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ACKNOWLEDGMENTS AND ADDRESSES

Received September 23, 1968, from the College of Pharmacy, University of Iowa, Iowa City, IA 52240

Accepted for publication November 13, 1968.

This research was supported in part by a grant from the Warner-Lambert Pharmaceutical Company, Morris Plains, N. J.

Measurement of Acidity and Equilibria in Glacial Acetic Acid with the Glass-Calomel Electrode System

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Abstract □ This work describes the use of the glass-acetous fiber calomel electrode system in potential measurements in glacial acetic acid. Using the Nernst relationship and other equations describing equilibria in glacial acetic acid solution, the measurement of acidity, in terms of the activity of H_2OAc^+ , and then the calculation of overall dissociation constants for some bases, salts, and perchloric acid have been carried out. The electrode system has been found to respond as predicted by theory. Most calculated values agree with literature constants. Discordant results are discussed. The choice of the acetous fiber calomel electrode is explained and other reference electrodes are treated. The use of electrochemical potentials, obtained from potentiometric titration curves, in the calculation of K_B and K_{BHCIO_4} for bases is described. Results compare well with other methods. This procedure is recommended in the interest of increasing the specificity of titrations in acetic acid solvent. Based on sound fundamental principles, this work establishes a practical method for the determination of acidity in glacial acetic acid.

Keyphrases □ Acetic acid, glacial—acidity, equilibria measurements □ Glass-acetous fiber calomel electrode—acetic acid potential measurements □ Dissociation constants, overall—salts, bases, acid □ Potentiometric titration—acidity measure

Potentiometry has been a useful means for the study of equilibria in glacial acetic acid solvent. The chloranil electrode, introduced by Hall and Werner (1), was used by Bruckenstein and Kolthoff (2) to evaluate overall dissociation constants for selected acids, bases, and salts. The latter potentiometric study formed part of a series of papers thoroughly describing equilibria in glacial acetic acid (2–6).

The glass electrode, proven as an invaluable pH sensing device in water, has been used successfully in acetous solution. Higuchi *et al.* (7) used the glass-

calomel cell to show that the glass electrode behaved according to theory in the study of salt phenomena. The general behavior of the glass electrode in acetous solution has been described by Cheng *et al.* (8). These workers suggested the use of this electrode for dissociation measurements. Measurements of dissociation constants using the glass electrode have been reported but agreement with constants obtained by other means is poor (9). Kolling *et al.* (10, 11) utilized the glass-calomel cell for determining dissociation constants for various bases and salts using a comparative potentiometric method. This procedure does not, however, involve the explicit measurement of solvated hydrogen ion activity.

This work reports the study of the use of the glass electrode to determine acidity, *viz.*, the activity of the solvated proton as H_2OAc^+ , in glacial acetic acid. First the *Theory* section treats the theoretical basis for the use of direct or static potential measurements in the evaluation of acidity and dissociation constants; the necessary equations are presented. Then the theoretical basis for the use of titration or dynamic potential measurements in the calculation of dissociation constants is treated. Several compounds have been examined by these methods and the results are discussed. The ability of the glass electrode to function satisfactorily is reestablished. The use of the titration curve potentials seems particularly attractive in light of the rather widespread use of potentiometric titrations in glacial acetic acid (12–14).

THEORY

When made with a hydrogen ion-sensitive electrode, potential measurements can be related to the hydrogen-ion activity

in acetous solution by means of the Nernst relationship (Eq. 1).

$$E = E^0 - 0.0592 \log a_{H^+(s)} = E^0 - 0.0592 \log [H^+(s)] \quad (\text{Eq. 1})$$

where E is the measured potential; E^0 is the cell constant and includes an indeterminate liquid-junction potential term which is assumed to be constant; $H^+(s) = H_2OAc^+$.

The successful use of this equation which defines a relationship between measured potential and the solvated hydrogen ion in acetic acid, H_2OAc^+ , permits the evaluation of many different equilibria and equilibrium constants which depend on this species. The validity of Eq. 1 may be established by classical means. If the acidities calculated from Eq. 1 for specified systems permit calculation of equilibrium constants which are reasonable and agree with the same constants evaluated by independent methods, the validity of Eq. 1 is indicated. Another test consists of dilution studies from which plots of E versus $\log [H^+(s)]$ may be constructed. If linear responses and proper slopes (related to 0.0592) are obtained from systems whose $[H^+(s)]$ values are known, the authenticity of Eq. 1 is reaffirmed.

The use of Eq. 1 in the evaluation of acidity which may then be used in various equilibrium calculations requires the evaluation of E^0 . A convenient means for the evaluation of E^0 may be developed if a base in glacial acetic acid is considered. An equation introduced by Bruckenstein and Kolthoff (2) describes the electrochemical potential sensed by a solvated proton-sensitive electrode (*e.g.*, the glass electrode) when immersed in an acetous solution of base, B , of analytical concentration, C_B , and strength K_B .

$$E = E^0 - 0.0592 \log K_s + 0.0296 \log K_B + 0.0296 \log C_B \quad (\text{Eq. 2})$$

in which K_s is the autoprotolysis constant for acetic acid. If a base is chosen whose overall dissociation constant, K_B , is known from some independent source, then, since K_s is known and C_B is a stoichiometric quantity, Eq. 2 may be used to evaluate E^0 , a constant characteristic of a particular cell. Once E^0 is known then Eq. 1 may be used to calculate solvated hydrogen-ion activities in acetous solutions of acids, bases, or salts, or during a potentiometric titration.

If potential measurements have been made on a solution of an acid, HX , or base, B (including acetate salts), the calculation of the overall dissociation is relatively simple. The use of Eq. 1 translates a potential reading into the activity of solvated proton. Then the following expressions are used, assuming $[H^+(s)] = [X^-]$ and $[B^+] = [OAc^-]$, respectively.

$$K_{HX} = \frac{[H^+(s)]^2}{C_{HX} - [H^+(s)]} \quad (\text{Eq. 3})$$

where C_{HX} is the stoichiometric concentration of acid, HX .

$$K_B = \frac{(K_s/[H^+(s)])^2}{C_B - K_s/[H^+(s)]} \quad (\text{Eq. 4})$$

A more complex situation arises when the dissociation of a salt, *e.g.*, $NaClO_4$, which does not directly affect the autoprotolysis relationship, is considered. If to an acetous solution of such a salt, *e.g.*, $BClO_4$, is added an acetate salt with the same cation and a known overall dissociation constant, *e.g.*, $BOAc$, then, by means of the common-ion effect, resultant equilibria, and the Nernst relationship, as in Eq. 1, the potential of this system may be written as Eq. 5 (2).

$$E = E^0 - 0.0592 \log K_s - 0.0296 \log (K_{BOAc} C_{BOAc} + K_{BClO_4} C_{BClO_4}) + 0.0592 \log K_{BOAc} C_{BOAc} \quad (\text{Eq. 5})$$

Since K_{BClO_4} is the only unknown quantity, this expression may be used for determining the overall dissociation constant of a perchlorate.

The work of Kolthoff and Bruckenstein (5) provides equations to describe the equilibrium situations during the course of a titration. These expressions may be easily rearranged to suit the purpose of these calculations. The simplest and most convenient expression is that which describes the situation at the end point. If Eq. 1 is used to measure $[H^+(s)]$ at the end point and if K_{HClO_4} , the overall dissociation con-

stant for the titrant perchloric acid, is known from an independent source or is itself evaluated by Eq. 1, then since K_s is known, K_B may be calculated from Eq. 6. It is noted that Eq. 6 is concentration independent.

$$K_B = \frac{K_{HClO_4} K_s}{[H^+(s)]^2} \quad (\text{Eq. 6})$$

A second useful equilibrium situation is noted from the Kolthoff and Bruckenstein (5) equations in terms of the 50% neutralization point. If $[H^+(s)]$ is measured at the half-neutralization point and K_B is known by prior calculation from Eq. 6, then, since K_s and C_B are known, it is possible to calculate K_{BClO_4} from Eq. 7.

$$K_{BClO_4} = \left(\frac{[H^+(s)] K_B}{K_s} \right)^2 C_B - K_B \quad (\text{Eq. 7})$$

The expression for the acidity to be measured during the titration beyond the equivalence point is Eq. 8. Inspection of Eq. 8 indicates that no additional equilibrium constant

$$[H^+(s)] = \frac{K_{HClO_4} [HClO_4]}{(K_{HClO_4} [HClO_4] + K_{BClO_4} [BHC lO_4])^{1/2}} \quad (\text{Eq. 8})$$

data may be calculated if Eq. 7 has been used.

From the equations presented it is clear that much useful information may be obtained from potential measurements. First, direct potential measurements of acetous solutions of acids, bases, and salts permit rather simple calculations to be made to obtain overall dissociation constants. Second, in addition to yielding analytical data, a titration curve may be used to calculate K_B and K_{BClO_4} , constants characteristic of a particular base. These data introduce specificity into titrations in glacial acetic acid.

EXPERIMENTAL

Chemicals—All chemicals, if not otherwise mentioned, were of the highest grade commercially available. These were: 2,5-dichloroaniline, m.p. 48.5–49.0° (uncorrected), recrystallized from *n*-heptane; tribenzylamine, m.p. 93–93.5° (uncorrected), recrystallized from 95% ethanol; triphenylguanidine, m.p. 144.5° (uncorrected), recrystallized twice from 95% ethanol.

Glacial acetic acid,¹ was analyzed by Karl Fischer titration and found to contain less than 0.03 *M* H_2O .

Methanol,² was allowed to stand overnight in contact with barium oxide and then distilled.

Solutions—Acetous solutions were prepared by dissolving accurately weighed quantities of the desired base in acetic acid and diluting the solution to volume. In many cases, solution concentrations were chosen to facilitate preparation of other solutions by simple dilution.

In the case of lithium acetate, a dihydrate, an amount of acetic anhydride calculated to react stoichiometrically with the water was introduced, the solution was allowed to stand overnight for complete reaction, and then diluted to volume with acetic acid.

Acetous perchloric acid, about 0.1 *N*, was prepared according to Fritz (15).

Apparatus—The potentials of the cells were measured using a pH meter³ equipped with a 10-ohm ($\pm 0.05\%$) resistor across the output resistor terminals. A recorder,⁴ 125 mv. full scale, equipped with a 5.0-mv. range plug and a 0.5 cm./min. (1/5-in./min.) chart-drive motor recorded the output of the pH meter to provide millivolt-time profiles. No solution ground was used but the negative input terminal of the recorder was grounded to its chassis and was also connected to the ground terminal of the pH meter. The ground terminal of the pH meter and the magnetic stirrer chassis were both connected to a common grounding stake.

¹ Fisher reagent.

² Baker Analyzed, J. T. Baker, Phillipsburg, N. J.

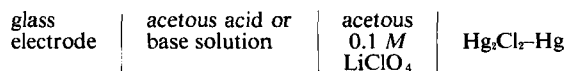
³ Leeds and Northrup model 7401.

⁴ Sargent model SR.

The cell consisted of a 400-ml. jacketed beaker, with a ground-glass cover provided with holes for the electrodes and a thermometer. The temperature of the jacketed cell was maintained constant at $25.0 \pm 0.2^\circ$. All of the potential values for the electrode pair are negative in acetous solution and were reproducible to ± 3 mv. The electrodes used were as follows: glass electrode⁶; fiber calomel electrode,⁹ modified by replacing the aqueous saturated potassium chloride with 0.1 M acetous lithium perchlorate solution; and platinum electrodes.⁷

The potentiometric titrations were carried out using the instrumentation described by Medwick and Kirschner (16).

Procedures and Calculations—The following cell and procedure was used for measuring potentials with the glass electrode:



A 50.00-ml. aliquot of acetous solution was transferred to the cell. The cell and its contents were permitted to equilibrate. The glass electrode, preconditioned in water before use, was wiped, rinsed with glacial acetic acid, again wiped, and then inserted into the cell. The calomel electrode, stored in glacial acetic acid when not in use, was rinsed with glacial acetic acid, wiped dry, and inserted into the cell. The recorder was then turned on to trace the potential as a function of time; the reading at the end of 15 min. was taken as the equilibrium potential. Preconditioning of the glass electrode by soaking in water for 0.5 hr. before each use was found to give best reproducibility of measured potentials.

The E° values for the glass electrodes were calculated using Eq. 2 from potential measurements made on about 0.5 M NaOAc acetous solutions assuming the Bruckenstein and Kolthoff (2) pK_B value of 6.57 for sodium acetate.

Calculations to convert measured potential values to acidities and then to the appropriate overall equilibrium constants were carried out using Eq. 1 and then, for acids, Eq. 3, and for bases, Eq. 4. The programs for each of these equations appropriate for the programmable calculator⁸ are available on request.

End points in the Karl Fischer titration for water were detected amperometrically with dual platinum electrodes following the procedure outlined in USP XVII (17) and using a pH indicator (18).⁹

The titrations were carried out by dissolving about 0.7 meq. of base in 50.00 ml. of acetic acid. The electrode treatment outlined for the glass electrode system was followed and, after the electrodes were immersed and the stirrer turned on, the solution was automatically titrated with about 0.1 N acetous perchloric acid until the total volume of about 10 ml. was delivered. The potential values were taken from the titration curve as described by Medwick and Kirschner (16).

Calculations to convert potential values at the end point to K_B values were made using Eqs. 1 and 6 whereas calculations to determine K_{BHClO_4} from potential readings at the half-neutralization point are made following the calculation of K_B values from end point data and use of Eqs. 1 and 7.

RESULTS AND DISCUSSION

Potential Measurements and Overall Dissociation Constants

—Potential measurements may be used to calculate various equilibrium constants. If well behaved, these constants should be reasonably precise and should agree with values obtained by independent, established methods. In addition, the production of reproducible constants is a means of establishing proper electrode behavior.

Table I is a compilation of the constants obtained using the glass-acetous calomel electrode system. The compounds

listed are three inorganic acetate salts, seven organic bases of varying strengths, one inorganic perchlorate salt, and perchloric acid. The average values and their average deviations (Table I, Column 4) represent at least a 10-fold concentration range of solute (Table I, Column 1), except for sodium acetate. More dilute solutions than those reported gave results which deviated somewhat from the mean values. It must be borne in mind that when potential measurements are made in nonaqueous media, the solution being studied may contribute to the IR drop when the ionic concentration is small (20). When 2,5-dichloroaniline, a weaker base, was studied, a higher concentration than that used for stronger bases was employed.

An examination of the sets of pK values presented for each compound points up a recurrent trend in all cases except for sodium perchlorate (in the presence of sodium acetate) and perchloric acid. In each instance, it is noted that the pK value is slightly larger at higher solute concentrations indicating that each species is a weaker electrolyte. This may be rationalized by recognizing the possibility of ion-pair formation in more concentrated solutions. However, since the differences in the pK values at the various concentrations are not large and are found to be within anticipated experimental error (*vide infra*), averages have been calculated over the reported concentration ranges and are felt to be valid.

The average deviations presented in Table I, Column 4 are, at the maximum, 0.13 units corresponding to an uncertainty of 4 mv. Since the determinate reading error is 1 mv. and the meter limits-of-error are specified as 5 mv. (21), it is noted that all of the reported values are within experimental uncertainty.

Since a reference compound is necessary to standardize an electrode in terms of an E° value, sodium acetate, 0.5 M acetone solution, was chosen and its $pK_B = 6.57$ as reported by Bruckenstein and Kolthoff (2) was used for calculations involving Eq. 2. Kolling (11) also used sodium acetate as a reference in studies involving the glass electrode. It should be noted that using sodium acetate presents some experimental problems. First, the hygroscopic nature of the anhydrous material makes it necessary for appropriate precautions to be taken, e.g., transferring the chemical in a dry box. Secondly, unless acetic acid solvent is added carefully to wet the crystals before a large volume of solvent is added, dissolution of sodium acetate becomes a slow, time-consuming process. Possibly the use of a different standard could be made. Tribenzylamine, or triphenylguanidine, relatively strong bases with large molecular weights, seem like good prospects. However, the commercially available chemicals need to be purified by recrystallization before they can be considered satisfactory. Triphenylguanidine has been used as a primary standard in glacial acetic acid titrations.

For comparative purposes, overall dissociation constants obtained by chloranil-electrode measurements (2), glass-electrode measurements reported by Kolling (11), and conductance determinations (19) have been included in Table I, Column 5, where available. At concentrations different from that used to standardize the electrode system, the value for sodium acetate is in good agreement with both the chloranil and conductance values. The value for lithium acetate agrees with the chloranil value but not the conductance method whereas the potassium acetate situation is the reverse. The value for tribenzylamine, thought to be potentially valuable as a standard for electrode calibration in this method, shows it to be the strongest base studied. However, comparison of this constant with the chloranil value shows a large discrepancy probably ascribable to the use of a recrystallized chemical in place of the commercial material reported in the chloranil study. Better agreement with the chloranil constants than with the Kolling values is noted in both the cases of *N,N*-diethylaniline and 2,5-dichloroaniline.

It should be borne in mind that the glass-electrode values reported by Kolling are for a single concentration of each base, viz., 4×10^{-3} M. In the instance of a weak base such as 2,5-dichloroaniline, at this concentration, the solution contribution the IR drop may result in deviations.

The value for sodium perchlorate was obtained by studying

⁶ Corning 476022.

⁷ Corning 476002.

⁸ Beckman 39271 and Leeds and Northrup 117157.

⁹ Mathatron Power Log model 848, Mathatronics, Waltham, Mass.

⁹ Leeds and Northrup model 7401.

Table I—Overall Dissociation Constants

Compd.	1	2	3	4	5	Compd.	1	2	3	4	5	
	Concn., $M \times 10^3$	E , mv.	pK , calcd. ^a	pK ^b	pK , ^b Literature Values		Concn., $M \times 10^3$	E , mv.	pK , calcd. ^a	pK ^b	pK , ^b Literature Values	
Sodium acetate	49.9	422	6.63			<i>N,N</i> -Diethylaniline		432	5.85			
		423	6.66								6.06	
	5.45	445	6.45				48.6	393	5.64		± 0.12	
		448	6.55	6.56 ± 0.08	6.57 $\pm 0.02^c$ 6.68 ^d		4.76	393	5.64			
Lithium acetate	462.5	402	6.92			Atropine	1.03	423	5.63			
		405	7.02					423	5.63		5.56	5.78
	46.3	429	6.83					423	5.63		± 0.10	$\pm 0.07^e$
		431	6.90					435	5.36		5.20 ^e	
	4.63	452	6.61			Benzocaine	99.6	397	6.09			
		456	6.75	6.82 ± 0.11	6.79 $\pm 0.00^c$ 6.22 ^d			393	5.95			
Potassium acetate	97.8	406	6.38					428	6.07			
		408	6.45					424	5.94			
	55.9	415	6.44				451	5.88		5.93		
		413	6.38				447	5.74		± 0.10		
	5.09	443	6.35			2,5-Dichloroaniline	257	433	7.71			
		440	6.25	6.37 ± 0.05	6.15 $\pm 0.05^c$ 6.44 ^d			433	7.71			
Triphenylguanidine	102.7	388	5.79					463	7.73			
		392	5.93					463	7.71			
	59.2	397	5.69				461	9.25				
		394	5.86				469	9.22				
	50.3	420	5.57				472	9.32				
	5.05	420	5.57				485	9.06				
				5.71 ± 0.13			488	9.16		7.60 ± 0.13		
Tribenzylamine	10.0	398	5.12			Sodium perchlorate (in presence of equimolar sodium acetate)	250	445	5.41			
		390	4.83					442	5.51			
	4.99	406	5.07					471	5.57			
		398	4.79					468	5.67			
	1.01	423	4.92				811	5.73				
		416	4.67	4.87 ± 0.10	5.36 $\pm 0.06^e$		812	5.76		9.17 ± 0.09	9.48 $\pm 0.01^e$ 10.25 ^e	
Tris (hydroxymethyl)- aminomethane	99.3	398	6.12			Perchloric acid	9.95	811	5.73			
		402	6.25					812	5.76			
	4.83	410	6.21					780	5.88			
		407	6.11					780	5.88			
	3.87	436	6.00							5.82 ± 0.07	4.87 $\pm 0.07^e$	

^a Calculations are based on potentials measurements made with two glass electrodes both having $E^{0'} = -1.043$ v. ^b Values are the respective average deviations. ^c Data of Bruckenstein and Kolthoff (2). ^d Data of Jones and Griswold (19). ^e Data of Kolling (11). ^f This value is the total concentration of equimolar quantities of sodium perchlorate and sodium acetate.

the potential values of solutions containing equimolar quantities of sodium perchlorate and sodium acetate and employing Eq. 5 as described in the *Theory* section. It is noted that agreement between the authors' results and those obtained from chloranil measurements is good. It should be recognized that the solution system used here corresponds to the point of half-neutralization of a titration.

A second, well-known criterion for establishing proper electrode function is noted from Eq. 2 which predicts a theoretical slope of $+0.0296$ v. for a linear plot of measured potential versus the logarithm of the base concentration. Table II presents data from dilution studies made with the glass electrode and compares them with chloranil-electrode values. All of the values approach the theoretical expectation again indicating proper behavior of the glass electrode in the glacial acetic acid solvent.

The constants for perchloric acid as determined by the glass and the chloranil electrodes show a disagreement of practically a whole pK unit. Bruckenstein and Kolthoff (4) have corrected their value for the effect of water. The value from these laboratories was determined in a medium containing a negligible (< 0.03 M H_2O) quantity of water and was not corrected. If the Bruckenstein and Kolthoff equations were used to correct this value the correction would be ≤ 0.14 units; this would not lead to substantial agreement between the discordant values. Use of the value from this

laboratory in calculations indicated it to be satisfactory. This point will be referred to subsequently.

In summary, the pK values reported in this work are in good agreement with independent values, in most instances. Logical explanations are available for those cases where devia-

Table II—Calculated Slopes Obtained from Dilution Studies

Compd.	Slope, (+), Glass Electrode ^a	Slope (-), Chloranil Electrode ^b (2)
Sodium acetate	0.028	0.030
Potassium acetate	0.025	0.027
Lithium acetate	0.026	0.030
Tribenzylamine	0.026	0.026
<i>N,N</i> -Diethylaniline	0.030	0.030
Triphenylguanidine	0.024	—
Atropine	0.027	—
Tris(hydroxymethyl) amino methane	0.025	—
Benzocaine	0.027	—
2,5-Dichloroaniline	0.024	0.030

^a Calculated from plots made with the data from Table I. ^b These slopes are expressed as negative but are positive according to the conventions used in this work.

tions are noted. In addition, the general agreement and reproducibility of the constants together with proper Nernstian-slope values from dilution studies has reaffirmed the satisfactory behavior of the glass electrode in glacial acetic acid. A convenient method is now available for the measurement of acidity and the overall dissociation constants of acids and bases in glacial acetic acid.

Choice of Reference Electrodes—The usual reference electrode of choice in potential measurements or titrations in glacial acetic acid is the calomel electrode. Although both the sleeve and fiber calomel electrodes are used, leakage from the sleeve calomel electrode introduces finite amounts of the salt-bridge solution into the test solution. If the bridge solution is an acetous lithium perchlorate, the latter salt, somewhat acidic in nature (22), becomes an undesirable test solution component, confusing equilibrium measurements and calculations. An aqueous potassium chloride salt bridge means the introduction of water as well as potassium chloride into the test solution. This solution is not desirable.

The fiber electrode is preferred since only negligible amounts of the bridge solution are lost eliminating solution contamination. In these laboratories, the bridge solution used is 0.1 M acetous lithium perchlorate. This solution provides the advantage over the usual aqueous solutions in that the possibility of precipitating bridge solution solute in the fiber orifice is diminished. The use of a silver metal reference electrode as recommended by Fleck (23) indicates that it cannot be used for amine bases possibly owing to the formation of silver-amine complexes.

Potentiometric Titrations and the Calculation of pK_B and pK_{BHClO_4} Values—When potentiometric titrations are conducted in a laboratory, the glass-calomel electrode system is used to record a potential *versus* titrant volume profile which may then be used in order to determine the end point graphically. No methods have been available up to this point which permit the interpretation of the potential readings as a measure of acidity or much less use of appropriate data for the calculation of useful constants.

Using the simple equations necessary to calibrate a glass electrode and then using the calibrated glass electrode in the titration, it is now possible to use potentiometric titration data in acetic acid to calculate the pK_B and pK_{BHClO_4} values for a titrated base. Consequently, a degree of specificity has been added to titrations in glacial acetic acid solvent. Table III is a presentation of pK_B and pK_{BHClO_4} values calculated from potentials obtained from potentiometric titration curves for four organic bases. Comparison of the pK_B values obtained from the titrations with the static potential values indicates agreement within experimental error except for 2,5-dichloroaniline, the weakest base studied. Even in this case, however, the value obtained is quite reasonable and is close to the chloroanil electrode value (4). It is not possible to compare each of the pK_{BHClO_4} values listed in Table III since independently determined constants are not available. However, Kolling (11) has reported a value of 5.73 for the pK_{BHClO_4} for 2,5-dichloroaniline. This is compared with 6.11 found in Table III. The agreement is not good but it must be remembered that Kolling's value of 10.25 for the pK_B for 2,5-dichloroaniline did not compare well with other values, as is noted in Table I. Consequently, since the pK_B is needed in the calculation for pK_{BHClO_4} , a difference in the pK_{BHClO_4} would be expected. It should be noted that a larger degree of uncertainty is to be expected when electrochemical potentials are read from titra-

tion curves. The titration is a dynamic process during which potentials are continually changing.

The agreement of the pK_B values presented in Table III with those listed in Table I reaffirms the correctness of the equilibrium expressions derived by Kolthoff and Bruckenstein (5). These expressions correctly describe the situations before, at, and after the equivalence point of titrations of a base with perchloric acid. Two of these, Eqs. 6 and 7, have been used to calculate the reported pK_B and pK_{BHClO_4} values. In each of these expressions the equilibrium constant for perchloric acid appears. In order to obtain values for the various pK_B measurements which are in good agreement with the static pK_B values, the pK_{HClO_4} , 5.82, measured in this work was used. When the Bruckenstein and Kolthoff (2) value for pK_{HClO_4} , 4.87, is used, the calculated results are not reasonable. This tends to corroborate the value found in these laboratories. The situation involving the perchloric acid equilibrium constant has been discussed in a preceding section.

The use of potentiometric data to calculate equilibrium constants is an attractive procedure. In addition to analytical data relating to the purity of a chemical, simple calculations will produce both a pK_B and a pK_{BHClO_4} . These constants give some insight into the nature of the base. In addition, there is no need to obtain or synthesize the base perchlorate in order to determine its overall constant. This is a distinct advantage over the static potentiometric procedure. It is strongly recommended that potentiometric titration data be gathered in the described manner which will permit routine calculation of pK_B and pK_{BHClO_4} data. Certainly this will add a degree of specificity to titrations in glacial acetic acid.

SUMMARY

The theoretical response of the glass-acetous fiber calomel electrode system has been reaffirmed.

The electrode system has been used to measure acidities after calibration against sodium acetate, a base of known strength.

Electrode potentials have been employed in the calculation of overall dissociation constants of some bases, salts, and perchloric acid. Programs suitable for a programmable calculator used in these calculations are available. The constants are generally in good agreement with literature values.

The choice of a reference electrode is discussed.

Electrochemical potentials, interpolated from potentiometric titration curves, are used to conveniently calculate K_B and K_{BHClO_4} values for bases being titrated. These constants agree with those available from other methods.

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Table III—Dissociation Constants Calculated from Titration Curve Data^a

Compd.	pK_B^b	$pK_{BHClO_4}^b$	No. of Titrations
Tribenzylamine	5.12 ± 0.20	4.79 ± 0.13	6
Triphenylguanidine	5.56 ± 0.17	5.45 ± 0.12	6
Atropine	5.64 ± 0.15	5.45 ± 0.10	6
2,5-Dichloroaniline	9.68 ± 0.07	6.11 ± 0.05	4

^a All titrations conducted with the same glass electrode, $E^0 = -1.043$ v. ^b Values are averages and their average deviation.

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Received August 29, 1968, from the *College of Pharmacy, Rutgers, The State University, Newark, NJ 07104*

Accepted for publication December 3, 1968.

Taken, in part, from a dissertation presented by Gerald Kaplan to The Graduate School, Rutgers, The State University, in partial fulfillment of Doctor of Philosophy degree requirements.

The authors are grateful to The American Foundation for Pharmaceutical Education and to Johnson and Johnson for financial aid to G. K. in the form of research fellowships. Thanks are due to Mr. Herman Hinitz for preparing the calculator programs as well as for many informative conversations. The technical assistance of Mr. Martin Zierold is appreciated. Discussions with Mr. Leonard Bailey and Mr. Stephen Baron were very useful.

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Enhancement of Gastrointestinal Absorption of a Quaternary Ammonium Compound by Trichloroacetate

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Abstract □ The hypothesis that ion-pair formation and transport across the lipid gastrointestinal barrier is an important mechanism for drug absorption has been examined using a quaternary ammonium compound, isopropamide, as the cationic component and trichloroacetate (TCA) as the anionic component of the ion pair. Studies of the effect of trichloroacetate on the partitioning of isopropamide between water and nonaqueous phases such as chloroform and *n*-octanol demonstrated that a highly lipid-soluble isopropamide-TCA ion pair can dissolve in such nonaqueous phases. Mydriasis tests in mice demonstrated that both the rate and efficiency of oral absorption of isopropamide are increased when it is administered in combination with 10-fold or 50-fold molar excesses of trichloroacetate in solution. Although the specific mechanism by which absorption is enhanced has not been determined, evidence is presented which clearly indicates that TCA, an anion capable of forming a lipid-soluble ion pair with isopropamide, significantly enhances the pharmacologic response of orally administered isopropamide.

Keyphrases □ Isopropamide absorption—trichloroacetate effect □ Ion-pair formation—*isopropamide*, *trichloroacetate* □ Partition coefficients—*isopropamide* □ Mydriasis, mice—absorption, dose-response indicator □ Colorimetric analysis—spectrophotometer

Current concepts regarding the mechanism by which drugs are absorbed suggest that the barrier membrane exhibits properties of a lipid-like substance (1). Many drugs are assumed to be absorbed passively across this

type of membrane. The pH-partition hypothesis (2) predicts that for acidic and basic drugs, absorption will be markedly influenced by the pH at the absorption site, since the pH at the site determines the fraction of the drug present as the unionized, lipid-soluble form.

These concepts of factors influencing drug absorption have been valuable despite the general recognition that there are important deviations from them. For example, quaternary ammonium compounds are completely ionized at all pH values, yet some of these compounds are absorbed appreciably (3). Also, some simple weak organic acids, such as salicylate, are absorbed rapidly and efficiently from the intestine when the pH is such that the acid is virtually completely ionized (2).

If these drugs are not absorbed by active transport processes, then it appears that adjunctive substances may play a role in their facilitated transport. Such adjunctive substances might combine with the drug to make it more lipophilic and, in this manner, facilitate diffusion of the drug across a lipid-like membrane. These substances might exist naturally in or near the absorption site or could be administered with the drug. It was the purpose of this investigation to test the hypothesis that some adjunctive substances combine with ionic drugs to form ion pairs which are lipophilic and might be transported across the gastrointestinal membrane. This report deals with the effect of trichloroac-