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THE RELATIONSHIP BETWEEN THE DISSOCIATION CONSTANTS IN WATER OF TWO SERIES OF ORGANIC BASES AND THEIR HALF-NEUTRALIZATION POTENTIALS IN FIVE ORGANIC SOLVENTS

DISSERTATION

Presented in Partial Fulfillment of the Requirements for the Degree Doctor of Philosophy in the Graduate School of the Ohio State University

by

Leslie George Chatten, B.Sc., M.Sc.

The Ohio State University
1961

Approved by

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DEDICATION

The author dedicates this work to his wife who not only provided encouragement and understanding, but also endured, with patience, the demands made upon the author's time in terms of long hours both at the laboratory bench and the desk.
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Because of the greatly increased importance of nonaqueous
titrmetry, it is of value in predicting the behavior of acids and bases
in organic solvents, to know whether the strength of a series of acids
or bases can be directly related to their dissociation constants in
water.

For the purpose of this study, representatives from two series
of organic bases, the phenothiazines and the sympathomimetic amines,
were selected. In a very general way, it was observed that the basic
strength of the respective members could be related to their dissociation
constants. There were several examples of anomalous behavior,
and the relationship between half-neutralization potentials and
dissociation constants did not form a linear relationship for all the
members of a series.

Attempts were made to interpret the cause of such anomalous
results on the basis of steric hindrance, hydrogen bonding, and the
presence of electrophilic groups. It was concluded that steric
hindrance played no part in such titrations, whereas electrophilic
groups influenced the results considerably. Of the phenothiazine
compounds studied, only one example of unpredictable strength could
be attributed to the effects of hydrogen bonding. On the other hand,
it was postulated that the leveling of the sympathomimetic amines in
isopropanol was caused by hydrogen bonding of the compounds with the
solvent.
I. INTRODUCTION

**Historical**

The study of Chemistry is profitable, not only inasmuch as it promotes the material interests of mankind, but also because it furnishes us with insight into those wonders of creation which immediately surround us, and with which our existence, life and development, are most closely connected.

Although the electrolytic theory of Svante Arrhenius was rejected initially, when it was proposed in 1887, later it was hailed as the key to the knowledge of the behavior of acids and bases. Although this concept still serves a useful purpose today, it is regrettable to report that unreasoning obedience to this theory was largely responsible for the lack of major advancements in this field for more than thirty years after its advent, and that it had a seriously detrimental effect upon the teaching of the fundamentals of chemistry for a much longer period than that.

It was during the zenith of this era of emphasis upon ions in chemical reactions that the concepts of acid-base behavior in nonaqueous solvents were born. In 1899, Collie and Tickle (1) reported on what they believed to be the similarity between oxonium and ammonium salts and, just after the turn of the century, Kahlenberg (2) published a paper dealing with what he chose to refer to as certain types of "ionic" reactions that occurred in benzene. In 1903, Vorlander (3), while studying the relationship between color change and structure of in-

---

dicators, noted that aniline could be titrated in benzene with hydrogen chloride by using p-dimethylaminoazobenzene (methyl yellow) as indicator. Unfortunately, he did not consider the analytical importance of his discovery and it was left to other workers to report the first quantitative determination of organic compounds in nonaqueous solvents.

To Folin and Wentworth must belong the distinction of recognizing the significance of nonaqueous titrimetry and of first utilizing it as an analytical tool. In 1910, these workers (4) reported the titration of a number of higher fatty acids with sodium alcoholate in chloroform, carbon tetrachloride, benzene and toluene. Two years later, Folin and Flanders (5) extracted hippuric acid from urine with chloroform and titrated it with sodium ethoxide. In a later publication of the same year, they (6) cast doubt upon the validity of the ionization theory when applied to all solvent systems. In 1915, Lapworth (7) attacked the Arrhenius-Ostwald theory of the catalytic activity of acids.

In 1905, Franklin (8) began the development of the theory of solvent systems which was, essentially, an application of the concepts of Arrhenius. Extending over a period of several years, two additional papers were published by the same author (9,10). Germann (11,12,13), and Cady and Elsey (14), extended the solvent system theory of acids and bases to include reactions in aprotic systems.

Nevertheless, contradictions to the Arrhenius theory had become apparent to some workers in the field and this did help to stimulate thought. Within a few years, new theories of acid-base behaviors appeared which were more in keeping with experimental observations. Bronsted (15) and Lowry (16) independently published their classical
works which resulted in their now well-known theory. About the same time, Lewis (17) developed his concept of reaction by electron pair transfer. Although much has been written about the supposed advantages of each of the two latest theories over the other, it is generally agreed by most workers in the field today that no incompatibility exists between them.

The fundamental investigations of Conant and Hall (18,19) on their studies of "Super Acids" led them to point out that

Much important chemistry has been obscured by our slavish devotion to water.

Their report showed that glacial acetic acid solutions of organic amines or metal acetates can be titrated electrometrically with solutions of the stronger inorganic acids and sulfonic acids. Potentials, reproducible within a few millivolts, were obtained by means of a cell containing, as the indicator electrode, a platinum foil in an acetic acid solution of chloranil and its reduction product. By conversion of the experimentally observed potentials to an arbitrarily chosen \( p\text{H}^{\text{HAC}} \) scale, it was possible to determine the relative strengths of various bases. Hall and Werner (20) showed the behavior of several bases in glacial acetic acid when titrated with perchloric acid. In 1930, Conant and Werner (21) followed the titration of a number of weak bases in the same solvent system by spectrophotometric measurements that used crystal violet as indicator.

With the completion of this aspect of the fundamental work on both acids and bases in noneaqueous solvents, the simplicity of the technique was apparent to other investigators. LaMer and Downs (22)
titrated acids and bases potentiometrically in the aprotic solvent, benzene. In 1933, Lavine and Toennies (23) distinguished between strong and weak acids in chloroform by using the two color changes of thymol blue. In the same year, Vorlander, Fischer, and Filicitas (24) and, a year later, Vorlander (25), studied the titration of amines and alkaloids in chloroform. They proposed that the titration of amine-like substances in nonaqueous solvents be referred to as aminometry. The dissociation of some acids, bases, and salts in glacial acetic acid was studied by the conductivity method by Kolthoff and Willman (26,27). They confirmed the ability of acetic acid to act as a differentiating solvent toward strong acids. On the basis of their measurements, the relative strengths of a number of acids are given by the following order:

\[ \text{HClO}_4 > \text{HBr} > \text{H}_2\text{SO}_4 > \text{HCl} > \text{HNO}_3 \]

The ratio of conductivities of these acids at a concentration of 0.005 molar is 400:160:30:9:1 respectively. The first method of acid-base titration in nonaqueous systems to find wide acceptance, however, was that used by Nadeau and Branchen (28), who determined amino acids in glacial acetic acid solutions. In 1941, Blumrich and Bandel (29) reported the quantitative analysis of several organic bases in the same solvent system by using perchloric acid as a titrant.

The true value of acid-base titrations in nonaqueous solvents was not fully appreciated, however, until some time after World War II. During the past decade there have been a great number of papers in many languages on the analytical applications of this technique. Numerous reviews on this aspect of nonaqueous titrimetry have been published (30 to 53) which provide any investigator with a complete background on the subject.
Theoretical

De Morveau has been quoted by Gautier (54) as saying:

Tenir la definition des acides, c'est
tenir la cle de la Chymie.

The answer to this problem has been sought by scientists all over the world, and even today there is not complete agreement on what constitutes an acid or a base. It is not the purpose of the present investigation to define acids or bases in their absolute sense, but rather to attempt to ascertain what relationship exists between dissociation constants and half-neutralization potentials of a series of organic bases in several nonaqueous solvents. The effect of hydrogen bonding, steric hindrance, and electronegativity will be considered also.

It would appear relevant, however, to compare the five main theories of acid-base behavior which are in existence at the present time. In addition, other phenomena which are related to the physical properties of solvents will be considered, also. Each of these is discussed below.

The Ionic Theory

Much has been published on the theory of electrolytic dissociation which has served as the basis for a great deal of the work on acids and bases in aqueous solution. The essentials of this theory are covered in detail in most good texts on general chemistry.

The Theory of Solvent Systems

The development of the theory of solvent systems was begun by Franklin (8) in 1905 and later extended by Germann (9). Drawing on the Arrhenius theory, Franklin postulated that ammonia must ionize in a
manner similar to water. In liquid ammonia, ammonium chloride is an acid and sodium amide is a base. Neutralization would occur in the following manner:

(1) \[ 2H_2O \rightleftharpoons H_2^+ O + OH^- \]
(2) \[ 2HN_3 \rightleftharpoons NH_4^+ + NH_2^- \]
(3) \[ NH_4Cl + NaNH_2 \rightarrow NaCl + 2NH_3 \]

Based upon analogy to the water system, an acid is defined as a solute which gives rise to a cation that is characteristic of the solvent, and a base is a solute which gives rise to an anion which is characteristic of the solvent. Neutralization, then, is a combination of the solvent cation and solvent anion to produce the solvent.

This concept has not received wide acceptance and as pointed out by Luder and Zuffanti (55), it suffers from two serious weaknesses:

(a) Limits reactions to the presence of solvent systems, and hence makes no allowance for acid-base reactions in the absence of a solvent.

(b) Places undue emphasis upon ionization as the most important factor in acid-base reactions, when there is ample evidence that such reactions can and do take place in aprotic solvent systems where ionization is unknown.

From the foregoing, it is obvious why this theory has not received wide acceptance.

The Positive-Negative Theory

In an attempt to reconcile the solvent system theory with that of Bronsted-Lowry, Uzanovich (56) defined an acid as any substance capable of giving up cations or of combining with anions, and a base as any substance capable of giving up anions or combining with cations. This
same chemist even suggested that oxidation-reduction reactions are only
a special incidence of acid-base phenomena. While the relationship is
close, the two types of reaction are not the same, as will become
apparent under a discussion of the Lewis theory. Typical neutralization
reactions according to this theory would be as follows:

\[
\text{Acid} + \text{base} \rightarrow \text{salt}
\]

\[(4) \quad \text{Sb}_2\text{S}_5 + 3(\text{NH}_4)_2\text{S} \rightarrow 2(\text{NH}_4)_3\text{SbS}_4\]

\[(5) \quad \text{Fe(CN)}_3 + 3\text{KCN} \rightarrow 3\text{Fe(CN)}_6\]

In 1954, Outmann and Lindquist (5?) proposed a theory that has
certain similarities to the postulate of Usanovich, but differs in that
their concept of ionotropy excludes all complex ions as migrating units
and also excluded redox reactions. The acid-base concept is based solely
on two solvent systems: cationotropic solvosystems, characterized by the
ion migration taking place by means of cations; and anionotropic solvosystems,
characterized by the ion migration occurring by means of anions.
Therefore, an acid in a cationotropic solvosystem is a cation donor and
in an anionotropic solvosystem is an anion acceptor. A base in a
cationotropic solvosystem would possess the reverse properties. Fundamen-
tally, Bronsted's prototropic solvosystem would be considered as a
special case of the cationotropic system.

The Protonic Concept

As previously indicated, both Bronsted (15) and Lowry (16) formulated
essentially the same definition at about the same time. Each worked
independently of the other, and their theory can be represented by the
equilibrium.

\[(6) \quad \text{A} \rightleftharpoons \text{B} + \text{H}^+ \]

(Acid) (Base) (Proton)
When expressed in words, an acid is a molecule or ion which is capable of donating a proton; a base is a molecule or ion which is capable of accepting a proton. Bronsted (58, 59) later amplified and clarified his original publication and, in 1934, he extended it to amphiprotic solvents (60). From equation (6), it is apparent that when an acid loses a proton it becomes a base and when a base accepts a proton it becomes an acid. An acid or a base may be an ion or an electrically neutral molecule.

\[
\text{(7)} \quad \text{H}_2\text{O} \rightleftharpoons \text{H}^+ + \text{OH}^-
\]

\[
\text{(8)} \quad \text{CH}_3\text{COOH} \rightleftharpoons \text{H}^+ + \text{CH}_3\text{COO}^-
\]

\[
\text{(9)} \quad \text{NH}_4^+ \rightleftharpoons \text{H}^+ + \text{NH}_3
\]

When a strong acid, such as perchloric, is dissolved in some amphiprotic solvent typified by water or glacial acetic acid, the following equilibrium occurs:

\[
\text{(10)} \quad \text{HClO}_4 + \text{H}_2\text{O} \rightleftharpoons \text{H}_3\text{O}^+ + \text{ClO}_4^-
\]

\[
\text{(11)} \quad \text{HClO}_4 + \text{CH}_3\text{COOH} \rightleftharpoons \text{CH}_3\text{COO}\text{H}_2^+ + \text{ClO}_4^-
\]

As in the case of water, glacial acetic acid accepts a proton from the much stronger acid, perchloric. When a base B is dissolved in glacial acetic acid and titrated with acetous perchloric acid, the following reactions take place:

\[
\text{(12)} \quad \text{B} + \text{CH}_3\text{COOH} \rightleftharpoons \text{BH}^+ + \text{CH}_3\text{COO}^-
\]

\[
\text{(13)} \quad \text{BH}^+ + \text{CH}_3\text{COO}^- + \text{CH}_3\text{COOH}_2^+ + \text{ClO}_4^- \rightleftharpoons \text{BH}^+ + 2\text{CH}_3\text{COOH} + \text{ClO}_4^-
\]

If the correct end-point is to be obtained, the reaction expressed compositely in equations (11 to 13) must go almost completely from left to right. It is obvious, therefore, that in the presence of perchloric acid, glacial acetic acid behaves as a base. The
resulting solvated ion is a powerful proton donor that will attack any base which is stronger than the solvent itself.

Many acid-base reactions occur, however, in aprotic solvents where little or no proton exchange between solvent and solute occurs. The manifestation of acidic character in these solvents depends on the capacity of the solute molecule to release the proton to other solutes which are capable of acting as bases. Aprotic solvents, because of their inert characteristics, their low dipole moment, and their small dielectric constant, possess a differentiating character, that is, the inherent acidity or basicity of the solute is revealed in such media.

The Electronic Concept

The establishment of the electronic theory of acids and bases is the contribution of Lewis (17). According to Sidgwick (61), the one property common to all acids is that they are acceptor molecules. Bases are donor molecules. A base has one or more lone electron-pairs which may be used in coordinate-bond formation. An acid can accept one or more electron-pairs from a base. Neutralization, therefore, is the formation of the coordinate covalent bond between the acid and the base. The definition is used to explain acid-base phenomenon either in the presence or the absence of a proton. When triethylamine neutralizes boron trichloride in chlorobenzene or even in the absence of any solvent, boron trichloride is an acid, since it accepts an electron-pair to complete the boron atom octet. Triethylamine is a base because of the lone electron-pair on the nitrogen atom which it can donate to form a coordinate covalent bond between the acid and the base. This
act is neutralization and removes the distinctive properties of both
the acid and the base.

\[
\begin{align*}
&: \text{Cl} : \text{Et} \\
&: \text{Cl} : \text{B} + : \text{N} : \text{Et} \\
&: \text{Cl} : \text{Et} \\
\end{align*}
\]

\[
\begin{align*}
&: \text{Cl} : \text{Et} \\
&: \text{Cl} : \text{B} + : \text{N} : \text{Et} \\
&: \text{Cl} : \text{Et} \\
\end{align*}
\]

In general, the Bronsted-Lowry theory and Lewis theory are com-
patible. In both instances, the bases are the same. Each, however, has
a different definition for an acid. Lewis includes all ions and molecules
that form covalent bonds with bases, whereas Bronsted and Lowry limit
their acids to ions or molecules that are capable of donating a proton.
Kolthoff (62) has suggested that the Bronsted-Lowry definition remain un-
changed and that those ions or molecules that require the broader
definition in order to qualify as acids be termed Lewis or L. acids. A
trend in this direction has already been established.

The physical influence of the solvent is of utmost importance in
nonaqueous titrimetry yet, with the exception of glacial acetic acid,
little information is available regarding this influence which is exerted
on the mechanism of action that occurs during the course of the titration.
The means by which a solvent may affect a solute can be divided into
several factors.

**Dielectric Constant**

According to the Nernst-Thomson rule, which states that if the
forces which hold a molecule together are electrical in origin, and this
is recognized to be so, these forces are greatly diminished when the
molecule is surrounded by a substance of high inductive capacity. To
cause charged particles to separate, it is essential to interpose between
them, or to surround one or both of them by a solvent layer which reduces
their attraction for each other. In a medium of low dielectric constant, the associating power of the solute ions for each other will be greater than in a solvent of high dielectric constant, and there will be an increased tendency for such ions to aggregate into inactive ion pairs or even larger complexes.

**Viscosity**

Viscosity is a physical property which is mentioned only because of the profound effect it has on the mobility of ionic species and the conductance of electrolytes in any specific solvent.

**Classification of Solvents**

Solvents can be classified and differentiated by several convenient means. Each method has its usefulness.

(a) Chemical character is probably the most obvious criterion for distinguishing between solvent types, although it may be of less significance than others. Such a classification is usually performed on the basis of distinctive groups which may be present in the molecule. The hydrides are probably the most useful solvents. They are frequently referred to as protonic solvents, although not all hydrogen-containing solvents dissociate the proton, as is implied by this particular designation. The hydroxylic solvents which resemble water are next in order of importance. In these, the hydrogen is replaced by some organic radical. They include the alcohols and polyhydroxy compounds and other oxygen-containing solvents, such as ethers, esters, aldehydes and ketones. The nitrogen-containing solvents also constitute a large and important group which are typified by ammonia, substituted amines, and polyamines. These latter two resemble ammonia in the same manner that alcohols
resemble water. They are poorer solvents than ammonia for ionic compounds, but are better solvents for organic materials.

Solvents that possess acid characteristics include such compounds as sulfuric acid, acetic acid, formic acid and hydrogen fluoride. Related to them are the acid chlorides, such as acetyl chloride, thionyl chloride, sulfuryl chloride, and the oxychlorides of phosphorus (V) and selenium (IV).

The hydrocarbons and their halogenated derivatives constitute a large group of inert solvents which are employed on a wide scale in synthetic organic chemistry. They are non-polar, or only slightly polar, and are generally very poor solvents for ionic compounds, but are excellent solvents for covalent and non-polar compounds.

(b) Solvents may be differentiated on the basis of their ability to coordinate the hydrogen ion.

Basic solvents, which include ammonia, the amines, hydrazine and derivatives, cyclic nitrogen compounds such as pyridine, as well as low molecular weight ethers, are those which readily form the onium ion.

Acidic solvents have been identified, previously. All tend to dissociate the hydrogen ion readily and none are capable of forming a very stable combination with the hydrogen ion. On the other hand, basic solvents tend to coordinate with the hydrogen ion or metallic ions to form solvated cations. Proton-containing acidic solvents are considered to solvate the anion through hydrogen bonding. A classical example of this is the formation of the very strong F-H-F bond.

Although amphoteric solvents possess the capacity to act as electron pair donors, under the proper circumstances they will dissociate the proton to a dissolved solute. Examples of such classes are water
and the hydroxylic solvents. The cation attaches itself to the water molecule through the electron pair on the oxygen atom. Water also forms stable cationic complexes with many metallic ions. In competition with such molecules as ammonia or such anions as the cyanide and carbonate ions, water will release the proton to them.

Those inert solvents, which have no affinity for the proton or which are incapable of dissociating the proton, are referred to as being aprotic. It may be incorrect to assume that there is any such thing as an inert solvent. However, when compared with those materials which have been designated previously as basic, acidic, or amphiprotic solvents, it is accepted that the hydrocarbons and their halogenated derivatives will not affect materially the properties of either a base or an acid which may be dissolved in them.

(c) Solvents may be classified according to behavior exhibited by typical electrolytes which are dissolved in them. Such a system labels a solvent as differentiating or leveling. Those in which such reference electrolytes exhibit equal strength are known as leveling solvents. Those in which a differentiation in strength of the respective electrolytes is exhibited are known as differentiating solvents. Common leveling solvents are water, methanol, ethanol and, in most instances, glacial acetic acid. On the other hand, acetonitrile, acetone, methylethyl ketone, and nitromethane are examples of differentiating solvents.

Type Reactions in Nonaqueous Solvents

Audrieth and Kleinberg (65), in their excellent book on nonaqueous solvents, have divided reactions which are influenced by the
solvent into three categories: (a) neutralization, (b) reactions of solvolysis, (c) reactions of solvation.

(a) Neutralization Reactions

Reactions involving salt formation by the interaction of an acid and a base vary from solvent to solvent, because the solvent may alter the acid or basic character of the solute. Both sodium acetate and ammonia behave as strong bases in glacial acetic acid. Potassium acid phthalate, which is an acidimetric standard in aqueous solutions, is used extensively as a primary base standard in glacial acetic acid.

(b) Solvolytic Reactions

The solute is considered to have undergone solvolysis when the dissolved solute reacts with the solvent in such a way that the normal anion and cation concentrations of the solvent are changed. Solvolytic reactions constitute the most important type of reactions which can occur in solvent systems, according to Audrieth and Kleinberg (63). These authors further state that it makes little difference whether water, ammonia, an alcohol, a primary or secondary amine, undergo reaction with an organic or an inorganic compound containing a reactive group. Compounds are obtained in each instance which are formally related in the same manner to each of the solvolytic agents as parent compounds.

(c) Solvation Reactions

The process, which results in the attachment of the solvent molecule to the cation, the anion, or a molecule of a solute, is known as solvation. This is accomplished either by coordination or by hydrogen bonding and results in products of varying stability.
Despite the development of several theories and the volume of work that has been published in this field, in general the choice of solvent systems for each compound to be titrated has been rather empirical. The analyst has relied, largely, on his or someone else's experience when attempting to choose a suitable solvent system for the titration of a great many compounds. Undoubtedly, it was this very situation that led Riddick (43), in 1952, to state:

The information on the strength of acids and bases in organic solvents is meagre. Present knowledge indicates that the strength will have to be determined for each acid and base for each amphiprotic solvent used.

In 1953, Fritz (64) reported a comparison of the $pK_a$ values of a few common laboratory reagents in water with their half-neutralization potentials in acetonitrile. Lemaire and Lucas (65) determined the $pK_a$ of three indicators and then utilized this information to obtain the basic strength of weak bases in glacial acetic acid.

The behavior of bases in glacial acetic acid has been the object of more intense study than that of any other nonaqueous solvent. In an excellent series of articles, Kolthoff and Bruckenstein (66 to 70) thoroughly investigated several aspects of acid-base equilibria in the aforementioned solvent. These included the potentiometric determination of dissociation constants of acids, bases and salts; the quantitative interpretation of acid-base titrations in glacial acetic acid; and the effect of water on potentiometric and indicator end-points of acid-base titrations in that solvent.
Rochlin and co-workers (71) established a constant for a series of 5-aminotetrazoles in glacial acetic acid, which they chose to refer to as the pH(HAC), and this they compared with the respective pK(H_2O) for each member of the series.

An outstanding contribution was made by Hall (72) in his report on the basic strength of a number of mono-, di-, and triamines in several nonprotolytic solvents. His investigations were made in nitromethane, ethylene dichloride, ethylacetate, nitrobenzene, and acetonitrile and included a comparison of the pK_a(H_2O) values of more than sixty compounds with their half-neutralization potentials (E_1/2) in the aforementioned solvents. This worker was able to show that a linear relationship existed between the E_1/2 values of certain m- and p-substituted anilines and the Hammett σ value of the substituent. Hall further showed that linearity occurred in a plot of E_1/2 values of many of his compounds in a specific solvent versus their pK_a values in water. He concluded that the base strength of an amine in water is, broadly speaking, a reliable index of its base strength in organic solvents. This is in agreement with the general conclusion of Chatten, Pernarowski and Levi (73) from their investigation of a series of chemically unrelated bases in nitromethane.

More recently, van der Heijde (74,75) developed an empirical acidity potential scale of twelve solvents and established a table of instructions for selecting the proper solvent-titrant combination for the differentiation of acid mixtures. In addition, he outlined five major factors having an influence on the half-neutralization potentials of acids and bases in various solvents:

(1) The acidity or basicity of the solvent medium
(2) The "intrinsic acidity" (basicity) of the titrated acid or base

(3) The tendency of the ions involved in the titration towards formation of extraordinary stable complexes or insoluble salts

(4) The liquid junction potentials occurring at the electrode boundaries

(5) The dielectric properties of the solvent medium

In addition, base strengths have been studied by other workers in the following non-protoolytic solvents: benzene (76 to 78), chlorobenzene (79, 80), anisole (80), acetonitrile (81), nitrobenzene (82, 83), tricresyl phosphate (84), nitromethane (85), chloroform (86 to 88), and carbon tetrachloride (88). Indicator color changes have been employed in most of these investigations and absorption measurements made in the visible region. Conductimetric determinations, although precise, present a complex problem in media of low dielectric constant. Reaction kinetics methods have been utilized but, according to Grunwald and Berkowitz (89), often give unharmonious pK values. Association phenomena which complicate the kinetics methods would be a serious obstacle in non-polar media. Potentiometric methods utilizing a glass indicating electrode together with a calomel reference electrode appear to hold the most practical approach to such an investigation, according to Hall (72).

The purpose of the present investigation is to determine the relationship between the dissociation constants \( pK_b (H_2O) \) of a number of bases in each of two chemically unrelated series and their half-neutralization potentials in five organic solvents. The influence of hydrogen bonding, steric hindrance, and electrophilic groups upon this relationship will be considered.
II. EXPERIMENTAL

Apparatus

(a) Fisher titrimeter, model No. 9-311A, range 0 to 1000 millivolts;
(b) Shielded glass electrode, Beckman No. 1190-80;
(c) Sealed calomel electrode, sleeve type, Beckman No. 1170-71;
(d) Microburette, graduated to 0.01 ml.

Reagents and Solutions

(1) Glacial acetic acid, A.C.S. grade;
(2) Acetone, A.C.S. grade;
(3) Acetonitrile, A.C.S. grade purified by stirring with alumina;
(4) Isopropanol, A.C.S. grade;
(5) Nitromethane, practical grade redistilled at 101°C prior to use;
(6) Dioxane, A.C.S. grade;
(7) Anhydrous methanol, A.C.S. grade;
(8) Perchloric acid, 70 to 72%;
(9) 0.1N Perchloric acid in glacial acetic acid;
(10) 0.1N Perchloric acid in dioxane;
(11) 0.1N Perchloric acid in acetonitrile;
(12) 0.1N Perchloric acid in isopropanol;
(13) 0.1N Perchloric acid in nitromethane;
(14) Potassium acid phthalate, primary standard;
(15) Diphenylguanidine, A.C.S. grade;
(16) Solutions of the twenty one compounds investigated in each of the five solvents, glacial acetic acid, acetone, acetonitrile, iso-
propanol, and nitromethane, at a concentration of 0.2 milli-
equivalents per 50 ml. of solvent;

(17) Reference standard solutions of diphenylguanidine (0.2 meq.
per 50 ml. of solvent for each of the five solvents).

The perchloric acid titrant was prepared in the same solvent as
that in which the titration was to be performed with only one exception.
For example, titrations in isopropanol were carried out with 0.1N
perchloric acid in isopropanol and those in glacial acetic acid with 0.1N
acetous perchloric acid, and so on. The one exception was acetone.
Because of the instability of perchloric acid in acetone, titrations in
that solvent were performed with 0.1N perchloric acid in dioxane.

The titrants, which were prepared in glacial acetic acid, dioxane
and isopropanol, were standardized against primary standard potassium
acid phthalate. For those titrants in acetonitrile and nitromethane,
diphenylguanidine was employed as primary standard. Since perchloric
acid solutions in these latter two solvents have a short stability,
these titrants were standardized every day.

Compounds Investigated and Their Purity

(A) Phenothiazine series:

(1) Chlorpromazine or 2-chloro-10-(3-dimethylaminopropyl) phenothiazine

(2) Promethazine or 10-(2-dimethylaminopropyl) phenothiazine

(3) Levomepromazine or 2-methoxy-10-(2-methyl-3-dimethylaminopropyl) phenothiazine

(4) Thioridazine or 2-methylmercapto-10-[2-(N-methyl-2-piperidyl) ethyl] phenothiazine

(5) Triflupromazine or 2-trifluoromethyl-10-(3-dimethylaminopropyl) phenothiazine

(6) Pyrathiazine or 10-[2-(/-pyrrolidyl) ethyl] phenothiazine
(7) Thiopropazate or 2-chloro-10-{3-[1-(2-acetoxyethyl)-4-piperazinyl] propyl} phenothiazine

(8) Trifluoperazine or 2-trifluoromethyl-10-[3-(1-methyl-4-piperazinyl) propyl] phenothiazine

(9) Prochlorperazine or 2-chloro-10-[3-(1-methyl-4-piperazinyl) propyl] phenothiazine

(10) Pipamazine or 2-chloro-10-[3-(4-carbamoylpiperidino) propyl] phenothiazine

The purity of each compound was determined by potentiometric titration of a weighed sample in glacial acetic acid, with acetic perchloric acid as titrant. This is a standard procedure which is recognized by the sixteenth revision of the United States Pharmacopoeia (90) as a criterion of purity for many organic bases. In each instance, the degree of purity exceeded 99 percent, with the exception of pyrathiazine. For this latter compound, the purity was found to be 96.5 percent and distillation under vacuum at 1 mm of mercury did not appear to improve it, materially.

All compounds were stored in vacuo, over phosphorus pentoxide, and protected from light. Solutions were prepared in light-resistant flasks and all operations were carried out in a semi-darkened room. Because of the possibility of light catalyzed degradation, no solution of any member of this series was used which had been prepared on the previous day.

(B) Sympathomimetic amine series:

(1) Ephedrine or 1-phenyl-2-methylaminopropanol

(2) Phenylpropylmethamphetamine or dl-N-methyl-2-phenylpropylamine

(3) d-Methamphetamine or d-l-phenyl-2-methylaminopropane

(4) dl-Amphetamine or dl-l-phenyl-2-aminopropane

(5) Methoxamine or 2-amino-l-(2,5-dimethoxyphenyl)-l-propanol
(6) Mephenteramine or 2-methylamino-2-methyl-l-phenylpropane
(7) Propylhexedrine or 1-cyclohexyl-2-methylaminopropane
(8) Cyclopentamine or 1-cyclopentyl-2-methylaminopropane
(9) 2-Aminoheptane or 1-methylhexylamine
(10) Methylhexylamine or 2-amino-4-methylhexane
(11) Naphazoline or 2-(1-naphthylmethyl) imidazoline

The purity of each member of this series was determined in the same manner as described for series (A). These compounds were also stored in vacuo, over phosphorus pentoxide and protected from light. After one week of storage under these conditions, sufficient water had been removed from ephedrine for the alkaloid to attain a purity of 98.8 percent, while both methoxamine and naphazoline exceeded 99 percent purity. The other members of this series were liquids and all, with the exception of dl-amphetamine, were distilled at the temperatures described in Merck Index (91) in order to obtain a purity in excess of 99 percent. dl-Amphetamine was obtained from the manufacturer in 5 ml. sealed ampoules. Prior to use, the contents of each ampoule was tested, and in every instance the material was found to have a purity above 99 percent.

**Procedures**

**Determination of Apparent Dissociation Constants**

Because of the very low water solubility of the free bases in series (A) as well as many of the series (B) free bases, Marshall's (92) method for the determination of apparent dissociation constants was employed. Methanolic solutions of the free bases were prepared and, from these, accurately measured aliquots were taken. Known dilutions were prepared with distilled water, and titrations were carried to
exactly half-neutralization with 0.1N HCl, so that the concentrations of total salt and free base did not exceed 0.001 to 0.002 molar. At that point the pH of the solution was measured on the Fisher titrimeter. Three such measurements were made for the same concentration of base but with varying percentages of methanol. The three pH readings were plotted against percentage methanol and the straight line extrapolated to zero percent alcohol. Three such series were run, which made a total of nine measurements for each organic base. The graph reading obtained in each instance by extrapolation was plotted against mg. of base. The straight line was extrapolated back to infinite dilution (the point of intersection with the ordinate) and the pH determined from the graph. Since pH = pK_a at half-neutralization, this same reading gives the pK_a value of the base. The pK_b is obtained by subtracting the pK_a from 14.00. Because of the dilutions in which the measurements were made, the activities were neglected.

Determination of E_q Values

Stock solutions of the bases were freshly prepared in each solvent, the day on which the measurements were performed. Concentration of these solutions was such that 50 ml. contained 0.2 milliequivalents of base. Reference standard solutions of diphenylguanidine in each of the five solvents were prepared, at the same concentration.

The titrimeter was pre-set at 200 mv. and the electrodes immersed in the appropriate diphenylguanidine reference solution. The cathode eye was properly adjusted by means of the eye adjustment, the reference standard was removed and the electrodes wiped dry with tissue. The solution to be titrated was placed in position and the zero reading
noted. In most instances, the titrant was added in 0.1 to 0.2 ml.
increments, except in the region of the half-neutralization potential
and the end-point. In these areas, the increments were reduced to 0.01
ml. or 0.005 ml. if necessary. A plot was made of millivolts vs. ml.
added and the $E_1$ read from the graph in the usual way. In most instances,
however, this was not necessary, since the end-point was well defined and
could be determined easily by inspection of the data.

At the end of each titration, the electrodes were washed well with
distilled water. The sleeve of the calomel electrode was removed, the
electrode wiped dry, and a fresh layer of saturated potassium chloride
solution allowed to flow between the electrode and the sleeve. The
exteriors of both electrodes were wiped dry and replaced in diphenyl-
guanidine reference solution in preparation for the next titration. Five
titrations were performed for every compound in each solvent system. The
average value was determined and employed in the respective plots and
calculations. When not in use, the electrodes were immersed in distilled
water. The calomel reference electrode was flushed out at regular
intervals and recharged with fresh saturated potassium chloride solution.

**Errors and Precision**

In order to permit an assessment of the postulations and con-
cclusions, it would be well to establish the validity of the experimental
results.

The possible errors in the measurement of base strengths may be
divided into three categories:

1. **Temperature**: deviations caused by fluctuations of temperature are
believed to be minor compared to those from other causes.
2. **Irreproducibility of glass electrode readings in organic solvents:**
it is considered that this effect has been reduced to a minimum by the
careful electrode standardization procedure.

3. **The shift in liquid junction potential of the sleeve-type calomel
electrode:** each time the sleeve is removed for washing and a fresh layer
of saturated potassium chloride solution introduced between the sleeve
and the electrode, a shift in potential may result. Again, it is
believed that the standardization procedure has reduced this effect
to a minimum.

The precision of the half-neutralization potential values in the
respective solvents compares favorably with the pK_u values in water.
Since, on a theoretical basis, 59 mv. correspond to one pK unit, then
\[ \pm 6 \text{ mv.} \quad \text{will correspond to an uncertainty of 0.10 pH unit in water.} \]
This is the maximum deviation that was noted in the experimental results,
and in many instances, the variation was as small as \[ \pm 2 \] or \[ \pm 3 \text{ mv.} \]
III. RESULTS AND DISCUSSION

The hydrogen ion concentration of a solution varies from approximately 1 in a 1 molar solution of a strong acid to about $1 \times 10^{-14}$ in a 1 molar solution of a strong base. Because of the unwieldy calculations which resulted, Sorensen devised his simplified and now well-known method of expressing hydrogen ion concentration. He established the term, pH, and defined it as the logarithm of the reciprocal of the hydrogen ion concentration:

$$\text{pH} = \log \frac{1}{[H_3O^+]} \quad (1)$$

By following the rules of logarithms, this equation can be written as

$$\text{pH} = \log 1 - \log [H_3O^+] \quad (2)$$

and since the logarithm of 1 is equal to zero,

$$\text{pH} = -\log [H_3O^+] \quad (3)$$

It is convenient to consider the dissociation of a weak acid such as acetic acid in water in the process of explaining the utility of dissociation constants. This concept can be converted then to the dissociation of weak bases.

The symbol c represents the initial molar concentration of acetic acid and x is the concentration of $[H_3O^+]$. The latter quantity is also equal to $[Ac^-]$ since both ions are formed in equimolar concentration. The concentration of acetic acid $[HAc]$ which remains at equilibrium can be expressed as $c-x$. The reaction becomes

$$\begin{align*}
HAc + H_2O & \rightleftharpoons H_3O^+ + Ac^- \\
(c-x) & \quad x \quad x
\end{align*} \quad (4)$$
and the equilibrium is expressed as

\[ K_a = \frac{x^2}{c-x} \quad (5) \]

In those instances where \( c \) is large in comparison with \( x \), the term \( c-x \) may be replaced by \( c \) to give the resulting equation

\[ K_a = \frac{x^2}{c} \quad (6) \]

Consequently,

\[ x^2 = K_a c \quad (7) \]

and hence

\[ x = [H_3O^+] = \sqrt{K_a c} \quad (8) \]

Taking the logarithm of both sides of the equation and reversing the signs, the equation becomes

\[ -\log [H_3O^+] = -\frac{1}{2} \log K_a - \frac{1}{2} \log c \quad (9) \]

Just as one substitutes the symbol \( pH \) for \( -\log [H_3O^+] \), so the symbol \( pK_a \) can be substituted for \( -\log K_a \), and \( pK_w \), the autoprotolysis constant, can be the replacement for \( -\log K_w \). Furthermore, as \( pH \) is frequently referred to as the hydrogen ion exponent since \( [H_3O^+] \) equals \( 10^{-pH} \), so \( pK_a \) and \( pK_b \) are known as dissociation exponents. The equation for a weak acid becomes

\[ pH = \frac{1}{2} pK_a - \frac{1}{2} \log c \quad (10) \]

One may use a similar approach for the derivation of the \( pH \) equation for a solution of a weak base

\[ BH^+ + \text{H}_2\text{O} \rightleftharpoons BH^+ + \text{OH}^- \]

\[ K_b = \frac{[BH^+][\text{OH}^-]}{[\text{B}]} \quad (11) \]

Therefore

\[ [\text{OH}^-] = \sqrt{K_{bc}} \quad (12) \]
Since \([\text{OH}^-] \times [\text{H}_3\text{O}^+] = K_w\) (13)
then \([\text{OH}^-] = \frac{K_w}{[\text{H}_3\text{O}^+]}\) (14)

Substitution in equation (12) yields

\[
\frac{K_w}{[\text{H}_3\text{O}^+]} = \sqrt{K_b c}
\]
and consequently

\[
[\text{H}_3\text{O}^+] = \frac{K_w}{\sqrt{K_b c}}
\]

Taking the negative logarithm of both sides of the equation, one obtains

\[
-\log [\text{H}_3\text{O}^+] = -\log K_w + \frac{1}{2} \log K_b + \frac{1}{2} \log c
\]

By appropriate substitution, one arrives at the final equation for a weak base

\[
pH = pK_w - \frac{1}{2} pK_b + \frac{1}{2} \log c
\]

For the purpose of determining the dissociation constants of weak acids and bases, it is necessary to use the Henderson-Hasselbach or buffer equation. The pH of a buffer solution and the change in pH upon the addition of an acid or base may be calculated by use of this equation. The expression is developed by considering the effect of a salt on the ionization of a weak acid when the salt and the acid have a common ion.

An example of the foregoing situation would be the addition of sodium acetate to a solution of acetic acid. The dissociation constant for the weak acid

\[
K_a = \frac{[\text{H}_3\text{O}^+][\text{Ac}^-]}{[\text{HAc}]}\]

is momentarily disturbed since the acetate ion supplied by the salt increases the \([\text{Ac}^-]\) term in the numerator. In order to re-establish the dissociation constant, the hydrogen ion term in the numerator \([\text{H}_3\text{O}^+]\)
is immediately decreased with a corresponding increase in \([HAc]\). Thus, the constant \(K_a\) remains unaltered and the pH of the final solution is obtained by rearranging the equilibrium expression for acetic acid to

\[
[H_3C^+] = K_a \frac{[HAc]}{[Ac^-]} \tag{19}
\]

Since the acid is weak and hence ionizes only slightly, the expression \([HAc]\) may be considered as representing the total concentration of acid, and it may be written as \([\text{acid}]\). In the slightly ionized acidic solution, the acetate concentration \([Ac^-]\) may be considered to have come entirely from the salt, sodium acetate. Hence, \([Ac^-]\) may be replaced by the term \([\text{salt}]\). Equation (19) may now be written,

\[
[H_3C^+] = K_a \frac{[\text{acid}]}{[\text{salt}]} \tag{20}
\]

Equation (20) may be expressed in logarithmic form, with the signs reversed,

\[-\log [H_3C^+] = -\log K_a - \log [\text{acid}] + \log [\text{salt}]\]

By making the appropriate substitutions from previously described equations, the Henderson-Hasselbach equation becomes

\[\text{pH} = pK_a + \log \frac{[\text{salt}]}{[\text{acid}]} \tag{21}\]

The buffer equation for solutions of weak bases and their corresponding salts may be derived in an analogous manner. Consequently,

\[\left[OH^-\right] = K_b \frac{[\text{base}]}{[\text{salt}]} \tag{22}\]

and employing the relationship 
\[\left[CH^-\right] = \frac{K_w}{[H_3O^+]} \]
the buffer equation becomes

\[\text{pH} = pK_w - pK_b + \log \frac{[\text{base}]}{[\text{salt}]} \tag{23}\]
When the half-neutralization point is reached during the course of a titration, the concentration of free base is equal to the concentration of salt. The expression $\frac{[\text{base}]}{[\text{salt}]}$ is equal to 1 and the log of that number is zero. Hence the equation becomes
\[ \text{pH} = \text{pK}_w - \text{pK}_b \] (24)
It is an easy matter, therefore, to obtain the pK$_b$ value from the measured pH and the already known pK$_w$. It is recognized that this is an over simplification and that in other than very dilute solutions such as those employed in this investigation, activities must be taken into account.

The concept of pH, however, has little or no meaning in most organic solvents. This situation is due mainly to the much lower dielectric constants which result in association phenomena, as well as to lack of knowledge of the autoprotolysis data for most of the organic solvents. Consequently, it has not been possible to develop a scale of dissociation constants for acids and bases in these solvents which would be comparable to the values in water.

With the greatly increased usage of nonaqueous techniques in the past decade, the establishment of fundamental behavior patterns of organic compounds in the commonly employed nonaqueous solvents promises to become a rewarding field of endeavor. Just as the chemist can predict the relative acidity or basicity of a substance in water by knowing its dissociation constant, so would it be equally convenient to be able to predict the behavior of a compound, or a series of compounds, in nonaqueous solvents by referring to some comparable physical constant. In this respect, Frits (64) was the first to report the value of the half-neutralization potential, when he employed acetonitrile as solvent.
The half-neutralization potential is the value expressed in millivolts at the theoretical half-way point of a titration and consequently can be considered to bear a direct relationship to the dissociation constant in water. Although the dissociation constant is expressed in terms of pK units, it could just as readily be considered in terms of millivolts by making use of the appropriate conversion factor, (ie.) 59 millivolts is equivalent to 1 pH unit. Of course, the substitution of millivolts would eliminate the relationship in water between acidity or basicity and hydrogen ion concentration and for this reason it is not done.

Fritz (64) plotted the half-neutralization potential for a number of organic bases in acetonitrile against their dissociation constants in water. From the resulting almost linear relationship, he concluded that such a physical constant in organic solvents was comparable to the dissociation constant in water. The work of Hall (72) as well as that of vander Heijde (74,75), both of whom extended the relationship of dissociation constants to half-neutralization potentials, has been referred to previously in this report. Streuli and Miron (93) studied the relative acidities of organic acids in pyridine and water and, in a later publication, Streuli (94) reported on the titration characteristics of organic bases in nitromethane and with special emphasis on the relationship between half-neutralization potentials and pKb values.

In order to obviate the necessity of using the rather cumbersome term of half-neutralization potential, one investigator (72) substituted the symbol, $E_2$. The use of $E_2$ appears to be well suited and will be employed throughout this dissertation.

In view of the chemical dissimilarity between the two series of bases in this investigation, it is proposed to present the data and the
discussion thereof for each series independently of the other one.

**Series A. The Phenothiazine Compounds**

Ten phenothiazine derivatives, which are employed in pharmaceutical preparations, were chosen for this study. The structural formulas of the respective members of this series are given in Table I. They were selected in such a manner that several chemically different groupings would be included in the substituents designated as R and X respectively. The particular purpose of the selection was to determine the effects of steric hindrance, electrophilic groups or hydrogen bonding upon the relationship between pKₐ values of the compounds when dissolved in water and the Eₒ values in a particular organic solvent when the compounds were titrated with perchloric acid.

The effect of resonance within the heterocyclic ring system of the phenothiazine derivatives is such that the electron density around the nitrogen in the ten position is so small that the nitrogen is incapable of attracting and holding a proton. Hence, from the standpoint of titratability, there are two distinctly different types of compounds. There are those which contain one titratable nitrogen (numbers 1 to 6 inclusive and number 10) and, in addition, those compounds which include a piperazine ring in their structure and hence possess two titratable nitrogens (numbers 7 to 9 inclusive). Chlorpromazine was chosen to represent the former group, whereas prochlorperazine became the representative of the latter. Percentage neutralized versus millivolts is plotted in Figures 1 to 5 to represent the titration curves of both chlorpromazine and prochlorperazine for each of the solvents studied.
Glacial Acetic Acid

Since glacial acetic acid is a leveling solvent, the titration curve for prochlorperazine shows only one inflection point. Although the two nitrogens in piperazine have quite different $pK_a$ values, in glacial acetic acid they are leveled to the same strength, and a plot of percentage neutralization versus millivolts gives no indication that the drug actually consumes two equivalents of titrant per equivalent of base. On this basis, the titration curves for prochlorperazine and chlorpromazine are remarkably similar in this solvent. At the end-point, for 0.01 ml of titrant added, the change in potential for chlorpromazine was about 40 millivolts, whereas it was only about 25 millivolts for prochlorperazine. This is understandable because the stronger and the weaker nitrogen in the piperazine moiety of the latter compound are leveled to about the same strength with the result that both are now weaker than the single titratable nitrogen in chlorpromazine.

Acetone and Acetonitrile

The plots of Figures 2 and 3, which represent the behavior of the two prototypes in acetone and acetonitrile respectively, can be considered jointly. In these solvents, the situation is entirely different. As a result of a large change in potential at the end-point, the single inflection point for chlorpromazine is much more pronounced than it is in glacial acetic acid. An examination of the prochlorperazine titration curves shows that differentiation between the two piperazine nitrogens occurs in both solvent systems, although both inflection points are more pronounced in acetone than they are in acetonitrile. The change in potential at the end-point for chlorpromazine in acetone ranges from 150 to 200 millivolts, and in acetonitrile the magnitude is 200 milli-
### Table 1. Phenothiazine Derivatives Investigated Showing Respective Substituents.

![Chemical Structure Diagram]

<table>
<thead>
<tr>
<th>No.</th>
<th>Compound</th>
<th>R</th>
<th>X</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Chlorpromazine</td>
<td>-(CH₂)₃-N(CH₃)₃</td>
<td>Cl</td>
</tr>
<tr>
<td>2</td>
<td>Promethazine</td>
<td>-(CH₂)₂-N(CH₃)</td>
<td>H</td>
</tr>
<tr>
<td>3</td>
<td>Levomepromazine</td>
<td>-(CH₂)₂-N(CH₃)</td>
<td>OCH₃</td>
</tr>
<tr>
<td>4</td>
<td>Thioridazine</td>
<td>-CH₂-CH₂-N(CH₃)</td>
<td>SCH₃</td>
</tr>
<tr>
<td>5</td>
<td>Trifluromazine</td>
<td>-(CH₂)₃-N(CH₃)</td>
<td>CF₃</td>
</tr>
<tr>
<td>6</td>
<td>Pyrathiazine</td>
<td>-CH₂-CH₂-N(CH₃)</td>
<td>H</td>
</tr>
<tr>
<td>7</td>
<td>Thiopropepatzate</td>
<td>-(CH₂)₃-N(CH₂)₂-O-C-CH₃</td>
<td>Cl</td>
</tr>
<tr>
<td>8</td>
<td>Trifluoperazine</td>
<td>-(CH₂)₃-N(CH₃)</td>
<td>CF₃</td>
</tr>
<tr>
<td>9</td>
<td>Prochlorperazine</td>
<td>-(CH₂)₃-N(CH₃)</td>
<td>Cl</td>
</tr>
<tr>
<td>10</td>
<td>Pipamazine</td>
<td>-(CH₃g)₃-N(O)C-NH₂</td>
<td>Cl</td>
</tr>
</tbody>
</table>
Figure 1. Titration of phenothiazines in glacial acetic acid.
Figure 2. Titration of phenothiaazines in acetone.
Figure 3. Titration of phenothiazines in acetonitrile.
volts or slightly greater for 0.01 ml of titrant. For prochlorperazine in acetone, a 50 millivolt change occurs at the initial end-point and 10 millivolts at the second for 0.01 ml of titrant. In acetonitrile, however, the respective figures are 20 and 5 millivolts. This would imply that, under the conditions of this investigation, acetone is superior to acetonitrile as a differentiating solvent for the two nitrogens of the piperazine group in this molecule.

**Isopropanol**

Figure 4 is a plot of the titration curves of the two drugs in isopropanol. An examination of the graph reveals that the curve for chlorpromazine is quite similar in this solvent to that for the same compound in glacial acetic acid. The potential change of 50 to 70 millivolts in isopropanol is of the same order as that in glacial acetic acid. The plot for prochlorperazine in isopropanol is unique in that the single inflection point occurs at half-neutralization and no end-point is detectable at or near 100 percent neutralization. A precipitate begins to form, soon after the half-neutralization point, which increases in quantity and this appears to interfere with the functioning of the electrodes and undoubtedly is largely responsible for the suppression of the second equivalence point. However, the solvent system is still quite satisfactory for the analysis of this type of compound, provided the operator utilizes the inflection point at half-neutralization. The change in potential at that point is 40 to 50 millivolts for 0.01 ml of titrant.

**Nitromethane**

Several years ago, Chatten, Pernarowski and Levi (73), in a report on the titration of organic bases in nitromethane, noted that two in-
Figure 4. Titration of phenothiazines in isopropanol.
flection points resulted even when only a single base had been dissolved in the solvent. They attributed this behavior to the existence of a small amount of aci-nitromethane which reacted with a fraction of the base to produce a substance that was materially weaker than the original base. Despite the fact that nitromethane has attracted some attention from other workers in the field (72,94,95), none of them have ever reported this finding. Examination of the curve for chlorpromazine in Figure 5, shows that, the same type of phenomenon is occurring as previously described. A millivolt maximum is noted between 97 and 98 percent neutralization which is followed by a slight reduction in the dE/dV ratio until 100 percent neutralization is reached. At that point, another major inflection occurs. The potential increase at the first point is about 50 millivolts and at the second point, it is approximately 70 millivolts for 0.01 ml of titrant. Three millivolt maxima are indicated in the titration curve for prochlorperazine, in Figure 5. The major inflection point occurs around 47 percent neutralization and is about 35 millivolts for 0.01 ml of titrant. This is followed by a reduction in the dE/dV ratio until a very small inflection point occurs at 50% neutralization, the magnitude of which is about 6 to 7 millivolts. Another and still smaller millivolt maximum occurs at 100 percent neutralization, which is of the order of 5 to 6 millivolts for the standard increment of titrant added.

The solvent is suitable as a titration medium for the analysis of those members of this series that possess a single titratable nitrogen. It leaves much to be desired for those compounds that have a group such as piperazine. One of the most interesting facets of the investigations in this solvent system is the fact that reaction between these pheno-
Figure 5. Titration of phenothiazines in nitromethane.
thiazine derivatives and perchloric acid produced a number of distinctly colored compounds which may be used as a means of identification and differentiation between the respective members. For five of the ten compounds observed, the first color change coincided with an inflection point. They are chlorpromazine, levopromazine, thioridazine, prochlorperazine, thiopropazate, and for these latter two, the color transition occurred at the half-neutralization point. The color development for the other five compounds is of a gradual nature and cannot be used as an indicator for titration purposes. It is still valuable, however, as a means of identification. Table II presents the data on the development of the colors for the ten derivatives studied.

It would be interesting to speculate on the reason for the appearance of intensely colored complexes in this solvent system and their failure to appear in the other solvents. Michaelis, Schubert and Granick (97) point out that in the presence of excess protons, methylene blue, a phenothiazine compound, undergoes formation of semi-quinones. These authors state further that to increase the stability of the resulting free radical, it is essential to bring about a state of equivalent resonance. They define equivalent resonance as a resonance between two limiting structures which, if written by the customary structural formulas, are indistinguishable except for orientation of the molecule as a whole in space.

Two types of equivalent resonance may be distinguished. The first occurs in the regular quinonoid dyestuffs which contain one or two benzenoid rings and one quinonoid ring. The resonance results from the ambiguity with regard to which ring is the quinonoid one and which
Table II. Colors Produced by Phenothiazine Derivatives upon Reaction in Nitromethane with Perchloric Acid

<table>
<thead>
<tr>
<th>Compound</th>
<th>Initial Color</th>
<th>Final Color</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Chlorpromazine</td>
<td>pink</td>
<td>rose red</td>
</tr>
<tr>
<td>2. Promethazine</td>
<td>deep yellow</td>
<td>brown orange</td>
</tr>
<tr>
<td>3. Levomepromazine</td>
<td>violet</td>
<td>deep purple</td>
</tr>
<tr>
<td>4. Thioridazine</td>
<td>pale green</td>
<td>dk. blue green</td>
</tr>
<tr>
<td>5. Triflupromazine</td>
<td>lt. orange</td>
<td>dk. orange</td>
</tr>
<tr>
<td>6. Pyrathiazine</td>
<td>lt. yellow green</td>
<td>brown</td>
</tr>
<tr>
<td>7. Thiopropazate</td>
<td>peach</td>
<td>dk. orange red</td>
</tr>
<tr>
<td>8. Trifluoperazine</td>
<td>pink</td>
<td>dk. red</td>
</tr>
<tr>
<td>9. Prochlorperazine</td>
<td>peach</td>
<td>dk. orange red</td>
</tr>
<tr>
<td>10. Pipamazine</td>
<td>peach</td>
<td>dk. orange</td>
</tr>
</tbody>
</table>
is the benzenoid. This resonance stretches over two rings (or three in the triphenylmethane dyes) and may be designated as quinone-benzene resonance.

The other type of equivalent resonance occurs in the semi-quinone radicals. It is restricted, or may be restricted, to a single ring. There is one unpaired electron, and the cause of the resonance is the uncertainty regarding the place of this electron upon writing down a structural formula. Thus equivalent resonance occurs when there is a pair of possible structural formulas, or "limiting states" which are indistinguishable.

The explanation which Michaelis et al. (97) offered for the development of color by methylene blue is satisfactory for that compound, since it possesses two auxochromic amino groups in the 3,7 positions. These groups are capable of participating in the development of semi-quinonoid structures, through resonance, and hence facilitate the production of color. Such an explanation is not satisfactory, however, for the compounds in this present investigation, since they bear no auxochromic groupings on the phenothiazine nucleus.

In a subsequent publication, Michaelis, Granick and Schubert (98) resolve the aforementioned objection by pointing out that semi-quinone radicals of phenothiazine, as they exist in very acid solution, possess a stabilizing factor which may be attributed to resonance that involves the two bridgehead atoms (nitrogen and sulfur). This latter
type of resonance is sufficient to stabilize those radicals stripped of all auxochromic groups.

The structure of the radical derived from phenothiazine I may be considered either as II, which differs from I by an H atom, or as III which differs from I by an electron only, and arises from II by addition of a proton in sufficiently acid solution. Structures II and III would be considered as semi-oxidized quinonoid forms. The stability of the radical III, with a proton attached to the nitrogen, as it exists in sufficiently acid solution, can be explained by the resonance of this structure with another, such as IV. The resonance between these two limiting states III and IV corresponds to a symmetrically oscillating electrical charge. In less acid solution, where no proton is attached to the nitrogen, the two limiting structures of the resonance would be II and V. This resonance is no longer symmetric with respect to the distribution of the electric charge. The coulombic forces will tend to maintain II, in general, and counteract the separation of electric
charges as they appear in $V$. So the supposition of the two states II and V is such that $V$ probably contributes only a small share; hence, the resonance is small and the stability of the radical diminished. Consequently, the higher stability of the radical in acid solutions is explainable. In this connection, it is interesting to note that Nakagawa, Kuboto and Mujazaki (99) report the development of stable colors in 98 percent sulfuric acid by chlorpromazine and promethazine.

In 1958, it was reported by Dusinsky (100) that during titration by ceric sulfate solution or bromide-bromate, phenothiazine derivatives formed a red colored semiquinonoid free radical, by the loss of one electron. The loss of a second electron resulted in decolorization of the compound. He noted that this phenomenon was greatest with chlorine substituted phenothiazine derivatives, and postulated that the electronegativity of the halogen was responsible for the increased polarizability of the molecule.

Perhaps the most interesting facet of the colors produced during this investigation is that they only occur in nitromethane and, secondly, in several instances, the colors appear during the course of the titration and certainly before there is any excess of protons from the titrant.

It is apparent, therefore, that the nature of the solvent is of utmost importance to the production of these colors. Nitromethane is
known to exist both as the carbanion and the aci-form or as a resonance hybrid, according to the following equation:

\[
\text{CH}_3\text{N}^\text{O} \quad -\text{H}^+ \quad \rightarrow \quad [\quad \text{-CH}_2\text{N}^\text{O} \quad \leftrightarrow \quad \text{CH}_2=\text{N}^\text{O} \quad ]
\]

The necessary excess protons could be supplied by the nitromethane itself as it produces the carbanion. This, together with the addition of protons by the titrant, may be sufficient to produce the intensely colored semiquinonoid free radical, or the color may be formed and stabilized by complexing of the resonating nitromethane with the titrated, resonating phenothiazine compounds. Such a complex could result from ionic attraction of the oppositely charged centers in the phenothiazine compound and the carbanion: aci-nitromethane resonate.

Comparison of \(pK_b\) and \(E^\prime\) Values

The data, resulting from the determination of the \(pK_b\) values in water and \(E^\prime\) values in five organic solvents, for certain selected phenothiazine type tranquillizers are presented in Table III. Figures 6 to 10 are graphic illustrations of these data. The straight lines, in all instances, are the result of calculation by the least squares method (96). The equations are given in Table IV where the number and letter for each equation corresponds to number of the figure and the letter of the appropriate line, where there is more than one line per figure. In the interests of clarity and convenience, Figures 6 to 10 will be discussed on the basis of each solvent.
### Table III. pK\(_b\) and E\(_2\) Values for Phenothiazine Derivatives

<table>
<thead>
<tr>
<th>No.</th>
<th>Compound</th>
<th>pK(_b)</th>
<th>E(_2) in Millivolts</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>H(_2)O</td>
<td>HAC</td>
</tr>
<tr>
<td>1</td>
<td>Chlorpromazine</td>
<td>4.78</td>
<td>223</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(4.70)</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Promethazine</td>
<td>4.90</td>
<td>225</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(4.92)</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Levomepromazine</td>
<td>4.85</td>
<td>223</td>
</tr>
<tr>
<td>4</td>
<td>Thioridazine</td>
<td>4.84</td>
<td>222</td>
</tr>
<tr>
<td>5</td>
<td>Triflupromazine</td>
<td>4.59</td>
<td>234</td>
</tr>
<tr>
<td>6</td>
<td>Fyrafthiazine</td>
<td>5.09</td>
<td>223</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(5.04)</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>Thiopropazate</td>
<td>6.61</td>
<td>260</td>
</tr>
<tr>
<td>8</td>
<td>Trifluoperazine</td>
<td>6.12</td>
<td>262</td>
</tr>
<tr>
<td>9</td>
<td>Prochlorperazine</td>
<td>6.93</td>
<td>260</td>
</tr>
<tr>
<td>10</td>
<td>Pamezine</td>
<td>5.40</td>
<td>223</td>
</tr>
</tbody>
</table>

Bracketed pK\(_b\)'s refer to literature values (92).

HAC refers to glacial acetic acid.

IPA refers to isopropanol.
Table IV. Equations of the Least Squares Lines in Plots of pK_b Versus E_i Values for Phenothiazines

<table>
<thead>
<tr>
<th>No.</th>
<th>Solvent</th>
<th>Equation</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>6a</td>
<td>Glacial Acetic Acid</td>
<td>$E_i = -0.07 \ pK_b + 223.5$</td>
<td>6</td>
</tr>
<tr>
<td>6b</td>
<td>Glacial Acetic Acid</td>
<td>$E_i = -2.64 \ pK_b + 277.9$</td>
<td>3</td>
</tr>
<tr>
<td>7</td>
<td>Acetone</td>
<td>$E_i = 62.06 \ pK_b + 195.0$</td>
<td>6</td>
</tr>
<tr>
<td>8a</td>
<td>Acetonitrile</td>
<td>$E_i = 112.89 \ pK_b + 98.7$</td>
<td>6</td>
</tr>
<tr>
<td>8b</td>
<td>Acetonitrile</td>
<td>$E_i = 140.39 \ pK_b - 296.3$</td>
<td>4</td>
</tr>
<tr>
<td>9a</td>
<td>Isopropanol</td>
<td>$E_i = 107.76 \ pK_b - 112.2$</td>
<td>4</td>
</tr>
<tr>
<td>9b</td>
<td>Isopropanol</td>
<td>$E_i = 96.24 \ pK_b + 3.1$</td>
<td>3</td>
</tr>
<tr>
<td>9c</td>
<td>Isopropanol</td>
<td>$E_i = 147.15 \ pK_b - 270.7$</td>
<td>3</td>
</tr>
<tr>
<td>10a</td>
<td>Nitromethane</td>
<td>$E_i = 139.64 \ pK_b - 348.8$</td>
<td>6</td>
</tr>
<tr>
<td>10b</td>
<td>Nitromethane</td>
<td>$E_i = 122.78 \ pK_b - 313.3$</td>
<td>4</td>
</tr>
</tbody>
</table>

n represents the number of compounds used in calculation of the respective equations.
Glacial Acetic Acid

As previously mentioned, this solvent has a marked tendency to level bases dissolved in it. Examination of Figure 6 shows there are two distinct lines, one at 223 millivolts and the other at 260 millivolts. The one identified as "a" represents those bases with a $pK_b$ range of 4.78 to 5.40. Those with a $pK_b$ above 6, as typified by thiopropazate, trifluoperazine, and prochlorperazine, compounds 7, 8, and 9 respectively, are identified by curve "b". Trifluromazine, number 5, was not included in the calculation of equation 6a (Table IV) by the least squares method, because it did not appear to belong to the remainder of the group. Repetitive determinations of $E_2$ values for this compound, on different stock solutions, resulted in the same value of 234 millivolts. This lack of harmony with the other compounds chosen might be explained by the presence of the strongly electrophilic trifluoromethane group on position two of the molecule. On the basis of the determination of $pK_b$ values by the method of Marshall (92), it seems to affect the $E_2$ value adversely, in this solvent. A similar argument could be advanced for trifluoperazine, but the $E_2$ value for this compound was considered to be sufficiently close in agreement to warrant its inclusion in the calculation of line "b". Since the difference between the $E_2$ of this compound and those of thiopropazate and prochlorperazine, numbers 7 and 9, is only two millivolts, it might be suggested that it is due only to experimental error. While this is conceded, repetitive determinations were so consistent it is believed that the small discrepancy is due to the influence of the trifluoromethane group.
Figure 6. Relationship of pK_b values in water for phenothiazines to their E_{1/2} values in glacial acetic acid.
Acetone

An excellent linear relationship is noted in Figure 7 between the \( pK_b \) and \( E_1 \) values for chlorpromazine, promethazine, levomepromazine, trifluromazine, thiopropazate, and prochlorperazine, numbers 1, 2, 3, 5, 7 and 9 respectively. Trifluoperazine was insoluble in this solvent, and thioridazine, pyrithiazine and pipamazine, numbers 4, 6 and 10, were not included in the calculation of the least squares line.

The question may be raised regarding the exclusion of the last three compounds referred to in the preceding paragraph. Justification for this decision is based upon four possible reasons. The first is that Figures 8, 9, and 10 show that thioridazine, pyrithiazine and pipamazine appear to form a separate series. Although they do not possess any inter-relationship between themselves in acetone, clearly these compounds do not correlate with the other members of the series. The second reason is that these are the only three derivatives, of those studied, whose structure includes a saturated, cyclic, single nitrogen moiety, such as piperidine or pyrrolidine. A further reason for the apparent behavior of thioridazine and pyrithiazine could be attributed to their substituents at X. The latter contains a hydrogen in that position and hence no electrophilic influence; the former possesses a \(-SCH_3\) group, which is the weakest electrophilic group among those considered in this investigation. The same argument does not hold for pipamazine, which has a chlorine group in the two position. However, construction of a model of this molecule shows that it may be possible for the R group to rotate in such a manner that the titratable nitrogen may actually assume a spatial conformation whereby it is so far removed from the halogen that the electrophile is unable to exert its electron attracting power on the
Figure 7. Relationship of pK\textsubscript{b} values in water for phenothiazines to their E\textsubscript{1/2} values in acetone.
unbonded electron pair of the nitrogen. And finally, if one examines the structures in Table I, it is apparent that pipamazine is the only member of the group that is capable of participating in hydrogen bonding with this solvent. Such a phenomenon could be accomplished through one of the hydrogens in the amide group and the ketone moiety of acetone. If hydrogen bonding occurs, this would allow a greater flow of electrons from the nitrogen to the ketone group of the amide and thus reduce any electronegative effect which the carbonyl may have on the titratable nitrogen.

**Acetonitrile**

The respective members of the series exhibit a behavior in this solvent which is similar to that in acetone, the main difference being that thioridazine, pyrathiazine and pipamazine, numbers 4, 6 and 10 respectively, appear to bear a linear relationship to each other as shown by the least squares line "b" in Figure 8. It is noteworthy that prochlorperazine, number 9, is a common point on both curves "a" and "b" in this solvent system. As far as this compound is concerned, acetonitrile appears to serve as a transition solvent between its behavior in acetone and its behavior in isopropanol or nitromethane. In these latter two solvents, prochlorperazine appears to align itself with thioridazine, pyrathiazine and pipamazine. The same reasoning for the failure of these last three compounds to coincide with curve "a" in acetonitrile can be applied as in acetone.

**Isopropanol**

In this solvent, thioridazine, pyrathiazine, prochlorperazine and pipamazine, compounds 4, 6, 9 and 10, again bear a linear relationship. The remaining six compounds are split in such a manner that
Figure 6. Relationship of pKb values in water for phenothiazines to their E1/2 values in acetonitrile.
levomepromazine, trifluromazine and thiopropazate, numbers 3, 5 and 7, have a straight line relationship, as shown by line "b" in Figure 9, and the plot of $pK_b$ versus $E_\alpha$ for the remaining three drugs is also on a straight line, as seen from curve "c". The anomaly in this solvent system appears to be the behavior of chlorpromazine, promethazine and trifluoperazine, numbers 1, 2 and 8. One would expect them to coincide with line "b", which seems to have a slope that is approximately parallel to that of line "a". Chlorpromazine and promethazine exhibit $E_\alpha$ values which are numerically lower than one would predict from their $pK_b$ values. This implies, therefore, that they are stronger bases than would be expected. Possible justification for the apparent increased strength of promethazine may be found in the fact that it has no electrophilic group in the two position. Such a situation may be of significance in isopropanol but not in the other solvents investigated. Furthermore, the properties of this solvent may be such that chlorpromazine is forced into a spatial conformation whereby the chlorine is unable to exert its electrophilic influence on the nitrogen because the two atoms have become so widely separated.

For trifluoperazine, it is difficult to say whether the trifluoromethane group exerts an excessive influence on one of the piperazine nitrogens by markedly reducing its electron density. It is suspected that this is so, however, when a comparison is made of the respective behaviors in nitromethane (Figure 10). It is unfortunate that trifluoperazine is insoluble in acetone and acetonitrile; otherwise, one might be in a better position to comment on this substance.
Figure 9. Relationship of $pK$ values in water for phenothiazines to their $E_{1/2}$ values in isopropanol.
Figure 10. Relationship of $pK_b$ values in water for phenothiazines to their $E_{1/2}$ values in nitromethane.
Nitromethane

There is little that remains to be said about Figure 10. Once again, thioridazine, pyrazidazine, prochlorperazine and pipamazine, compounds 4, 6, 9, and 10 respectively, appear to bear a linear relationship and the data for these compounds were employed in the calculation of the least squares line, as illustrated by curve "b". The remainder of the data were used in the calculation of line "a".

Series B, Sympathomimetic Amines

Eleven sympathomimetic amines, which are utilized in pharmaceutical preparations, were chosen for this study. They were selected purposely in such a manner that a heterogeneous group resulted. The names of the compounds and their chemical structure are given in Table V. From this, it is noted that only the first six compounds comprise a homogeneous series. Numbers 7 and 8 are closely related to each other, as are 9 and 10. Naphazoline, which is number 11, is not chemically related to any of the other members.

Since the only common denominators to all the compounds are that they are bases and that all possess similar pharmacological properties, it appeared interesting to note the effect of steric hindrance, electronegativity and possible hydrogen bonding upon the relationship between \( pK_a \) and \( E_1 \) values. Furthermore, it was of interest to determine whether structural differences of the last five members would eliminate any tangible relationship with the half-neutralization potentials of the first six.

Since the first six compounds in Table V represent the only homogeneous series, the strongest member, mephenteramine, and the weakest, methoxamine, were selected in order to study their titration
Table V. Sympathomimetic Amines Investigated Showing Structural Formulas

<table>
<thead>
<tr>
<th>No.</th>
<th>Compound</th>
<th>Structure</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Ephedrine</td>
<td>![Ephedrine Structure]</td>
</tr>
<tr>
<td>2</td>
<td>Phenylpropylmethylamine</td>
<td>![Phenylpropylmethylamine Structure]</td>
</tr>
<tr>
<td>3</td>
<td>d-Methamphetamine</td>
<td>![d-Methamphetamine Structure]</td>
</tr>
<tr>
<td>4</td>
<td>dl-Amphetamine</td>
<td>![dl-Amphetamine Structure]</td>
</tr>
<tr>
<td>5</td>
<td>Methoxamine</td>
<td>![Methoxamine Structure]</td>
</tr>
<tr>
<td>6</td>
<td>Mephenteramine</td>
<td>![Mephenteramine Structure]</td>
</tr>
<tr>
<td>7</td>
<td>Propylhexedrine</td>
<td>![Propylhexedrine Structure]</td>
</tr>
<tr>
<td>8</td>
<td>Cyclopentamine</td>
<td>![Cyclopentamine Structure]</td>
</tr>
<tr>
<td>9</td>
<td>2-Aminoheptane</td>
<td>![2-Aminoheptane Structure]</td>
</tr>
<tr>
<td>10</td>
<td>Methylhexylamine</td>
<td>![Methylhexylamine Structure]</td>
</tr>
<tr>
<td>11</td>
<td>Naphazoline</td>
<td>![Naphazoline Structure]</td>
</tr>
</tbody>
</table>
curves in each of the five solvents. Figures 11 to 16, inclusive, represent the graphs of millivolts versus percentage neutralized for the two compounds. For ease of discussion, each solvent system will be dealt with separately.

Glacial Acetic Acid

The plot of the titration curves for methoxamine and mephen- teramine is given in Figure 11. Although there is an obvious difference in their half-neutralization potentials, the behavior of the two compounds at the end-point is almost identical. This is to be expected because of the known leveling property of the solvent. However, the change in potential at the equivalence point is slightly greater for mephtenteramine than for methoxamine.

Acetone

The marked difference in $E_1$ values between the two prototypes is evident in Figure 12. In addition, at the end-point, mephtenteramine shows a change in potential of 270 mv for 0.01 ml of titrant, whereas for methoxamine, this value is approximately equal to 200 mv for the same increment of titrant. Both of these factors are a result of the superior strength of the former over the latter compound. It is doubtful, however, whether the differences in behavior of the two drugs, in this solvent, are sufficient to permit a differential titration.

Acetonitrile

Figure 13 illustrates the titration curves of the two sympatho- mimetic amines, and it is noted that there is little difference in their behavior in this solvent. As would be expected methoxamine, the weaker compound, has a somewhat higher $E_1$ value. At the end-point, however, both substances behave in much the same manner. The change in potential for each ranges from about 170 to 220 millivolts.
Figure II. Titration of sympathomimetic amines in glacial acetic acid.
Figure 12. Titration of sympathomimetic amines in acetone.
Figure 13. Titration of sympathomimetic amines in acetonitrile.
Isopropanol

The behaviors of methoxamine and mephenteramine in this solvent are remarkably similar, as shown by Figure 14. The unexpected development is the basic strength exhibited by methoxamine which shows a half-neutralization potential in excess of that for mephenteramine. A possible explanation for this phenomenon will be presented under the discussion of Figure 19.

Nitromethane

In the previously referred to investigations of Chatten, Pernerowski and Levi (73), the strongest base titrated in nitromethane was dl-amphetamine. On the basis of the findings at that time, it was assumed that all organic bases with $pK_b$ values below 11 would have two equivalence points when titrated in this solvent. The present work, demonstrates that this assumption is not entirely correct. While all those bases with $pK_b$ values weaker than 4.00 did exhibit two millivolt maxima, none of those compounds with a $pK_b$ stronger than 4.00 showed more than one equivalence point. For the latter group, this indicated that only one titratable species was present, while solutions of the weaker bases contained two titratable species.

It is difficult to offer an absolute explanation of these observations but one could speculate that reaction of the stronger bases with aci-nitromethane is forced to completion by the actual strength of the bases themselves, whereas with the weaker bases, an equilibrium is established so that the major portion of the base is not combined with the weak aci-nitromethane. About 5 percent is combined with the aci-portion and the result is a species which is much weaker than the free base. The other explanation may be that
Figure 14. Titration of sympathomimetic amines in isopropanol.
the strong bases also undergo a similar equilibrium but that the resulting product maintains the strong basicity of the parent compound. Hence a plot of millivolts versus percentage neutralized would appear as though only one species was present. Such a situation is illustrated in Figure 15.

Mephenteramine gives a smooth titration curve in nitromethane, with a potential change of 85 millivolts at the end-point for 0.01 ml of titrant. Methoxamine has one equivalence point at about 95 percent neutralization, with a change in potential of only 50 millivolts for the same increment of titrant, and has at complete neutralization, a second change equal to approximately 8 mv. The titration must be performed with care in order to detect the theoretical neutralization point for this compound.

Comparison of $pK_b$ and $E_1$ Values

The data resulting from the determination of the $E_1$ values of certain sympathomimetic amines together with their $pK_b$ values are reported in Table VI. Figures 16 to 20 are graphic illustrations of these data, and the straight line, in each instance, is the result of calculation by the least squares method (96). The number and letter for each equation in Table VII corresponds to the number of the figure and the letter of the appropriate line, where there is more than one line per figure. Figures 16 to 20 will be discussed on the basis of each solvent.

Glacial Acetic Acid

The data obtained in this solvent are plotted against the respective dissociation constants in Figure 16. As expected from the
Figure 15. Titration of sympathomimetic amines in nitromethane.
Table VI. $pK_b$ and $E_1$ Values for Sympathomimetic Amines

<table>
<thead>
<tr>
<th>No.</th>
<th>Compound</th>
<th>$pK_b$</th>
<th>$E_1$ in Millivolts</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>$H_2O$</td>
<td>HAC</td>
</tr>
<tr>
<td>1.</td>
<td>Ephedrine</td>
<td>**4.42</td>
<td>231</td>
</tr>
<tr>
<td>2.</td>
<td>Phenylpropyl Methylamine</td>
<td>**4.12</td>
<td>223</td>
</tr>
<tr>
<td>3.</td>
<td>d-Methamphetamine</td>
<td>***3.80</td>
<td>216</td>
</tr>
<tr>
<td>4.</td>
<td>dl-Amphetamine</td>
<td>**4.23</td>
<td>217</td>
</tr>
<tr>
<td>5.</td>
<td>Nethoxamine</td>
<td>*4.82</td>
<td>239</td>
</tr>
<tr>
<td>6.</td>
<td>Mephenyleramine</td>
<td>*3.62</td>
<td>205</td>
</tr>
<tr>
<td>7.</td>
<td>Propylhexedrine</td>
<td>**3.48</td>
<td>220</td>
</tr>
<tr>
<td>8.</td>
<td>Cyclopentamine</td>
<td>*3.53</td>
<td>214</td>
</tr>
<tr>
<td>9.</td>
<td>2-Aminoheptane</td>
<td>*3.53</td>
<td>247</td>
</tr>
<tr>
<td>10.</td>
<td>Methylhexylamine</td>
<td>*3.46</td>
<td>247</td>
</tr>
<tr>
<td>11.</td>
<td>Naphazoline</td>
<td>*3.86</td>
<td>209</td>
</tr>
</tbody>
</table>

* Values determined in this laboratory

** Data obtained from Leffler et al (101)

*** Data obtained from Kisbye (102)

HAC - represents glacial acetic acid, and IPA is abbreviation for isopropanol
Table VII. Equations of the Least Squares Lines in Plots of pK\textsubscript{b} Versus E\textsubscript{2} Values for Sympathomimetic Amines

<table>
<thead>
<tr>
<th>No.</th>
<th>Solvent</th>
<th>Equation</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>16.</td>
<td>Glacial Acetic Acid</td>
<td>$E_2 = 19.04 \ pK_b + 143.4$</td>
<td>9</td>
</tr>
<tr>
<td>17.</td>
<td>Acetone</td>
<td>$E_2 = 71.03 \ pK_b + 111.3$</td>
<td>8</td>
</tr>
<tr>
<td>18.</td>
<td>Acetonitrile</td>
<td>$E_2 = 33.34 \ pK_b + 215.9$</td>
<td>6</td>
</tr>
<tr>
<td>19.</td>
<td>Isopropanol</td>
<td>$E_2 = 1.97 \ pK_b + 328.2$</td>
<td>8</td>
</tr>
<tr>
<td>20a</td>
<td>Nitromethane</td>
<td>$E_2 = 104.24 \ pK_b - 99.0$</td>
<td>5</td>
</tr>
<tr>
<td>20b</td>
<td>Nitromethane</td>
<td>$E_2 = 56.58 \ pK_b + 76.1$</td>
<td>4</td>
</tr>
</tbody>
</table>

n represents the number of compounds used in calculation of the respective equations.
Figure 16. Relationship of $pK_b$ values in water for sympathomimetic amines to their $E_{1/2}$ values in glacial acetic acid.
structures appearing in Table V, reasonable linearity is noted between the first 6 numbers of the series and it is not even too surprising that propylhexedrine and cyclopentamine, compounds 7 and 8, seem to conform. The fact, that naphazoline, number 11, appears to exhibit a similar behavior while 2-aminoheptane and methylhexylamine do not, is unexpected. The relatively small slope of the line is certainly attributable to the leveling property of the solvent.

**Acetone**

Figure 17 shows that a linear relationship exists between the \( pK_a \) and \( E_1 \) values for the first 8 members of the series. It is apparent that 2-aminoheptane, methylhexylamine, and naphazoline, numbers 9, 10, and 11 respectively, do not share this relationship and they were omitted from the calculation of the least squares line. Although propylhexedrine and cyclopentamine have saturated cyclic groups rather than benzene-type rings, this does not prevent them from conforming to the pattern of phenylpropylamine compounds, numbers 1 to 6 inclusive. The slope of the line indicates that acetone is a good differentiating solvent but it would require more work in order to determine at what level differentiation would occur.

**Acetonitrile**

Of the five organic solvents investigated, only in acetonitrile does 2-aminoheptane and methylhexylamine appear to exhibit the same behavior as the first six members of the series. It is noted also in Figure 18 that propylhexedrine and cyclopentamine give anomalous results in this solvent, whereas in all the others they correspond to the phenylpropylamine type of compound. No logical explanation can be offered for this reversal of behavior.
Figure 17. Relationship of $pK_b$ values in water for sympathomimetic amines to their $E_{1/2}$ values in acetone.
Figure 18. Relationship of $pK_b$ values in water for sympathomimetic amines to their $E_{1/2}$ values in acetonitrile.
Although acetonitrile is known to be a differentiating solvent, the slope of the line, as given in Table VII, is sufficiently similar to that of glacial acetic acid that this solvent holds little prospect for differentiation, as far as this series of drugs is concerned.

Isopropanol

Figure 19 shows that the most striking feature about the behavior of the compounds in this solvent is the marked leveling effect. Furthermore, methoxamine, number 5, which has the weakest dissociation constant in water of the six phenylpropylamine compounds studied, actually exhibits the strongest half-neutralization potential in isopropanol.

The two aforementioned phenomena may be explained by the possibility of hydrogen bonding between an amino hydrogen of the compounds and the oxygen of isopropanol. Such a situation would result in removing the hydrogen farther from the nitrogen by a distance which would be greater than the normal nitrogen-hydrogen bond distance. Thus, the hydrogen would have less attraction for the electrons on the nitrogen and the net effect would be an increase in the electron density around the latter atom. If this situation occurred to the same degree, one would expect these compounds to be leveled to the same extent. The fact that methoxamine has an $E_1/2$ value which is consistently lower than that of mephenteramine would indicate that there are small differences in the degree of hydrogen bonding.
Figure 19. Relationship of $pK_b$ values in water for sympathomimetic amines to their $E_{1/2}$ values in isopropanol.
Nitromethane

The relationship of $pK_b$ to $E_1$ values, in this solvent, is plotted in Figure 20. d-Methamphetamine, dl-amphetamine, mephenteramine, propylhexedrine, and cyclopentamine (numbers 3, 4, 6, 7, and 8 respectively) comprise straight line "a" with a large slope, while ephedrine, phenylpropylmethyamine, methoxamine, and mephenteramine (numbers 1, 2, 5, and 6 respectively) make up line "b" with a much smaller slope. No explanation can be offered for the unexpected base strength of compounds 1, 2 and 5 in this solvent.

Inter-relationship of Solvent Systems

A number of instances of anomalous behavior have been pointed out in the foregoing discussion and postulations have been made with regard to their cause. The question may be raised that these anomalies may be due to the irregular behavior of the respective compounds in water rather than in the various nonaqueous solvents. While this possibility is admitted, it must be pointed out that one must accept the results in one of the six solvents as a criterion and use it as a standard against which to compare all other experimental results. Previous workers (64, 72, 93, 94) in this field have selected the $pK_b$ values in water to serve as that criterion. Grunwald and Berkowitz (89) pointed out that

Water is used as the reference solvent since the data for aqueous dissociation are the most accurate.

The equations for the least square lines in Tables IV and VII are readily recognizable as $y = mx + b$, where $y$ is represented by $E_1$, $x$ by $pK_b$ and $m$ and $b$ are the slope and intercept respectively. One
Figure 20. Relationship of $pK_b$ values in water for sympathomimetic amines to their $E_{1/2}$ values in nitromethane.
could postulate that the magnitude of the slope might be an indication of the differentiating capability of the solvent for titrations carried out under identical experimental conditions. From Table IV, equations 6a and 6b show that the slope in glacial acetic acid is insignificant when compared to that of the other solvents. This would imply that glacial acetic acid has virtually no differentiating capacity. Such a conclusion is in agreement with the known physical characteristics for this solvent. Of the other solvents, acetonitrile, isopropanol and nitromethane appear to have about equivalent differentiating capacity. The slope of the line in acetone, although significantly less than that of the latter three, still gives considerable evidence that it is a good differentiating solvent. From Table VII, it is noted that the line in glacial acetic acid has a much smaller slope than it has in either acetone, acetonitrile or nitromethane, thus indicating its leveling properties, again.

The surprising feature of this aspect of the investigation is the very small slope of the line in isopropanol for the sympathomimetic amines as compared to the slope obtained for the phenothiazines in this solvent. This fact indicates that these sympathomimetic amines are leveled to about the same basic strength in this solvent. Such a situation is confirmed by observing the $E_4$ values as they appear in Table VI. Since the only variable in the experimental conditions is the difference in the fundamental structures of the two series of compounds, it is apparent that their difference in behavior must be attributed to the respective structures of the two series. This observation is in agreement with Hall's conclusion (72) when he stated that the $E_4$ value of an amine is dependent upon its structure as well as the nature of the solvent.
From a practical standpoint, it might be interesting to speculate on what would be the preferred solvent in which to titrate these two series of compounds. The most suitable solvent is the one in which the drugs exhibit the strongest basic properties. The only question that remains is what criterion to use in assessing the basicity of the compounds. It might be suggested that the $E_2$ value could be used as an indication for this purpose. In this investigation, it is noted that the smaller the $E_2$ value, the stronger the basic property exhibited by the drug. One might conclude, therefore, that it is only necessary to examine the $E_2$ values and to select the solvent for each compound in which the $E_2$ value is the smallest. Such reasoning ignores certain other vital facts. For example, the millivolt range covered by a titration curve in glacial acetic acid is always small and consequently, a low $E_2$ value will always result. On the other hand, Tables III and VI show much higher $E_2$ values in acetone for both series, yet, this solvent is eminently satisfactory as a medium for the titration of any of the compounds included in this investigation.

A very useful criterion in choosing the best solvent is the numerical value of $dE/dV$ at the end-point. This expression is the relationship of the change of potential in millivolts in relation to an accurately measured increment of titrant. By this standard, acetone and acetonitrile reveal themselves to be highly satisfactory, whereas, glacial acetic acid might be considered to be much less satisfactory. Results based on percentage recoveries as well as on ease of end-point detection show that acetone and acetonitrile are highly satisfactory for the purpose of titrating any of the compounds in this investigation. Although the $dE/dV$ for glacial acetic acid is much less than that for the two aforementioned
solvents, the change in potential at the end-point is still sufficient to permit detection of the end-point in an accurate and reproducible manner for all compounds studied. In fact, glacial acetic acid is the solvent of choice in the United States Pharmacopoeia (90), for the determination of purity of numerous organic bases. It should be remembered, however, that all the drugs mentioned in this report are relatively strong organic bases. There are many bases which are too weak to be titrated satisfactorily in glacial acetic acid. It becomes necessary, at that time, to perform the titration in some differentiating solvent such as acetone or acetonitrile. More work is necessary in order to determine that transition point. Furthermore, glacial acetic acid is quite unsatisfactory as a titration medium for most pharmaceuticals. The presence of excipients, diluents, and lubricants, usually interfere with a quantitative determination, because of the wide solubilizing properties of this solvent.

Isopropanol is a satisfactory solvent for all the members of both series, but for those phenothiazine compounds that have two titratable nitrogens, it is essential to select the end-point at 50 percent neutralization. Slightly beyond that point, a precipitate forms that affects the functioning of the electrodes and prevents the appearance of the second inflection point.

Nitromethane is a satisfactory titration medium only for those bases that have a pKb stronger than 4.00. With such compounds, only one inflection point occurs and it is readily detectable. Consequently, for all the phenothiazine derivatives in this report as well as for most of the sympathomimetic amines, this solvent would be considered to be unsatisfactory.
It is pertinent to point out the significance of the $E_1$ value, since the author did not make direct use of it in reaching a decision on the preferred solvents. The present data allows an investigator to predict the behavior of compounds that are related chemically to the ones studied. The $E_1$ values of chemically similar compounds may be predicted, or if desired, they may be determined. From this information, the operator will be able to predict whether a certain solvent is a suitable titration medium for a particular compound without actually having to perform the titration.
IV. CONCLUSIONS

In a previously mentioned publication, Hall (72) made the following general observation:

The base strength of an amine in water is, broadly speaking, a reliable index of its base strength in organic solvents.

The findings reported in this present work support this observation in a very general way. From the discussions on the behavior of the respective compounds in each of the solvents, it will be recalled that anomalies occurred in each series, and therefore, it was not always possible to predict the basicity of a compound by comparing it with similar members, even in a homogeneous series. Such a situation is particularly true with the phenothiazines.

It was stated in the introduction that an attempt would be made to correlate anomalous behavior with either steric effects, hydrogen bonding, or the existence of electrophilic centers. The only examples of sterically hindered compounds occur in the sympathomimetic amine series. They are methoxamine and, particularly, mephenteramine. In every instance, mephenteramine behaves in a normal manner as shown by its linear relationship with the other six members of the series which are closely related, on a chemical basis. Methoxamine differs only in nitromethane. The fact that steric hindrance does not appear to affect base strength in these solvents is to be expected when one considers the diameter of a proton which is about $10^{-13}$ mu. It is hard to imagine a compound so sterically hindered that the proton could be
blocked. Such a conclusion is in agreement with Hall (72) who found that piperidine and its 2,2,6,6-tetramethyl derivative have identical base strengths.

Although only one instance of nonconforming behavior among the phenothiazines could be attributed to hydrogen bonding, this phenomenon should not be disregarded. As previously noted, the unexpected strength of pipamazine in acetone may be due to hydrogen bonding with the solvent. Such a situation may also be true for naphazoline in acetone, acetonitrile, and nitromethane, although it is more likely due to major differences between the imidazole derivative and the other members of the sympathomimetic amines. The leveling effect observed for many of the sympathomimetic amines in isopropanol has been attributed to hydrogen bonding with the solvent.

Centers bearing electrophilic groups appear to play a much larger part in the unpredictable behavior of many compounds than either of the other two factors that have been considered. There are several such instances in the phenothiazine series. It will be recalled that even though glacial acetic acid is a leveling solvent, the electrophilic effect of the trifluoromethane group is so pronounced on the base strength of triflupromazine that this compound is apparently weaker than comparable members of the series.

In addition, the unexpected strength of thioridazine and pyrathiazine in acetone, acetonitrile, isopropanol, and nitromethane is probably due to the presence of a weakly electrophilic group on the former compound and the absence of such a group on the latter. Although pipamazine possesses a chlorine on the 2-position, this compound is stronger in acetonitrile, isopropanol, and nitromethane than
would be predicted from its $pK_b$ value. While it might be argued that such a behavior could be due to hydrogen bonding with the solvent, as postulated for it in acetone, it would seem more plausible to suggest that the unexpected strength in these solvents may be due to the inability of the chlorine to exert its electrophilic influence on the titratable nitrogen, because of a change in the conformation of the compound. A similar situation may account for the unexpected strength of prochlorperazine in both isopropanol and nitromethane. These solvents may induce the molecule to assume such a spatial conformation that once again the chlorine is unable to exert its influence on the first nitrogen to be titrated. A similar reason may be suggested for the unexpected strength of chlorpromazine in isopropanol.

On the other hand, trifluoperazine is much weaker in isopropanol, and there is a hint that it may be weaker in glacial acetic acid than would be predicted. Such a situation may be explained by the possibility that the solvent is unable to inhibit the rather large electrophilic influence of trifluoromethane group upon the titratable nitrogen.

With regard to the sympathomimetic amine series, the only other anomalous behavior appears to be the unexpected strength of ephedrine, phenylpropylmethylamine, and methoxamine in nitromethane. No logical explanation can be offered for this situation.
38. Wichtl, M., Scientia Pharm. 21, 30 (1953).
I, Leslie George Chatten, was born in Calgary, Alberta, Canada, May 10, 1920, and received my secondary-school education in the high school at Swalwell, Alberta. My undergraduate studies at the University of Alberta were interrupted by four years of war service in the Canadian Army, but requirements for the Bachelor of Science degree in Pharmacy were completed in 1947. In 1949, the same institution granted me the degree of Master of Science. Since that time, I have been employed by the Government of Canada, in the Food and Drug Directorate at Ottawa, as head of the Pharmaceutical Chemistry Section. I enrolled in the Graduate School of the Ohio State University in 1959, and spent one year completing the academic requirements. Since that time I have been registered in off-campus research.

On September 1, 1943, I married Isabella Mary Richardson of Fort Macleod, Alberta. We are the parents of three daughters, Myrna Lynn, Valerie Ann, Marcia Dawn.

I am a member of the Professional Institute of the Public Service of Canada, the American Pharmaceutical Association, and the Society of Sigma Xi.