Pharmaceutical Research, Vol. 6, No. 2, 1989

Report

The Determination of Microscopic Ionization Constants of a Substituted Piperazine Using Estimates from Model Compounds

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Received June 9, 1988; accepted September 14, 1988

The microscopic ionization constants of 1-[3-(4-chlorophenyl)propyl] piperazine (I) were determined using piperazine (P) and 1,4-bis[3-(4-chlorophenyl)propyl] piperazine (II) as models for one of the ionizations. The macroscopic ionization constants for all three compounds were measured potentiometrically, and the micro constants of P and II, which are symmetrical molecules, were calculated from their macro constants. Only one micro constant of either P or II was suitable as a model for elucidating the micro constants of I.

KEY WORDS: ionization constants; piperazines; microscopic ionization constants; potentiometric titration; acid–base equilibria.

INTRODUCTION

When a compound contains more than one ionizable group, such as a dibasic acid, determination of its pK becomes complicated. For such compounds, we can define macroscopic ionization constants (macro constants; representing the overall loss/gain of a proton) and microscopic ionization constants (micro constants; representing the ionization of each ionizable group). The concept of micro and macro constants has been discussed (1–3) and is commonly used for elucidation of zwitterionic equilibria (4–7). It is equally applicable to other polyprotic compounds. Knowledge of the micro constants of these compounds is necessary for the calculation of the concentration of each ionized species at any pH, which is important for complete understanding of the physiochemical behavior of such molecules.

For example, the ionization of a dibasic acid can be represented as follows:

place diagram here

where k_1, k_2, k_3, and k_4 are the micro constants for each ionization pathway. For symmetrical dibasic acids, $k_1 = k_2$ and $k_3 = k_4$.

Potentiometric measurement of ionization constants of such molecules gives two pK values representing the two macro constants, K_1 and K_2. The micro constants can be related to the experimentally measured macro constants by the following relationships:

$$K_1 = k_1 + k_2 \quad (1)$$

$$1/K_2 = 1/k_3 + 1/k_4 \quad (2)$$

$$K_1K_2 = k_1k_3 = k_2k_4 \quad (3)$$

The knowledge of K_1 and K_2 through experimental measurements is not adequate to calculate all four micro constants using eqs. (1)–(3). In general, one of the micro constants has to be independently measured or estimated in order to obtain the others. Several approaches to doing this have been discussed in the literature. Often, one or more micro constants can be measured spectrophotometrically (4,6). In other cases, one of the ionizing groups can be blocked, for example, by esterification, with the assumption that the remaining ionization is unaffected; problems with this approach have been discussed (8). A better approach is to estimate one of the micro constants using a model compound, with appropriate corrections for substituent effects (8,9).

We report here the determination of the micro constants of an *N*-substituted piperazine, 1-[3-(4-chlorophenyl)propyl] piperazine (I) (see Scheme I). The suitability of two compounds, piperazine (P) and 1,4-bis[3-(4-chlorophenyl)propyl] piperazine (II), as models for estimating one of the micro constants of I was investigated. The ionization schemes of P, I, and II are shown in Fig. 1. The macro constants of these three compounds were determined potentiometrically; all three compounds have two well-separated pK values. None of the micro constants could be determined spectrophotometrically because the compounds are not good chromophores. The solubility method of pK determination was not used because the hydrochloride salts of I and II tended to

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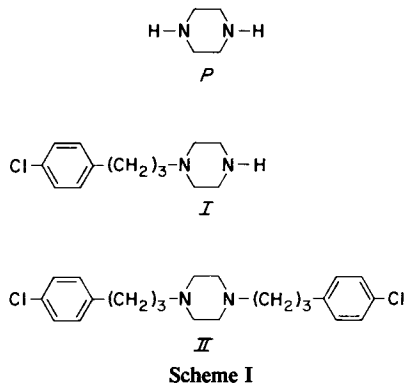

Scheme I

supersaturate in solution, and reliable measurements of solubility as a function of pH were difficult to obtain.

Since P and II are symmetrical, their micro constants could be directly calculated from their macro constants. Any one of these micro constants can then be used to elucidate the micro constants of I. The results of four different ways of calculating the micro constants of I are reported, and the relative merits of these four approaches are discussed.

MATERIALS AND METHODS

Piperazine dihydrochloride was obtained from Sigma and was used without further purification. I and II were synthesized as the dihydrochloride salts and their structure and purity were confirmed by nuclear magnetic resonance (NMR) and thin-layer chromatography (TLC), respectively.

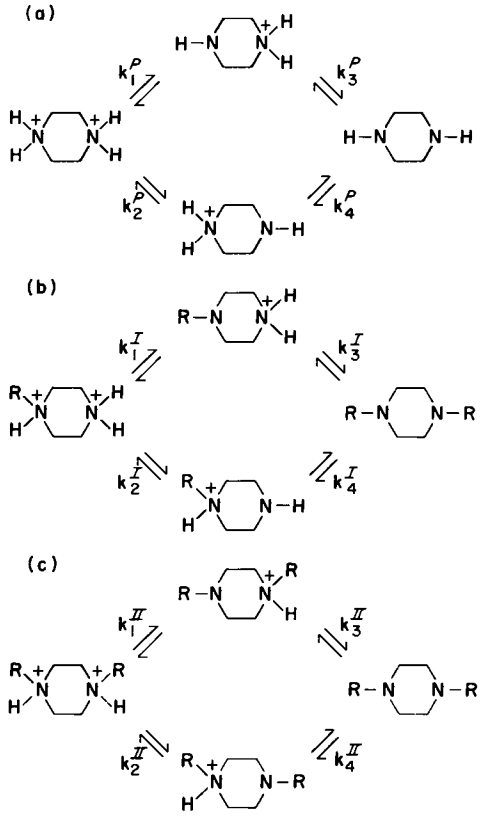

Fig. 1. Ionization schemes for (a) P, (b) I, and (c) II.

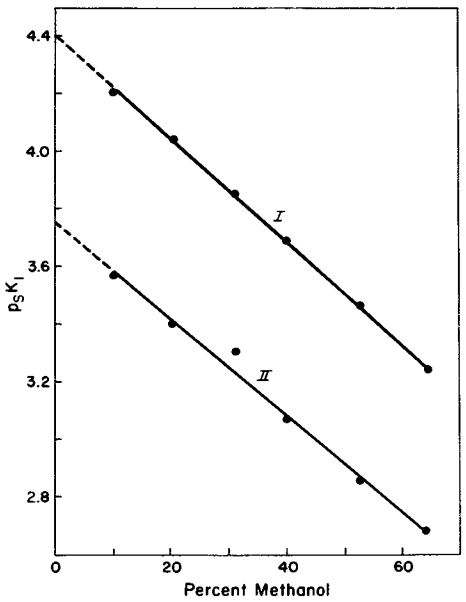

Fig. 2. Plot of $p_sK_1^I$ and $p_sK_1^{II}$ versus percentage (w/w) methanol.

Water used was freshly distilled. Methanol [high-performance liquid chromatography (HPLC) grade] and potassium hydroxide (ACS grade) were used without further purification. Acid potassium phthalate (NBS) was used for the standardization of potassium hydroxide solutions.

Titrations were conducted in a 100-ml jacketed beaker connected to a circulating water bath which controlled the temperature at 25 ± 0.5°C. The pH values were measured with an Orion Model 901 microprocessor Ionalyzer equipped with a combination glass electrode. Titrant was added from a buret or syringe; nitrogen was bubbled through the titrant immediately prior to titration to make it CO_2-free. For all titrations, the titrant was prepared and standardized in the same solvent as the sample being titrated. A swamping elec-

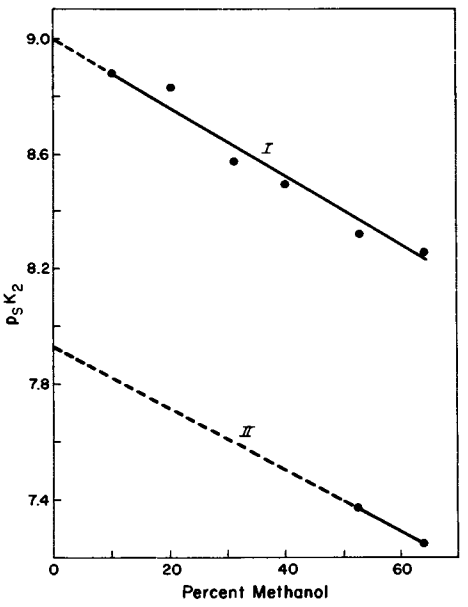

Fig. 3. Plot of $p_sK_2^I$ and $p_sK_2^{II}$ versus percentage methanol.

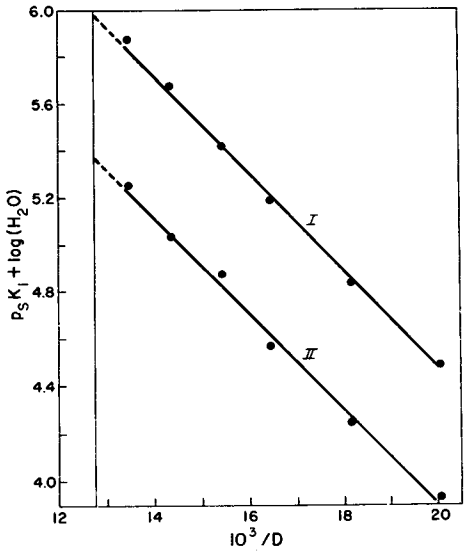

Fig. 4. Plot of $p_sK_1^I$ and $p_sK_1^{II}$ according to Eq. (4).

trolyte was not added to the sample solutions because this adversely affected the solubility of the compounds.

Titrations were carried out using the procedure recommended by Albert and Sergeant (1). Both macro constants of P and I (K_1^P, K_2^P, K_1^I, and K_2^I) were measured in water, while only K_1^{II} could be measured in water due to the poor solubility of II in water above pH 5. Since a swamping electrolyte was not added, the "mixed" ionization constants obtained were converted to thermodynamic ionization constants as follows. The ionic strength of the solution was calculated for each added aliquot of titrant. This was used to obtain the activity of each species from its concentration during the course of the titration. The activities, along with the measured pH, were then used to calculate ionization constants. This method of calculation has been discussed in detail by Albert and Sergeant (1). A correction for the change in volume during the titration was also applied.

Methanol–water mixtures (10–60%, w/w, methanol) had to be used to determine K_2^{II}. These mixed constants also had to be corrected for ionic strength changes during titration to give thermodynamic pK values. Corrections for activity effects in such mixed solvent systems are dependent on the dielectric constant of each mixture and were made using the equations described by Butler (10). The dielectric constants of the various methanol–water mixtures were obtained from the literature (11). In general, activity corrections for both the aqueous and the methanol–water titrations were negligible. The mixed constants obtained were then corrected for the variation of response of the glass electrode in methanol–water mixtures (12).

After making these corrections, the thermodynamic pK values in methanol–water mixtures (p_sK values) of varying composition can be extrapolated to pure water to obtain the aqueous thermodynamic pK (p_wK); the subscripts s and w refer to solvent and water, respectively. The disadvantages of using mixed solvents to determine the ionization constants of poorly water-soluble compounds has been discussed (1–3). In order to estimate the error that this approach could introduce in the value of K_2^{II}, we carried out methanol–water titrations for I as well and compared the extrapolated p_wK values to the p_wK values measured directly in water.

RESULTS AND DISCUSSION

Comparison of pK Values in Water and Methanol–Water Mixtures

As stated under Materials and Methods, p_sK_1 and p_sK_2 values for I and II were obtained in methanol–water mixtures and extrapolated to pure water to give the aqueous p_wK_1 and p_wK_2 values. Two approaches were used to carry out this extrapolation, one based on plotting p_sK versus solvent concentration (i.e., %, w/w, methanol) and the other based on an approach used in the literature (13), employing the following equation:

$$p_sK + \log [H_2O] = e^2/2.303akTD - \log B_H \qquad (4)$$

where $[H_2O]$ is the molar concentration of water in the methanol–water mixture, e is the ionic charge, a is the mean cation–anion diameter, k is the Boltzmann constant, D is the dielectric constant of the methanol–water mixture, and B_H is a constant. The left side of the equation is plotted versus $1/D$, and the line is extrapolated to $1/D = 0.01273$, the value for pure water. When log $[H_2O]$ (which equals 1.74 for pure water) is subtracted from this value, we obtain p_wK. Figures 2 and 3 show the results graphically for the percentage methanol approach, and Figs. 4 and 5 show the results using Eq. (4).

The determination of $p_wK_1^I$, $p_wK_2^I$, and $p_wK_1^{II}$ was also independently carried out in water. Due to the poor solubility of II above pH 5, $p_wK_2^{II}$ could not be determined in water and needed to be estimated using the methanol–water results. A comparison of directly measured p_wK values and those obtained through extrapolation using the two approaches discussed above is shown in Table I. The p_wK values obtained for P are also shown. Both methods of extrapolation give similar results, although the values obtained from the percentage methanol extrapolations are closer to those obtained from direct aqueous titration. In all further calculations, we used the extrapolated value of 7.93 for

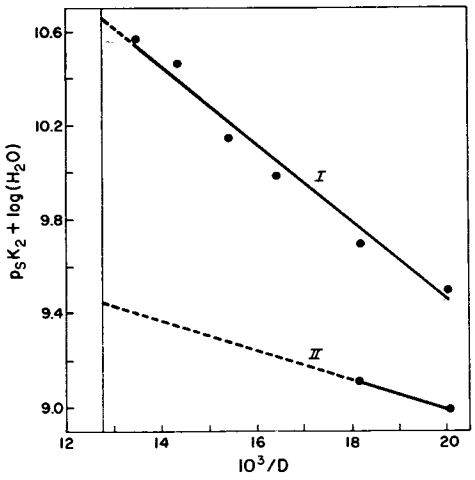

Fig. 5. Plot of $p_sK_2^I$ and $p_sK_2^{II}$ according to Eq. (4).

Table I. Comparison of Aqueous Thermodynamic Macro Constants (p_wK) Obtained by Titration in Water and by Extrapolation from Titrations in Methanol/Water Mixtures

Solvent	P		I		II	
	$p_wK_1^P$	$p_wK_2^P$	$p_wK_1^I$	$p_wK_2^I$	$p_wK_1^{II}$	$p_wK_2^{II}$
Water	5.36[a]	9.82[b]	4.35	8.99	3.72	—[c]
Methanol/water[d]	—	—	4.40	9.01	3.76	7.93
Methanol/water[e]	—	—	4.26	8.92	3.72	7.76

[a] Literature $pK_1 = 5.33$ (6).
[b] Literature $pK_2 = 9.73$ (6).
[c] Could not be determined due to solubility limitations.
[d] Extrapolated by plotting p_sK versus percentage methanol.
[e] Extrapolated by plotting according to Eq. (4).

$p_wK_2^{II}$ and directly measured p_wK values for all other macro constants.

Calculation of Micro Constants

The ionization schemes for P, I, and II are shown in Fig. 1. As stated in the Introduction, the micro constants are related to the macro constants through Eqs. (1)–(3). Because P is a symmetrical molecule,

$$k_1 = k_2 = 1/2K_1 \tag{5}$$

and

$$k_3 = k_4 = 2K_2 \tag{6}$$

This enables the micro constants of P to be calculated directly from the experimentally measured macro constants. Similarly, because II is a symmetrical molecule, its micro constants can be calculated from its macro constants. The calculated micro constants and corresponding micro pk values for P and II are listed in Table 2.

The micro constants of I cannot be obtained directly from its macro constants; an independent estimate of one of the micro constants is needed. For this purpose, we can use either P or II as a model. Both are suitable models based on Taft constants, which show that the effect on the pK of an aliphatic amine due to a secondary or tertiary amine substituent on the beta carbon is the same; alicyclic structures behave similarly (14). Therefore, we can neglect the substitution on the beta carbon and make the following assumptions:

$$k_1^I = k_1^{II} = k_2^{II} \tag{7}$$
$$k_2^I = k_1^P = k_2^P \tag{8}$$

Table II. Micro Constants (k) and Micro pk Values for the Symmetrical Molecules P and II

	P	II
k_1 (pk_1)	2.18×10^{-6} (5.66)	9.53×10^{-5} (4.02)
k_2 (pk_2)	2.18×10^{-6} (5.66)	9.53×10^{-5} (4.02)
k_3 (pk_3)	3.03×10^{-10} (9.52)	2.35×10^{-8} (7.63)
k_4 (pk_4)	3.03×10^{-10} (9.52)	2.35×10^{-8} (7.63)

$$k_3^I = k_3^P = k_4^P \tag{9}$$
$$k_4^I = k_3^{II} = k_4^{II} \tag{10}$$

Knowing the macro constants of I and using any one of the above estimates, we can calculate all the remaining micro constants of I through Eqs. (1)–(3). If the assumptions are all equally valid, the same set of micro constants for I should be obtained using any one of the four estimates.

However, we find that using Eq. (7) or Eq. (9) as a model gives negative values for two of four micro constants of I, making these estimates unsuitable. Equations (8) and (10) work well and give consistent values for the micro constants of I. Thus, P is a good model for the first ionization and II is a good model for the second ionization. Table III shows the micro constants of I calculated using all four approaches.

The ratio of concentrations of the monoprotonated secondary amine form (NH_2^+; obtained via the k_1^I step) to the monoprotonated tertiary amine form (NRH^+; obtained via the k_2^I step) is given by

$$[NH_2^+]/[NRH^+] = k_1^I/k_2^I = k_4^I/k_3^I \tag{11}$$

From this we calculate that 95% of the monoprotonated species exists in the NH_2^+ form and only 5% exists in the NRH^+ form; i.e., the k_1^I–k_3^I pathway dominates over the k_2^I–k_4^I pathway. As seen from Table III, estimates of k_2^I or k_4^I, the minor pathway, define the entire ionization scheme better than estimates of k_1^I or k_3^I, the predominant pathway. Model compounds P and II give estimates rather than precise values for the micro constants of I. Thus, a small error in the estimate of k_1^I or k_3^I, if in the wrong direction, can give negative values for the k values of the minor pathway. This is particularly evident in our case because the minor pathway contributes only to the extent of 5%. A similar error in the estimate of k_2^I or k_4^I will not give negative values for the k values of the major pathway. Thus, for our compounds, the use of estimates of the minor pathway are appropriate.

Equation (8) or (10) can therefore be used to obtain all the micro constants for I. Doing it both ways provides a good check on the validity of our assumptions and approach. We obtain excellent agreement in the micro constants of I when an estimate for k_2^I is used (P as a model) and when an estimate for k_4^I is used (II as a model), as shown in Table III. Thus, using model compounds is a suitable way of estimating micro constants of a complex molecule, provided the appropriate ionization pathway is chosen for comparison.

Table III. Calculation of Micro Constants of I Using One of the Micro Constants of *P* or II as a Model (The Corresponding p*k* Values Are Shown in Parentheses)

	Model			
	$k_1^I = k_1^{II}$	$k_2^I = k_1^P$	$k_3^I = k_3^P$	$k_4^I = k_3^{II}$
k_1^I (pk_1^I)	9.53×10^{-5}	4.25×10^{-5} (4.37)	1.50×10^{-4}	4.27×10^{-5} (4.37)
k_2^I (pk_2^I)	—[a]	2.18×10^{-6} (5.66)	—[a]	1.94×10^{-6} (5.71)
k_3^I (pk_3^I)	4.88×10^{-10}	1.07×10^{-9} (8.97)	3.03×10^{-10}	1.07×10^{-9} (8.97)
k_4^I (pk_4^I)	—[a]	2.10×10^{-8} (7.68)	—[a]	2.35×10^{-8} (7.63)

[a] Negative value.

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