pKa Determination of Benzhydrylpiperazine Antihistamines in Aqueous and Aqueous Methanol Solutions

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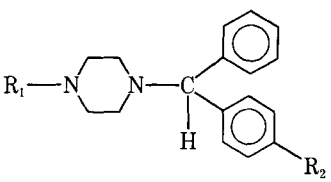
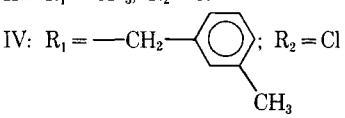
Abstract □ The pKa_1 and pKa_2 values of three benzhydrylpiperazine antihistamines, cyclizine (I), chlorcyclizine (II), and hydroxyzine (III), were determined at 24.5 ± 0.5° by potentiometric titration in aqueous solution to be 2.16 ± 0.02 and 8.05 ± 0.03, 2.12 ± 0.04 and 7.65 ± 0.04, and 1.96 ± 0.05 and 7.40 ± 0.03, respectively. The pKa_2 values were also determined by titration in seven aqueous methanol solutions in the range of 11.5–52.9% (w/w) methanol. The apparent dissociation constants of I–III in the aqueous methanol solutions, p_sKa_2, were plotted according to two linear regression equations from which the values in water, $p_\omega Ka_2$, were extrapolated. The plotted variables were p_sKa_2 *versus* methanol concentration (% w/w) and p_sKa_2 + log (water concentration, *M*) *versus* $1000/\epsilon$, where ϵ is the dielectric constant of the aqueous methanol solution. The maximum difference between pKa_2 and $p_\omega Ka_2$ was observed in the case of II where $p_\omega Ka_2$ was 5.23% higher. Statistical analysis of the linear regression data obtained from the plots showed that slightly better accuracy ($p < 0.13$) and correlation ($p < 0.16$) were obtained, but the precision was essentially equal with both methods. The observed ratio of K_{a1}/K_{a2} in I–III, 2.75×10^5–7.76×10^5, was attributed to solvent- and space-mediated field effects and electrostatic induction between nitrogen atoms in the piperazine ring.

Keyphrases □ Benzhydrylpiperazines—antihistamines, pKa determination in aqueous and aqueous methanol solutions □ Dissociation—pKa determination of benzhydrylpiperazine antihistamines in aqueous and aqueous methanol solutions □ Antihistamines—benzhydrylpiperazines, pKa determination in aqueous and aqueous methanol solutions

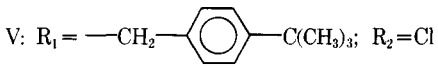
Five benzhydrylpiperazine antihistamines are currently marketed in the U.S.: cyclizine (I), chlorcyclizine (II), hydroxyzine (III), meclizine (IV), and buclizine (V).



I: $R_1 = CH_3$; $R_2 = H$
II: $R_1 = (CH_2)_2O(CH_2)_2OH$; $R_2 = Cl$
III: $R_1 = CH_3$; $R_2 = Cl$



IV: $R_1 =$ —CH_2— (p-CH_3 phenyl); $R_2 = Cl$



V: $R_1 =$ —CH_2— (p-$C(CH_3)_3$ phenyl); $R_2 = Cl$

Although some pKa[1] data for I (1, 2), II (1–3), III (4–7), and IV (6, 8) have been reported (Table I), much of it is based on titrations in 30–50% aqueous alcohols and chloroform–aqueous buffer partition experiments. More recent values of pKa_1 determined potentiometrically for III and IV (6) and spectrophotometrically for III (7) appear to have been conducted more precisely in aqueous solution.

The benzhydrylpiperazine antihistamines are popularly used as prescription and nonprescription dosage forms for their antiemetic, antipruritic, and sedative effects. It was the purpose of this investigation to determine the pKa_1 and pKa_2 values of these drugs for application to various pharmaceutical situations and to evaluate the accuracy of two methods for extrapolating an aqueous pKa estimate from apparent pKa values obtained in aqueous methanol solutions.

BACKGROUND

The low aqueous solubility of nonprotonated amine bases or nondissociated organic acids appears to be the consensus nemesis to determining pKa values of these substances by potentiometric titration. Even the lower limit of 5×10^{-4} *M* for potentiometry (9) is often not achievable. The use of mixed solvent systems, *e.g.*, an alcohol–water and dioxane–water, has been the method most commonly used to surmount this solubility problem. There is little or no disadvantage to this practice if the purpose merely is to compare the relative acidities or basicities of a series of chemical analogs. If, however, the objective is to make judgments pertaining to the aqueous environments of *in vivo* phenomena, the discrepancy between pKa values determined in aqueous and those in aqueous organic solvent solutions could be consequential.

Estimates of aqueous pKa values for inadequately soluble substances have usually been obtained by plots of the apparent pKa values in aqueous organic solvents *versus* solvent concentration (*e.g.*, % w/w) (10, 11):

$$p_sKa' = [\text{solvent}] + p_\omega Ka \qquad \text{(Eq. 1)}$$

where p_sKa' is the apparent dissociation constant in the aqueous organic solvent system, [solvent] is the organic concentration (% w/w), and $p_\omega Ka$ is the value of p_sKa' extrapolated to 0% (w/w) organic solvent or 100% (w/w) water. This method was used extensively in pharmaceutical studies during the 1950s and early 1960s (1–3, 12–15). The errors inherent in pKa estimates with this method have been addressed elsewhere (16–18). In 1959, two authors independently proposed a relationship that they rationalized should provide a more accurate estimate of aqueous pKa values

Table I—Acid Dissociation Constant (pKa) Values Reported for Some Benzhydrylpiperazine Antihistamine Drugs

Drug	pKa_1	pKa_2
Cyclizine (I)	2.54[a]	7.92[a], 8.16[b]
Chlorcyclizine (II)	2.44[a], 2.43[c]	7.78[a], 8.15[b], 7.81[c]
Hydroxyzine (III)	2.13[d], 1.83[e], 2.0[f]	7.9[g]
Meclizine (IV)	3.1[h], 2.05[i]	6.2[h]

[a] In 50% methanol (Ref. 1). [b] In 30–50% alcohol (Ref. 2). [c] In 20–80% alcohol (Ref. 3). [d] *Via* partitioning between 0.5 *M* H_3PO_4 and chloroform (Ref. 4). [e] In aqueous solution at an ionic strength <0.001 (Ref. 6). [f] Spectrophotometrically in aqueous solution (Ref. 7). [g] In unspecified aqueous methanol solutions (Ref. 5). [h] *Via* partitioning between 0.5 *M* H_3PO_4 and chloroform (Ref. 8). [i] In aqueous solution at an ionic strength of 0.005 (Ref. 6).

[1] The symbol pKa is used throughout in reference to the acid dissociation constant. Formally, K_a is the acid dissociation constant for proton loss by neutral and cationic acids or protonated bases, and $pKa = \log(1/K_a)$.

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obtained by extrapolation of p_sKa' values in aqueous organic solvent mixtures (19, 20):

$$p_sKa' + \log [H_2O] = \frac{1}{\epsilon}(e^2/2.303\,akT) - \log B_H \qquad \text{(Eq. 2)}$$

where p_sKa' is the apparent pKa value in aqueous organic solvent mixtures uncorrected for electrode response, $[H_2O]$ is the water concentration (M), ϵ is the dielectric constant, e is the ionic charge, a is the mean cation–anion ionic diameter, k is the Boltzmann constant, T is the absolute temperature, and B_H is a constant based on the assumption that $[H_3O^+] \gg [\text{solvent } H^+]$. The values of p_sKa' are corrected by subtracting a constant, δ, which takes into account the variability of glass electrode response in aqueous methanol solutions. This gives the actual pKa value in the mixed solvent system, p_sKa (21, 22):

$$p_sKa = p_sKa' - \delta \qquad \text{(Eq. 3)}$$

Thereafter, a plot of $p_sKa + \log [H_2O]$ *versus* $1/\epsilon$ that is essentially linear may be extrapolated to obtain the ordinate intercept value for $p_\omega Ka$, the estimated aqueous pKa when $\log [H_2O]$ is 1.74 and $1/\epsilon$ is 0.01273 [2]. The linearity of the plots may decrease appreciably when $1/\epsilon > 0.02$ (*e.g.*, ≥70% w/w methanol). This corresponds to the value of $\epsilon \simeq 50$, below which ionic dissociation begins to diminish with a concomitant increase in ion-pair association and perturbation of the equilibrium between the neutral and ionic species (18, 21).

The original solubility method for determining pKa values (23) has been applied to determining pKa values of acidic, basic, and amphoteric substances with low aqueous solubility (9, 24–26). This method has the advantage of providing thermodynamic pKa estimates when the ionic strength of the samples is low (*e.g.*, <0.0005). Its disadvantages include the failure to achieve equilibrium conditions and separate emulsified or suspended neutral species from the saturated salt solutions in equilibrium with them. Potential errors in solubility estimates resulting from supersaturation of ionic and/or neutral species and the instability of some compounds also jeopardize the accuracy of this method. Another method involving a single pKa titration in an aqueous organic solvent mixture has been proposed, but it was judged by its author to be generally inapplicable to the estimation of $p_\omega Ka$ values (27).

It is reasonable to expect that the widespread use of organic solvent–water mixtures for pKa titrations of substances with intrinsic water solubilities of <0.0005 M will continue. This is because of historical precedents and the expedient manipulative techniques that can be accomplished using aqueous organic solutions.

EXPERIMENTAL

Materials—Cyclizine hydrochloride (I)[3], chlorcyclizine hydrochloride (II)[4], hydroxyzine dihydrochloride (III)[5], meclizine dihydrochloride (IV)[6], and buclizine dihydrochloride (V)[7] were used as received. Methanol, hydrochloric acid, and potassium hydroxide solutions were ACS analytical reagent grade, and freshly boiled water with a resistivity ≥10^7 ohm cm were used in the solvent systems and titrants.

Procedures—Titrations were conducted in a 25- or 50-ml multinecked glass flask fitted with a thermometer calibrated in 0.1° units. Agitation was provided by a polytef-coated magnetic stirring bar, and pH values were measured with a digital pH meter[8] equipped with a combination glass electrode[9]. The ambient temperature of the systems varied from 24.0 to 25.0° with an average value of 24.5°. Titrant increments were added from a pipet[10] in 0.25-ml portions.

The $p_sKa'_2$ values of 0.002 M I–III were determined in seven aqueous methanol solutions in the range of 11.5–52.9% (w/w) with a titrant of 0.020 N KOH prepared in aqueous methanol that contained to within 0.1% (w/w) the same methanol concentration as the solutions of I–III. Values of pKa'_2, the apparent constant in aqueous solution, were determined in aqueous 0.001 M I and III titrated with aqueous 0.010 N KOH and in aqueous 0.0005 M II titrated with aqueous 0.005 N KOH. The pKa'_1 values of I and II were obtained from titrations of 0.015 M aqueous solutions with aqueous 0.030 N HCl. The pKa'_1 of III was determined by titrating aqueous 0.015 M III with aqueous 0.030 N KOH.

Activity Corrections—Values of p_sK_a' obtained from titrations of I–III in aqueous methanol solutions were corrected to p_sKa values with Eq. 2 using δ values reported elsewhere (22). The pKa'_2 values of I–III were corrected for activity effects of the K_2 equilibria in Scheme I[11] (16, 18, 28–30):

$$HB^+ + OH^- \overset{K_2}{\rightleftharpoons} B + H_2O$$

Scheme I

$$pKa_2 = pKa'_2 - \frac{0.51\sqrt{I}}{1 + 1.6\sqrt{I}} \qquad \text{(Eq. 4)}$$

where I is the ionic strength of the solution, and the entire negative term estimates the logarithm of the activity coefficient, $-\log \gamma_i$. A similar activity correction was used for the K_1 equilibria shown in Schemes II and III[11] (28):

$$H_2B^{+2} + OH^- \overset{K_1}{\rightleftharpoons} HB^+ + H_2O$$

Scheme II

$$HB^+ + H_3O^+ \overset{K_1}{\rightleftharpoons} H_2B^{+2} + H_2O$$

Scheme III

$$pKa_1 = pKa'_1 = \frac{1.5345\sqrt{I}}{1 + 1.6\sqrt{I}} \qquad \text{(Eq. 5)}$$

RESULTS AND DISCUSSION

The values of pKa_1 for I–III were determined to be 2.16 ± 0.02, 2.12 ± 0.04, and 1.96 ± 0.05, respectively. The corresponding values of pKa_2 are 8.05 ± 0.03, 7.65 ± 0.04, and 7.40 ± 0.03[12].

The plots of the data for p_sKa_2 *versus* methanol (% w/w) are shown in Fig. 1 and that for $p_sKa_2 + \log [H_2O]$ *versus* $1000/\epsilon$ in Fig. 2 for I–III. Least-squares regression lines were plotted for all I–III data sets to permit comparison of the accuracy and precision of $p_\omega Ka_2$ extrapolations derived from each set of ordinate and abscissa coordinates. The ϵ values in Fig. 2 were calculated for each aqueous methanol solution from a linear regression equation derived from data for 10–60% (w/w) methanol (31):

$$\epsilon = -0.4523C + 78.9307 \qquad \text{(Eq. 6)}$$

where C is the methanol concentration (% w/w)[13]. The linear regression data for the plots in Figs. 1 and 2 are summarized in Tables II and III, respectively.

A comparison of R values for I–III (Tables II and III) shows that, based on the Student's t test (32), there was a better linear correlation of the p_sKa_2 titration data plotted according to Eq. 2 ($p < 0.16$). There was, however, essentially no difference ($p < 0.001$) in the precision of the plots of Eqs. 1 and 2 based on a comparison of $S_{y,x}$ values (Tables II and III). The accuracy of $p_\omega Ka_2$ values for I–III, *i.e.*, the differences from pKa_2 (Tables II and III), was also better by Eq. 2 than Eq. 1 plots ($p < 0.13$). The slightly improved linear correlation of the Eq. 2 plot may explain, in part, why it has been advocated instead of Eq. 1 (16, 18). Furthermore, the unreported linear regression data for plots of $p_sKa_2 + \log [H_2O]$ *versus* methanol (% w/w) were virtually identical with those reported in Table III. This would be expected from the nearly linear relationship expressed by Eq. 6 (31).

Doubts about the accuracy of $p_\omega Ka$ values extrapolated from aqueous organic solvent mixtures containing >20% solvent have been expressed elsewhere (16–20); curves shaped like hockey sticks have resulted from Eq. 1 plots. One contributing cause of this could be plotting erroneous high values of p_sKa' uncorrected for δ (Eq. 3). The value of δ ranged from 0.02–0.12 in these titrations, increasing with methanol concentration. Failure to have corrected p_sKa' to p_sKa values would have caused progressive decreases in the slopes of Eq. 1 plots. The resulting horizontal inclinations, *i.e.*, the hockey stick appearance, at high methanol concentrations would have produced greater inaccuracy in the extrapolated

[2] The values of $\log [H_2O]$ and $1/\epsilon$ correspond to $[H_2O] = 55.3\ M$ and $\epsilon = 78.54$, respectively, for water at 25°.
[3] Lot 9C0080, Burroughs Wellcome Co., Greenville, N.C.
[4] Lot 8J0053, Burroughs Wellcome Co., Greenville, N.C.
[5] Lot 17583-27EA, 99.6%, Pfizer Inc., Brooklyn, N.Y.
[6] Lot 2F268-81EA, 100.0%, Pfizer Inc., Brooklyn, N.Y.
[7] Lot AN52650, Stuart Pharmaceuticals, Wilmington, Del.
[8] Model 125, Corning Scientific Products, Medfield, Mass.
[9] No. 476050, Corning Scientific Products, Medfield, Mass.
[10] Eppendorf Model 4700, Brinkmann Instruments Inc., Westbury, N.Y.

[11] B, HB^+, and H_2B^{+2} refer to the nonprotonated, monoprotonated, and diprotonated benzhydrylpiperazines, respectively.
[12] Values of pKa_1, pKa_2, and p_sKa_2 represent the means ± standard deviations of seven values in each set of ten titrations.
[13] The correlation coefficient, R, is 0.9997.

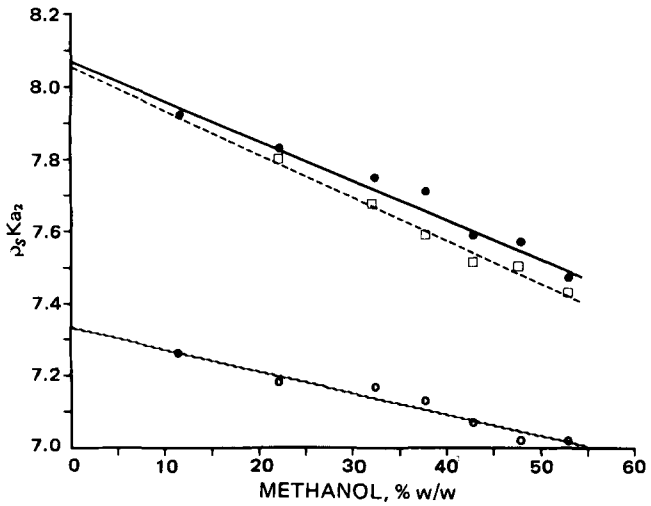

Figure 1—*Plot of p_sKa versus methanol (% w/w) for cyclizine (I), chlorcyclizine (II), and hydroxyzine (III). Key: (●) I; (□) II; (○) III.*

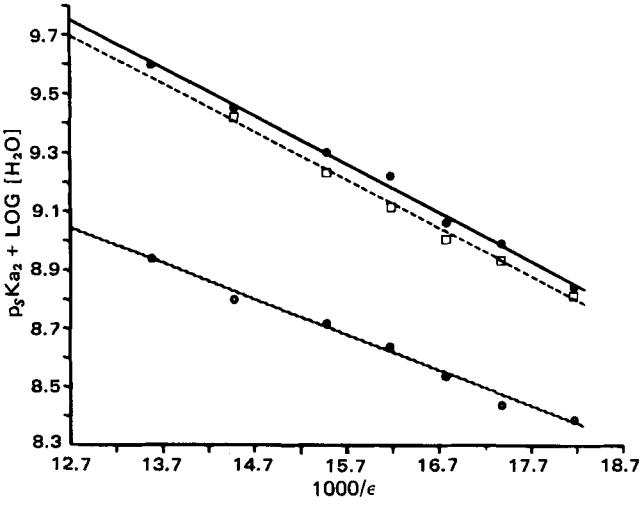

Figure 2—*Plot of p_sKa + log [H_2O] versus 1000/ε for cyclizine (I), chlorcyclizine (II), and hydroxyzine (III). Key: (●) I; (□) II; (○) III.*

$p_\omega Ka_2$ values. Therefore, the I–III p_sKa_2 data were calculated for 37.7% (w/w) ≤ methanol ≤52.9% (w/w) and 16.2 ≤ 1000/ε ≤ 18.2 (Table IV). Statistical analysis showed no difference in the accuracy and precision of I–III $p_\omega Ka_2$ values ($p < 0.001$) and the linear correlation of Eq. 1 and Eq. 2 plots ($p < 0.001$) between the data in Tables II and IV or Tables III and IV. These findings pertain only to I–III under the conditions stated, and they do not warrant general advocation of extrapolating $p_\omega Ka$ values from p_sKa data obtained in >35% (w/w) methanol.

A literature search yielded one similar study of some phenothiazine derivatives (33). Those plots were based on fewer data (mostly three points) obtained in a higher methanol concentration range (mostly ≥40%) and lacked the statistical data necessary for comparing pKa with $p_\omega Ka$ values derived from Eqs. 1 and 2. The plots apparently consisted of empirically connecting the sets of coordinates rather than calculating least-squares regression lines (33).

The magnitude of error in calculating the percent of monoprotonated I–III that would result from using $p_\omega Ka_2$ values to estimate otherwise unreported pKa_2 values for I–III was determined for pH 7.4. The error ranged from 0.72% for I (Table III) to 17.70% for II (Table II) (34):

$$\text{Percent } HB^+ = 100/[1 + 10^{(pH - pKa_2)}] \quad \text{(Eq. 7)}$$

$$\text{Percent } HB^+_\omega = 100/[1 + 10^{(pH - p_\omega Ka_2)}] \quad \text{(Eq. 8)}$$

$$\text{Error, \%} = |\text{Eq. 7} - \text{Eq. 8}| \quad \text{(Eq. 9)}$$

where HB^+ is the monoprotonated conjugate acid of I–III. From Eqs. 7 and 8, as the absolute values of the quantities pH − pKa_2 and pH − $p_\omega Ka_2$ increase, the value of Eq. 9 decreases.

A specific reason for the differences between $p_\omega Ka_2$ and pKa_2 values of I–III obtained by either Eq. 1 or Eq. 2 is not readily apparent. The fact that the titrants and I–III solutions were prepared in the same aqueous methanol concentrations, *i.e.*, within 0.1% (w/w), precluded stoichiometric errors in precision resulting from the nonadditivity of volumes and negative heats of solution. The variability in solvation phenomena

Table II—Linear Regression Data for Plots of Equation 1 [a]

Drug	Equation, p_sKa_2[b] =	$p_\omega Ka_2$[c]	pKa_2[d]	Absolute Value Difference, %[e]	R[f]	$S_{y,x}$[g]
I	−0.011C + 8.067	8.07	8.03	0.50	0.983	0.032
II	−0.012C + 8.052	8.05	7.65	5.23	0.995	0.015
III	−0.006C + 7.332	7.33	7.40	0.95	0.972	0.023

[a] When 11.5% (w/w) ≤ methanol ≤ 52.9% (w/w). [b] This refers to straight line plots for I–III (Fig. 1) where C is the methanol concentration (% w/w). [c] The value of p_sKa_2 extrapolated to 0% (w/w) methanol. [d] The value of pKa'_2 determined in aqueous solution and corrected for $-\log \gamma_i$ (Eq. 4). [e] Calculated from $|(pKa_2 - p_\omega Ka_2)|$ (100/pKa_2). [f] Correlation coefficient. [g] Standard error of the estimate of p_sKa_2 based on the methanol concentration.

Table III—Linear Regression Data for Plots of Equation 2 [a]

Drug	Equation, p_sKa_2 + log [H_2O][b] =	$p_\omega Ka_2$[c]	pKa_2[d]	Absolute Value Difference, %[e]	R[f]	$S_{y,x}$[g]
I	−0.164 (1000/ε) + 11.838	8.01	8.03	0.25	0.997	0.022
II	−0.164 (1000/ε) + 11.785	7.96	7.65	4.05	0.997	0.019
III	−0.121 (1000/ε) + 10.584	7.30	7.40	1.35	0.994	0.023

[a] When 14.5 ≤ 1000/ε ≤ 18.2. [b] This refers to straight line plots for I–III (Fig. 2) where [H_2O] and ε are the molarity of water and dielectric constant, respectively, of the aqueous methanol solvents. [c] This is the extrapolated value of p_sKa_2 obtained when log [H_2O] = 1.743, where 55.3 is the molarity of water at 25°, is subtracted from the quantity (p_sKa_2 + log [H_2O]) when the latter is calculated for 1000/ε = 12.73 where ε = 78.54 for water at 25°. [d] Footnote *d*, Table II. [e] Footnote *e*, Table II. [f] Footnote *f*, Table II. [g] Standard error of the estimate of p_sKa_2 + log [H_2O] based on 1000/ε values.

Table IV—Linear Regression Data for Plots of Equations 1 and 2[a]

Drug	$p_\omega Ka_2$ Eq. 1[b]	$p_\omega Ka_2$ Eq. 2[c]	pKa_2	Difference, %[d] Eq. 1	Difference, %[d] Eq. 2	R[e] Eq. 1	R[e] Eq. 2	$S_{y,x}$[f] Eq. 1	$S_{y,x}$[f] Eq. 2
I	8.25	8.09	8.03	2.74	0.75	0.971	0.990	0.029	0.027
II	7.97	7.87	7.65	4.18	2.88	0.985	0.997	0.014	0.012
III	7.40	7.32	7.40	0	1.08	0.938	0.977	0.022	0.029

[a] Where 37.7% (w/w) ≤ methanol ≤ 52.9% (w/w) and 16.2 ≤ 1000/ε ≤ 18.2, respectively, for Eqs. 1 and 2. [b] Footnote *c*, Table II. [c] Footnote *c*, Table III. [d] Footnote *d*, Table II. [e] Footnote *f*, Table II. [f] Footnote *g*, Table II.

and electrolytic equilibria of I–III in aqueous methanol solutions may partially account for the discrepancies between the pKa_2 and $p_\omega Ka_2$ values (16–19, 21, 22, 33). For example, different solvation mechanisms are possible with III than with I or II because the hydroxyethoxyethanol substituent, R_1 on III, is both a hydrogen bond acceptor and donor. Furthermore, the R_2 chloro substituent on II would increase its partition coefficient over that of I (35, 36). In fact, 0.002 *M* II was inadequately soluble in 11.5% (w/w) methanol while titrating its p_sKa_2, which is attributed to the enhanced hydrophobicity conferred by the chloro group, R_2 (35, 36). The p_sKa_1 values of 0.0005 *M* IV and V were obtainable only in solvents containing ≥47.8% (w/w) methanol. As noted earlier, titration data derived from the latter solutions would be poorly applicable to $p_\omega Ka_1$ estimates (18, 21).

Finally, it remains to be determined why the ratios of K_{a1}/K_{a2} for I–III show a variation of 2.75×10^5 to 7.76×10^5. The comparable ratio of K_{a1}/K_{a2} for piperazine (VI) was reported to be 1.38×10^4 (37)[14]. There are four main types of electrochemical effects that can account for these K_{a1}/K_{a2} ratios: (*a*) mesomerism or resonance in aromatic compounds, (*b*) inductive effects of substituents in aliphatic and aromatic compounds, (*c*) field effects such as intramolecular hydrogen bonding, and (*d*) molecular symmetry or statistical effects (38–42).

Because the piperazine ring is nonaromatic, mesomerism does not explain the observed K_{a1}/K_{a2} ratios. Secondly, the inductive effects of the R_1 and benzhydryl substituents on the piperazine group in I–III account for a maximum difference between K_{a1} and K_{a2} of ~62 as seen from the quotient of $(K_{a1}/K_{a2})_I/(K_{a1}/K_{a2})_{VI}$. It has been shown that electron-withdrawing (*-I*) groups have a marginal influence on K_a values of acids when the *-I* and ionogenic groups are separated by more than two $-CH_2$ residues (38, 40). These inductive effects account primarily for the differences between either K_{a1} or K_{a2} values of I–III. Thirdly, the statistical symmetry factor in VI and its analogs accounts for only a fourfold difference in K_{a1} and K_{a2} values (38–40, 42).

Solvent- and space-mediated field effects and inductive forces between nitrogen atoms of the piperazine ring appear to be the most plausible explanation for the large K_{a1}/K_{a2} ratios in I–III, VI, and similar compounds. Electrostatic attraction between the protonated and neutral nitrogen atoms of the piperazine ring has been alluded to (43), and it has been studied by conformational analysis using molecular orbital methods. (44). However, field effects mediated through solvent molecules may also contribute to these large observed ratios.

CONCLUSIONS

Aqueous pKa_1 and pKa_2 values for I and II, and pKa_2 for III, apparently heretofore unpublished, were determined. These pKa_2 values of I–III were also obtained in aqueous solutions of 11.5–52.9% (w/w) methanol. There was no substantial difference in the precision of $p_\omega K_2$ extrapolated from linear regression plots of p_sK_2 data according to Eqs. 1 and 2. However, Eq. 2 did yield slightly better correlation of the plotted coordinates. The overall accuracy of $p_\omega Ka_2$ compared to pKa_2 values for I–III also was better according to Eq. 2 plots ($p < 0.13$). The maximum difference observed between any pKa_2 and $p_\omega Ka_2$ value occurred in the case II using Eq. 1 by which $p_\omega Ka_2$ was 5.23% higher.

The large ratios of K_{a1}/K_{a2} for I–III and piperazine are attributed to field effects and intramolecular electrostatic attraction or induction in the piperazine ring.

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[14] The pKa_1 and pKa_2 values of VI are 5.68 and 9.82, respectively (37).

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