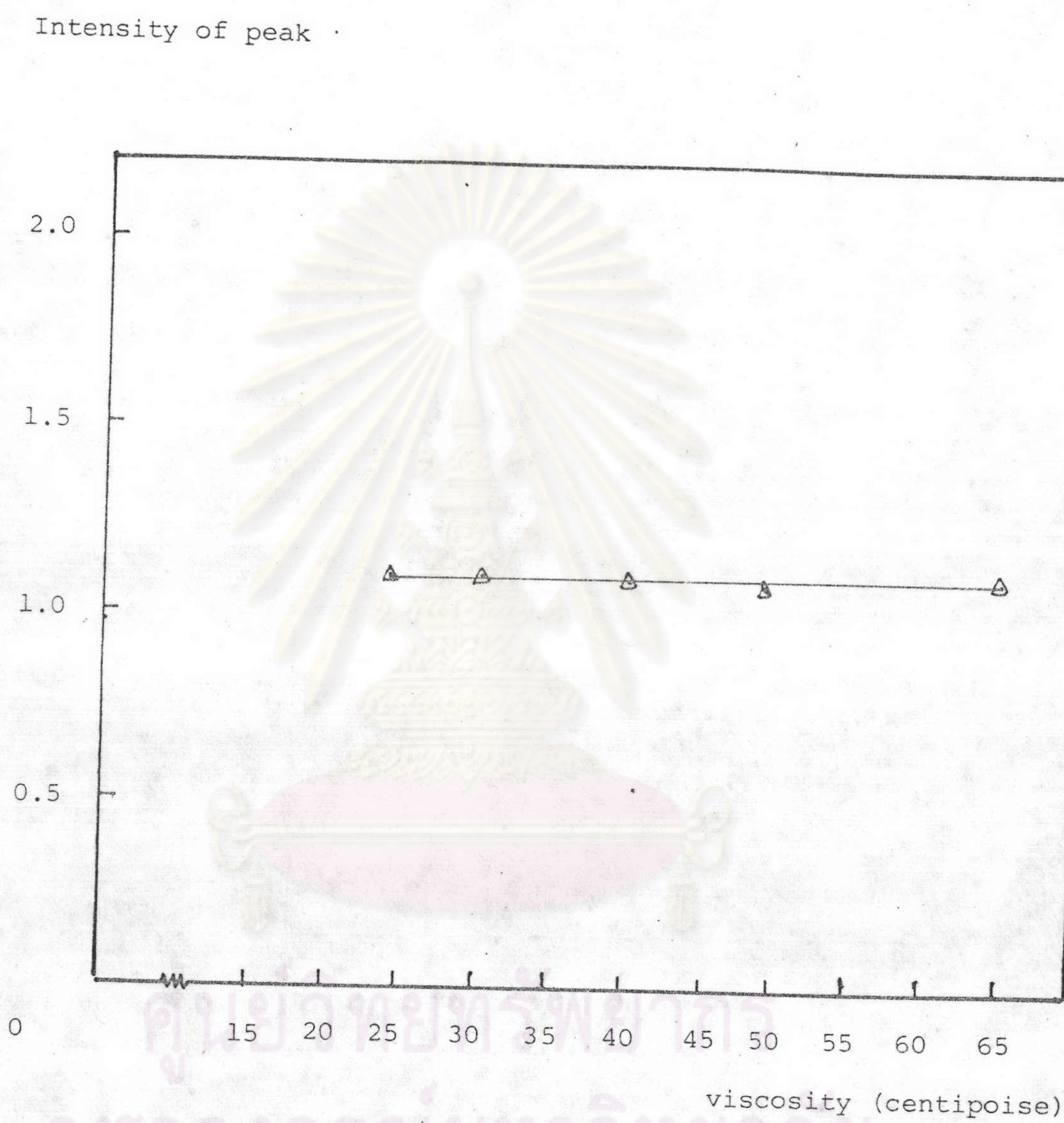


Figure 4: Effect of viscosity

Figure 5: NMR peak of Standard codeine phosphate solution

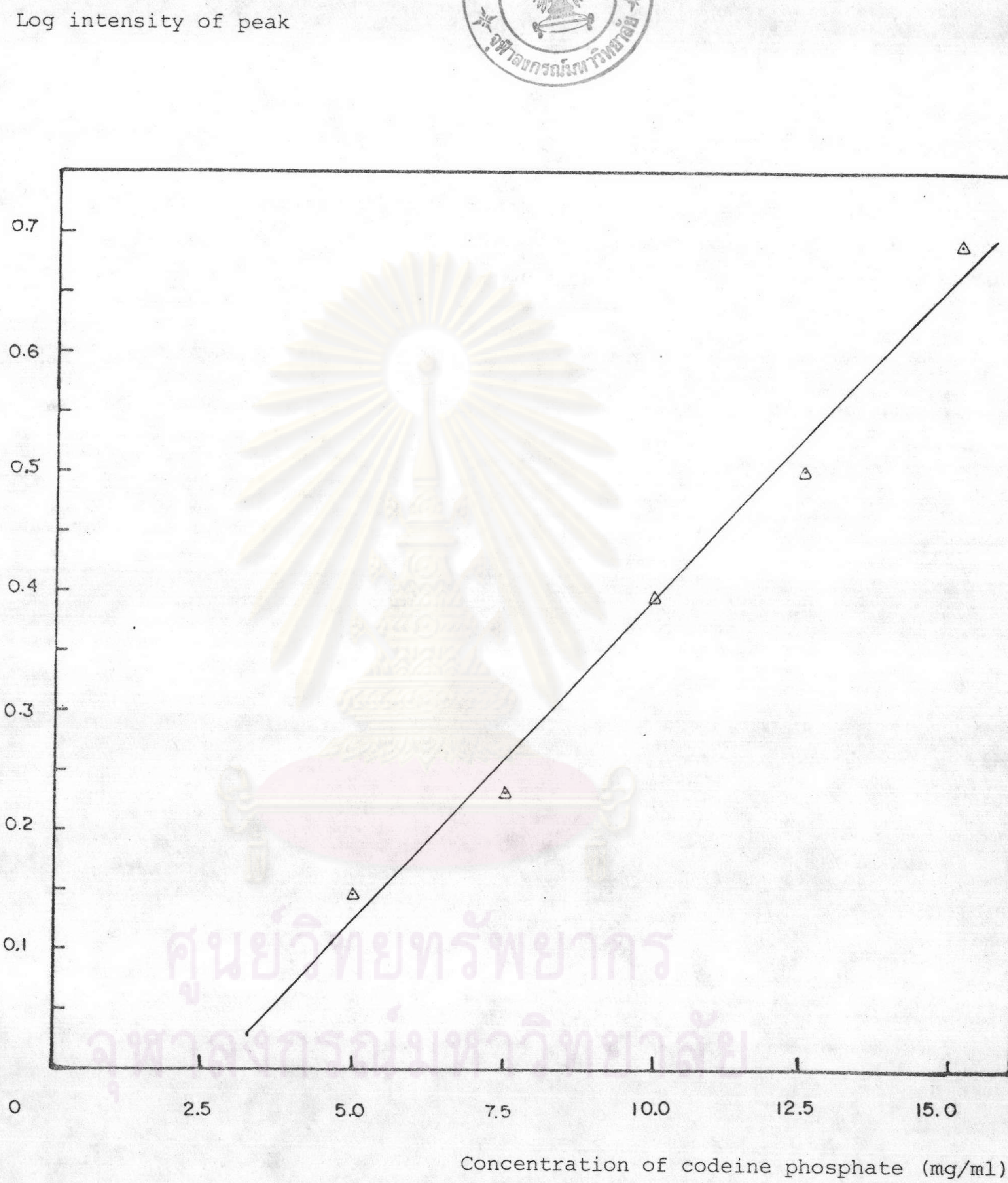


Figure 6: Standard curve of codeine phosphate solution

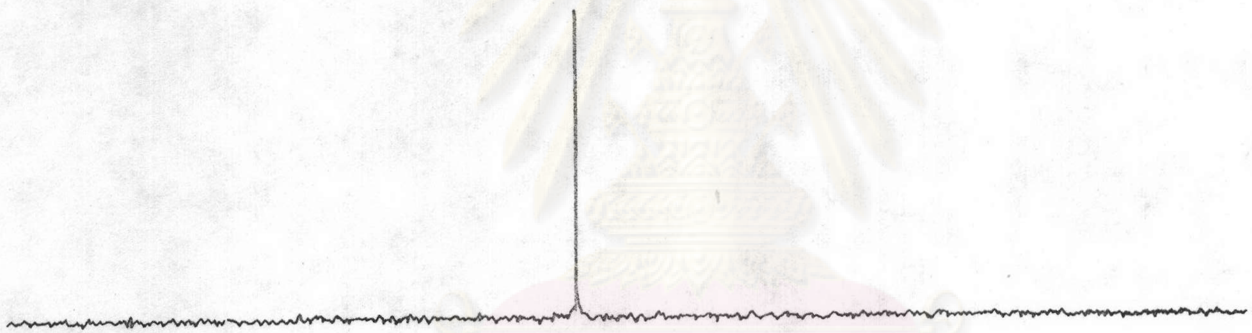


Figure 7: NMR peak of codeine phosphate injection

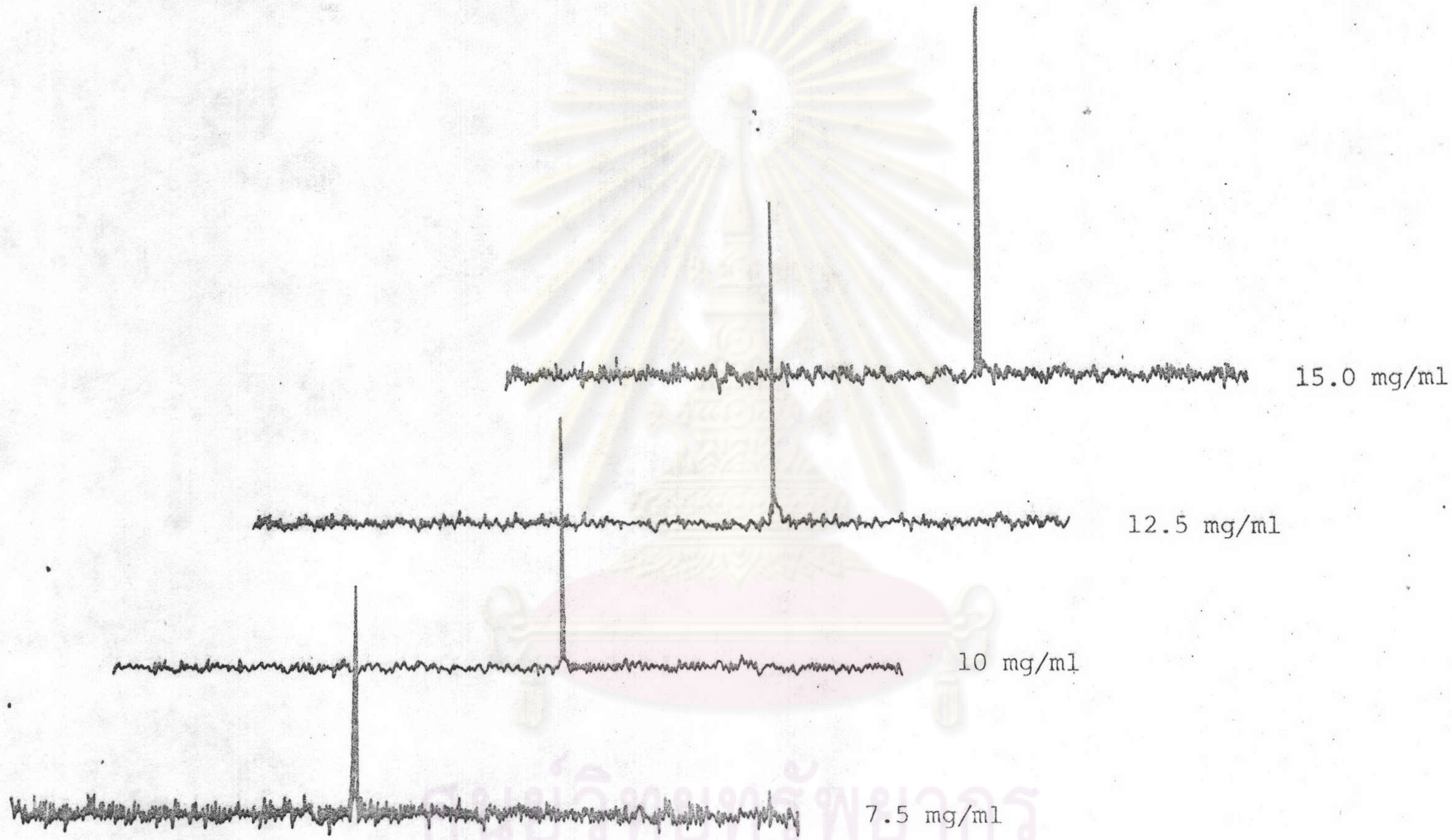


Figure 8: NMR peak of Standard codeine phosphate syrup

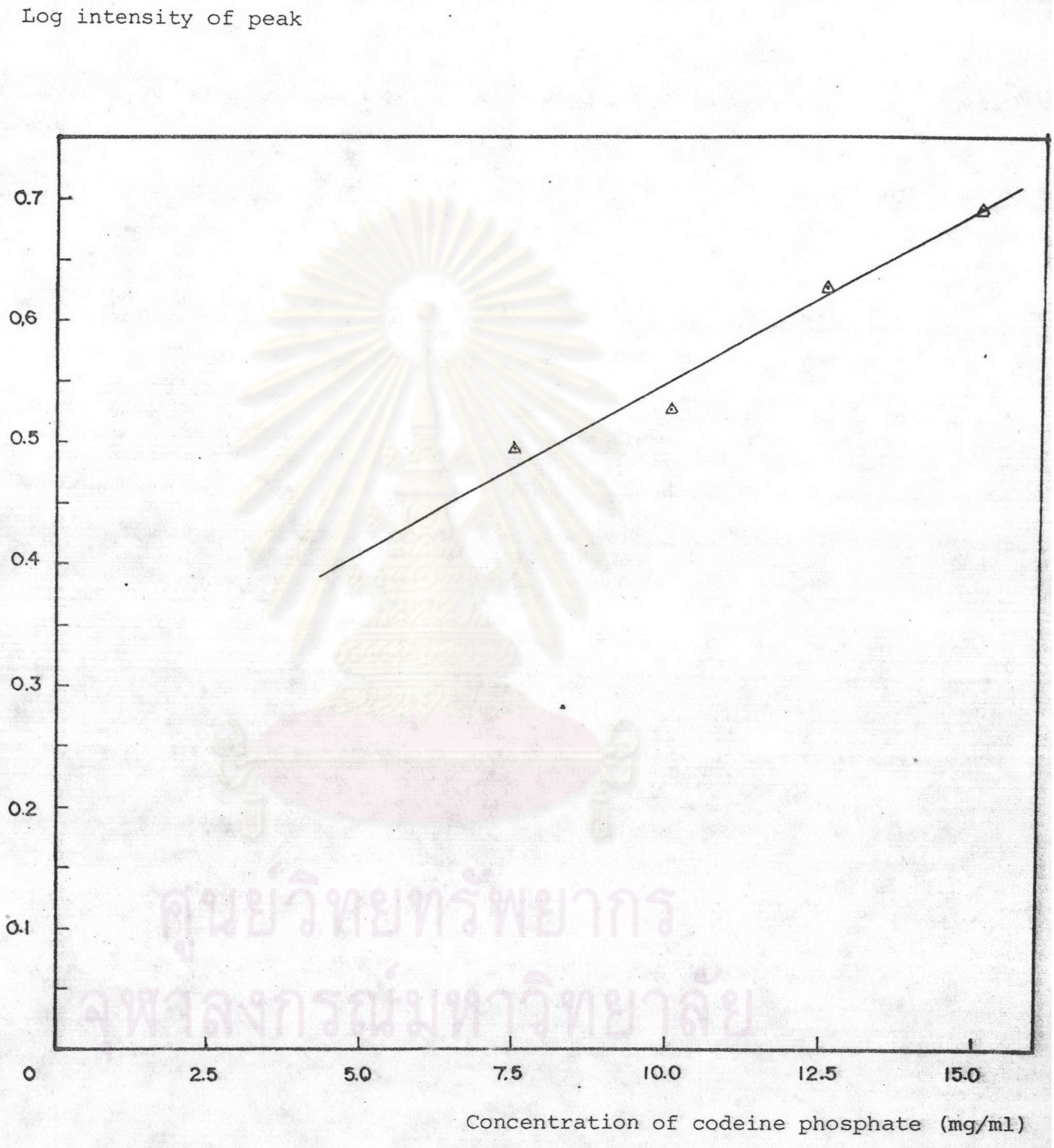


Figure 9: Standard curve of codeine phosphate syrup

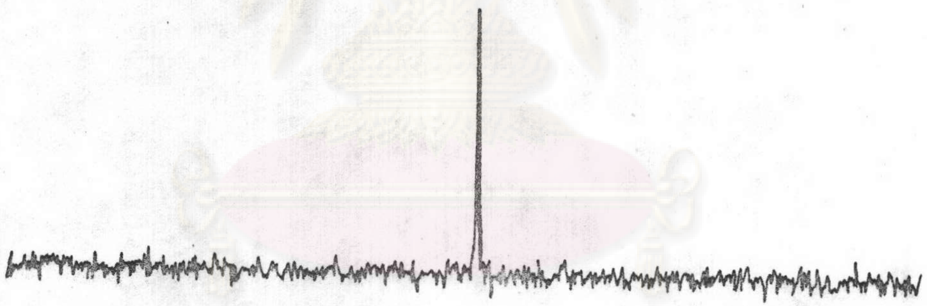


Figure 10: NMR peak of codeine phosphate syrup (sample)

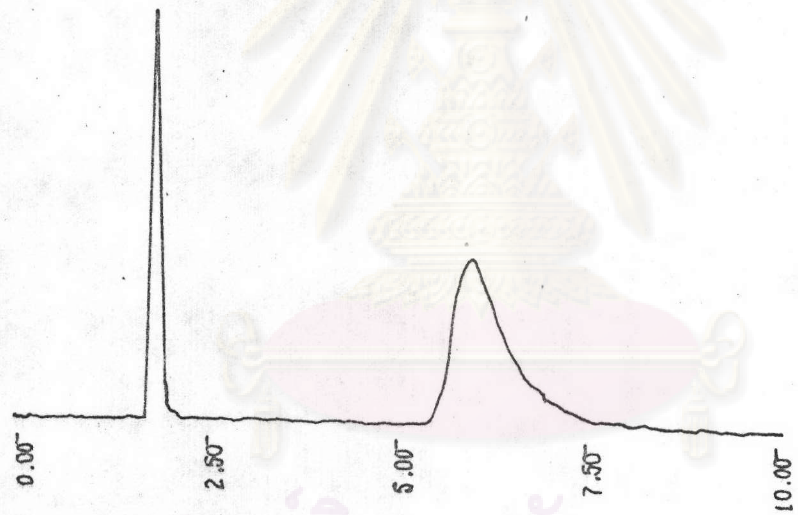


Figure 11: HPLC peak of standard codeine phosphate syrup

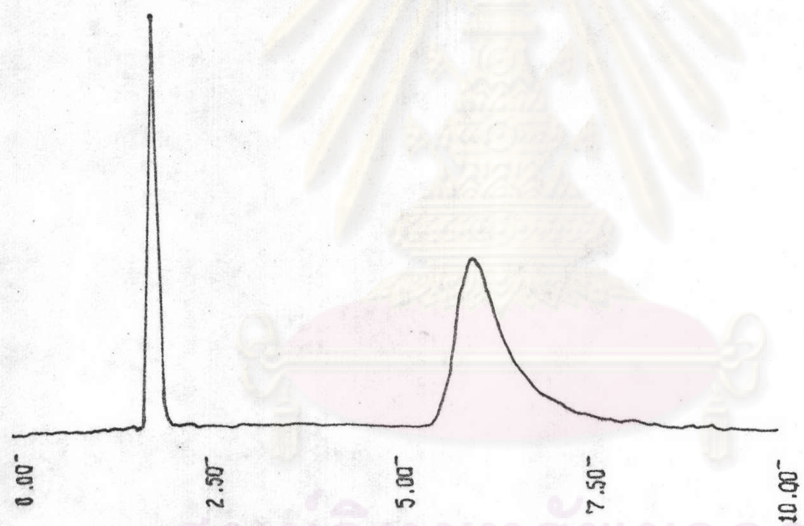


Figure 12: HPLC peak of codeine phosphate syrup (sample)

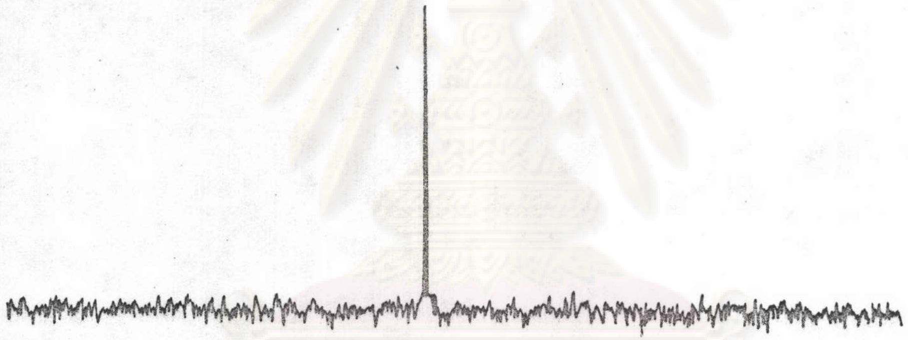


Figure 13: NMR peak of Actifed compound linctus

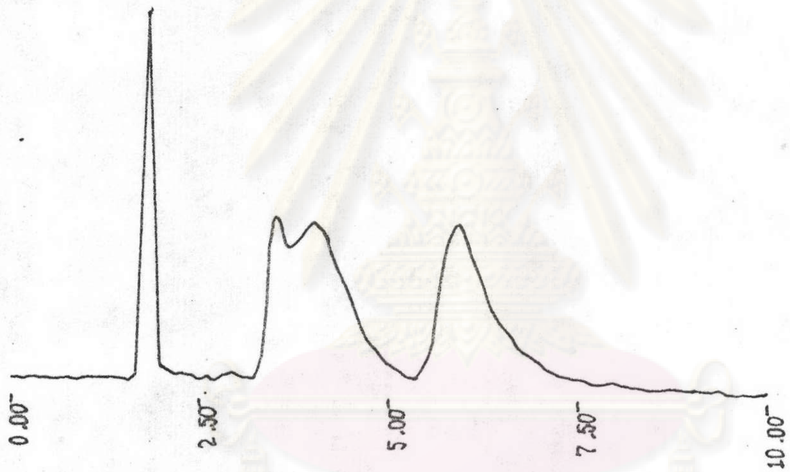


Figure 14: HPLC peak of Actifed compound linctus

VITA

Miss Amornrat Ratanakiethavorn was born on January 14, 1962. She got her degree in Bachelor of Science in Pharmacy in 1984 from Faculty of Pharmaceutical Sciences, Chulalongkorn University, Bangkok, Thailand.