containing boron(III) bis-(β-chloroethoxy)-chloride. This white solid was quite soluble in boron(III) bis-(β-chloroethoxy)-chloride. Wiberg and Sütterlin[4] observed the formation of boron oxychloride when boron(III) ethoxydichloride decomposed as follows

$$C_2H_5OBCl_2 \longrightarrow C_2H_5Cl + BOCl$$
$$3BOCl \longrightarrow B_2O_3 + BCl_3$$

URBANA, ILLINOIS RECEIVED AUGUST 11, 1950

[CONTRIBUTION FROM RESEARCH LABORATORIES OF SCHOOL OF PHARMACY, UNIVERSITY OF WISCONSIN]

Behaviors of Several Compounds as Indicators in Lithium Aluminum Hydride Titration of Functional Groups[1]

BY T. HIGUCHI AND DONALD ANTON ZUCK[2]

An investigation has been made on behaviors of several possible indicators which may be useful in alkalimetric determination of very weak acids and other oxygenated compounds including alcohols, esters, phenols, ketones, aldehydes, etc., which react with lithium aluminum hydride. The possible mode of action of the indicators and experimental analytical results for a number of compounds are presented. The data indicate that the method presented provides a simple and rapid means of determining the combined oxygen content of any of the above listed compounds or their mixtures. The possible value of these indicators in organic synthesis involving the use of lithium aluminum hydride is pointed out. Recently it was shown that various functional groups which react with lithium aluminum hydride including hydroxyl, carbonyl, ester, etc., can be determined volumetrically. The titration end-point in the method described was established potentiometrically, there being a large difference in the reduction potential of a system in presence and absence of unreacted lithium aluminum hydride.[3-6] In the present study an investigation has been carried out on the behaviors of possible chemical indicators for detection of this end-point.

Discussion of Theory

In the method mentioned above the sample is treated with a given volume of a solution of lithium aluminum hydride. The excess hydride is determined by back titration with a standardized solution of one of the lower primary alcohols in benzene. The end-point reaction then can be loosely pictured as neutralization of a strong base, lithium aluminum hydride, by a weak acid, alcohol.

$$\underset{\text{acid}}{ROH} + \underset{\text{base}}{{}^1/_4LiAlH_4} \longrightarrow \underset{\text{salt}}{{}^1/_4LiAl(OR)_4} + H_2$$

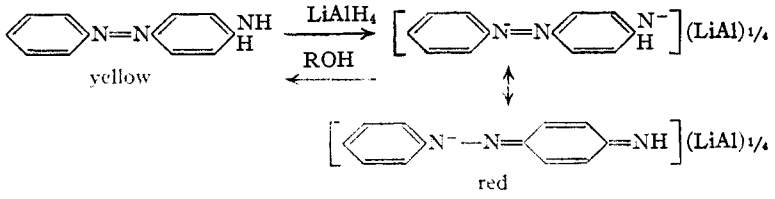
It is evident, however, that any suitable chemical indicator for such a system must necessarily be a very weak acid.

Since the pK_a values of alcohols which are used as the acid in the system are estimated to be of the order of 16–17, the hypothetical pK_I of suitable indicators must be 20 or greater. This requirement leaves for consideration, in main, substances having acidic hydrogen attached to either carbon or nitrogen atoms.

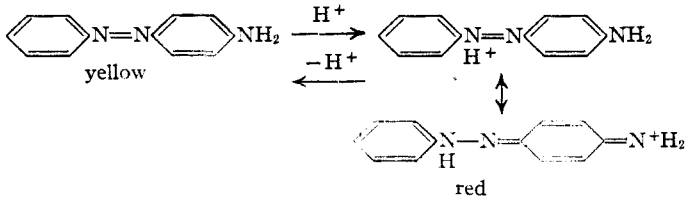
A number of hydrocarbons containing acidic hydrogen including triphenylmethane, tridiphenylmethane, phenylacetylene, fluorene and phenylfluorene were investigated as possible indicators. Although several in this group showed some promise, none proved entirely satisfactory.

In the present investigation greater attention was paid to the possible application of N–H acidic hydrogens to the indicator problem, mainly because of ready availability or ease of synthesis of promising compounds having this group. It is evident that the amino group in any suitable indicator must be conjugated to the chromophoric grouping. This fact plus the observation that azo linkages are not attacked by lithium aluminum hydride would indicate that compounds such as, for example, *p*-aminoazobenzene may be suitable indicators.

At least on paper, the latter compound can be expected to undergo the changes



The electronic configuration of the postulated resonating salt form is very similar to that generally accepted for the same compound in strongly acidic solutions. That is



This postulated similarity in the electronic configurations of *p*-aminoazobenzene under strongly basic and strongly acidic conditions is actually manifested by many common indicators. Phenolphthalein, for example, exists in red quinoid forms both in alkaline and strongly acid solutions.

p-Aminoazobenzene itself is not totally satisfactory as an indicator for investigational purposes as it possesses two replaceable hydrogens with

(1) This paper is in part based on a Master's dissertation submitted to the Graduate School of the University of Wisconsin by Mr. D. A. Zuck in partial fulfillment of the requirements of the M. S. degree.

(2) Fellow of American Foundation for Pharmaceutical Education.

(3) T. Higuchi, C. Lintner and R. H. Schleif, *Science*, **111**, 63 (1950).

(4) C. Lintner, R. H. Schleif and T. Higuchi, *Anal. Chem.*, **22**, 534 (1950).

(5) C. Lintner, D. Zuck and T. Higuchi, *J. Am. Ph. A., Sc. Ed.*, **39**, 418 (1950).

(6) T. Higuchi, *Anal. Chem.*, **22**, 955 (1950).

widely differing dissociation constants. Attention in the present study, therefore, has been focused on those compounds which are derivatives of *p*-aminoazobenzene, having one of the amino hydrogen replaced either by an alkyl or aryl group.

The choice of amines as indicators need not necessarily be restricted to those containing the azo linkage as the chromophoric group. Any color-producing group which does not contain a strongly polarized linkage and is conjugated to the amino group may be reasonably expected to be satisfactory for the purpose. A strongly polarized linkage would be attacked by lithium aluminum hydride.

Color Response of Several *p*-Aminoazobenzene Derivatives

In Figs. 1, 2 and 3 are shown the color response of *p*-aminoazobenzene, N-methyl- and N-phenyl-. The color changes and the potentiometric curves were obtained by titrating solutions containing the indicators and lithium aluminum hydride with a standardized solution of *n*-butyl alcohol in benzene. Also shown on the charts are runs made after weighed amounts of purified cyclohexanol had been added to the reaction system. The difference between the solution consumptions in presence and absence of cyclohexanol would correspond stoichiometrically to the amounts of cyclohexanol taken in each case. Subjective observations on the color changes obtained with the above and related indicators are summarized in Table I.

TABLE I

OBSERVATIONS ON COLOR CHANGES FOUND WITH *p*-AMINOAZOBENZENE DERIVATIVES

Indicator	Color at start	Color change during titration and at the end-point
N-Phenyl-*p*-amino-azobenzene	Red	Color changes to a darker red prior to the end-point. Color changes sharply to yellow at the end-point
N-Ethyl-*p*-amino-azobenzene	Pale red	Color changes to yellow then to a reddish orange during titration. Color change at the end-point is a pale greenish yellow
N-Methyl-*p*-amino-azobenzene	Pale red	Same as above
p-Aminoazobenzene	Reddish-orange	Color change is gradual to an orange yellow at the end-point
N,N-Dimethyl-*p*-phenylazoaniline	Yellow	No color change

The first four indicators listed in the table have at least one active hydrogen available on each molecule. All of these changed color at the stoichiometric end-point; some, however, had sharper and better changes than others. As may be expected from the preceding discussion, the dimethyl derivative, which does not have any active hydrogen, did not change color on addition of lithium aluminum hydride. This would indicate that at least one hydrogen atom is necessary on the amino nitrogen for the compounds to act as an indicator. The color change in the case of N-phenyl-*p*-aminoazobenzene appeared to be the most easily detectable. This may be due to the higher degree of conjugation possible in the ionic form of this compound as compared to the others.

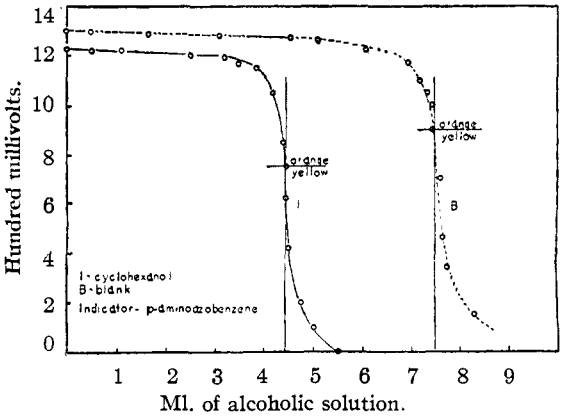


Fig. 1.—Curves showing the color response of *p*-aminoazobenzene. One run was made without sample and two after different amounts of cyclohexanol had been added.

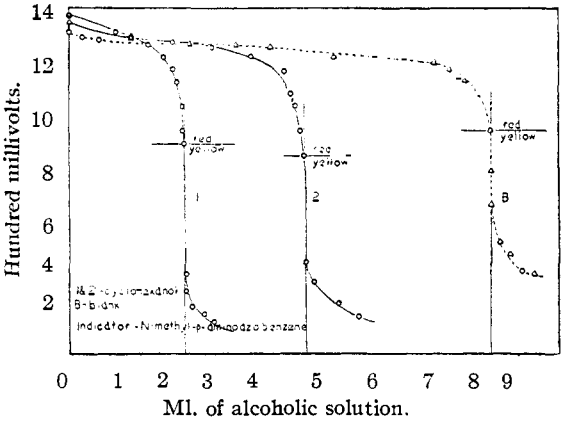


Fig. 2.—Curves showing the color response of N-methyl-*p*-aminoazobenzene. Runs 1 and 2 were made after addition of cyclohexanol. Since the electrodes are probably irreversible, the absolute e.m.f. readings are without significance.

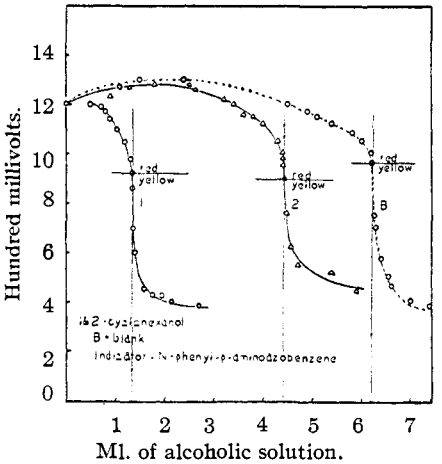


Fig. 3.—Color changes of N-phenyl-*p*-aminoazobenzene. The change with this indicator appeared to be the sharpest of all those tried.

Experimental data illustrating the possible applications of these indicators to the determinations of functional groups which react with lithium aluminum hydride are presented in the following sections.

Experimental

Apparatus.—An earlier model of the apparatus employed has already been described in detail.[4] The principal modification has been the introduction of another inlet for the nitrogen used as a cover. A magnetic stirrer was used for agitation purposes in all cases. Where only colorimetric data were obtained, the electrodes were usually omitted.

Materials.—Reagents were prepared in the following manner: Tetrahydrofuran, technical grade from du Pont and Co., was purified by distilling twice over lithium aluminum hydride. The purpose of the double distillation was to remove water, residual peroxides, inhibitor and other impurities which might interfere with the titration. Waste solvent remaining after titration was recovered in the same manner. Since purified THF forms peroxide rapidly, no more than a few days' supply was ever prepared at any time.

Lithium aluminum hydride solution was prepared by refluxing 25 g. of the compound with 1 l. of tetrahydrofuran for 24 hours. The solution was decanted and centrifuged. The clear supernatant liquid was decanted into a dry bottle. Nitrogen was blown into the bottle to remove the air after each removal of the reagent. In this manner the reagent remained stable and clouding was prevented.

The standard alcohol solution was prepared from *n*-butyl alcohol. Reagent grade alcohol was distilled over sodium, the middle third portion being collected. Exactly 50 g. of this was diluted to one liter with dry, thiophene-free benzene and stored in an automatic buret. In some cases the solution was made approximately and later standardized against benzoic acid by the procedure described.

The several indicator solutions were prepared by dissolving sufficient quantity of the respective compounds in benzene to produce 0.1% solutions. N-Phenyl-*p*-aminoazobenzene was prepared according to the method outlined by Torrey and MacPherson.[7] The crude product worked as indicator as well as the purified compound obtained by chromatographic purification (m.p. 80°). The N-methyl compound was prepared by the method of Miller and Baumann.[8] The N-ethyl derivative was prepared in the same manner.

The compounds which were analyzed were mostly of reagent purity and subjected to appropriate drying procedures.

Procedure.—The procedure has been essentially described in previous publications.[3,4] The principal changes consisted of use of nitrogen cover[6] and those arising from the use of indicator.

Weigh the sample directly into a dry 125-ml. erlenmeyer flask. Direct a stream of nitrogen into the flask and pipet 15 ml. of pure tetrahydrofuran. Pipet 5 ml. of the $LiAlH_4$ reagent and let the mixture react. Add 5 drops of indicator and titrate with the standardized alcohol mixture rapidly at first, then slowly as the end-point is approached. There is a tendency for the color of the indicator to reverse. The point at which the color did not reverse after a lapse of three minutes was considered the end-point in all cases. All conditions were duplicated during the blank determination.

The following formula was used to calculate the number of gram equivalents of functional groups present in each sample.

Number of gram equivalents = $(B - V)M/1000$ where

B = ml. of standardized alcohol solution consumed by the blank

V = ml. of standarized alcohol solution consumed by the sample titration.

M = molarity of the standardized alcohol.

(7) H. A. Torrey and W. MacPherson, THIS JOURNAL, **31**, 582 (1909).

(8) J. A. Miller and C. A. Baumann, *Cancer Research*, **5**, 157 (1945). The crude product obtained gave results equal to those found with highly purified sample furnished through the courtesy of Dr. J. A. Miller. Eastman Kodak Co. *p*-aminoazobenzene was used without further purification.

Results

Results obtained for cyclohexanol and benzoic acid by the previously reported potentiometric method and the indicator method are compared in Table II. The theoretical and experimental results by both techniques appear to check within the experimental care employed in pipetting and other manipulations. Since the endpoint detection is very good by both methods, even better accuracy can probably be attained with some refinements.

TABLE II

COMPARISON STUDY OF ELECTROMETRIC AND COLORIMETRIC METHODS OF TITRATION

Sample	Sample, wt., g.	Indicator	Diff. in vol. of alc. reagent by blank and with sample, ml.	Milliequiv./millimoles Exptl.	Milliequiv./millimoles Predicted
Cyclohexanol	0.2716	*p*-Aminoazobenzene	3.72[a]	0.99	1
Cyclohexanol	.2716	Potentiometer	3.82[a]	1.01	1
Cyclohexanol	.2897	N-Ethyl-*p*-aminoazobenzene	4.34[a]	1.08	1
Cyclohexanol	.2897	Potentiometer	4.30[a]	1.07	1
Benzoic acid	.2595	N-Methyl-*p*-aminoazobenzene	8.28[b]	2.98	3
Benzoic acid	.2595	Potentiometer	8.37[b]	3.01	3
Benzoic acid	.2932	N-Phenyl-*p*-aminoazobenzene	9.20[c]	3.00	3
Benzoic acid	.2932	Potentiometer	9.30[c]	3.03	3

Molarity of alcoholic reagent used: [a] 0.720, [b] 0.763, [c] 0.783.

The type of data obtainable with the indicator method is further demonstrated in Table III for a number of oxygenated compounds. These results were all based on use of N-phenyl-*p*-aminoazoben-

TABLE III

ANALYTICAL RESULTS OBTAINED WITH SOME ORGANIC COMPOUNDS

Sample	Sample, wt., g.	Diff. in vol. of alc. reagent consumed by blank and with sample, ml.	Milliequiv./millimoles Expt.	Milliequiv./millimoles Predicted
3,4,5-Trimethoxybenzoic acid[a]	0.2716	4.94	3.03	3
Succinic acid[b]	.0804	5.26	6.05	6
Benzophenone[c]	.2824	1.96	0.99	1
Suberic acid[d]	.1420	6.32	6.07	6
Cyclohexanol[a]	.4037	5.18	1.01	1
Octadecyl alcohol[a]	.4543	2.12	1.00	1
Benzoic acid[a]	.2931	9.20	3.00	3
Aspirin[a]	.1249	4.43	5.01	5
Coumarin[e]	.1936	3.41	2.02	2
Anisic acid[f]	.2085	5.37	3.05	3
Menthol[a]	.2464	2.08	1.00	1
Naphthol[a]	.0933	0.88	1.03	1
Cinnamic acid[g]	.3530	11.51	3.68	4
Cinnamic acid[c]	.2805	9.51	3.82	4
Naphthalene[a]	.2607	0.10	0.04	0

Molarity of the alcoholic solution 0.783 M except for the last 5 compounds at 0.761 M. [a] Reaction time of 5 minutes at room temperature. [b] Reaction time of 120 minutes under reflux conditions. [c] Titrated immediately. Refluxed: [d] 5 minutes, [e] 30 minutes, [f] 15 minutes, [g] 60 minutes.

zene as the indicator. Here again satisfactory correlations between experimental and predicted values were obtained. Longer reaction times and higher temperatures, however, were required for a certain number of compounds to achieve the theoretical value. This is attributed to the low rate of reaction of certain dicarboxylic acids which precipitate partly out of solution and some compounds of the cinnamic acid type which undergo reduction at the carbon-carbon double bond. Occurrence of such a behavior can be detected by titrating the sample after different reaction times. This is illustrated in Fig. 4 showing the moles of alcohol equivalent per mole of succinic acid as function of the reaction time.

When the lithium aluminum hydride reagent was added to separate samples of aniline, methylaniline and diphenylamine a vigorous evolution of hydrogen resulted. It was found that the amount of alcohol to neutralize the solution is essentially the same in the presence or absence of these aromatic amines when either N-phenyl-*p*-aminoazobenzene or N-methyl-*p*-aminoazobenzene were employed as indicators. This can be rationalized on the basis that the indicators employed were stronger acids than the amines.

Discussion

In the introductory portion of this article it was pointed out that the present treatment was based on the concept that the system was of acid–base type. This approach is actually an extension of earlier investigations on titration of very weak acids in non-aqueous solvents such as ethylenediamine.[9;10] The restriction of the bases used in these instances to alkoxides or weaker bases ruled out the possible applications of the methods to acids weaker than water.

In the method reported here, lithium aluminum hydride was employed as the primary base. It is convenient for this purpose because of its ready solubility in a number of solvents, its high reactivity and its availability. Other strong bases, can, however, be used also. Certain salts, *e.g.*, lithium aluminum salts of piperidine, have shown some promise especially since they appear to have much smaller reductive tendencies.

Theoretically, at least, it seems possible to differentially titrate complex mixtures of weak acids by using a number of bases and different indicators. For the latter purpose it was hoped when N-methyl- and N-phenyl-*p*-aminoazobenzene were prepared that they would possess widely differing pK_I values. The data obtained indicate that they may not be too different from each other in acid strength. Further studies are, however, necessary to obtain the relative pK_I values.

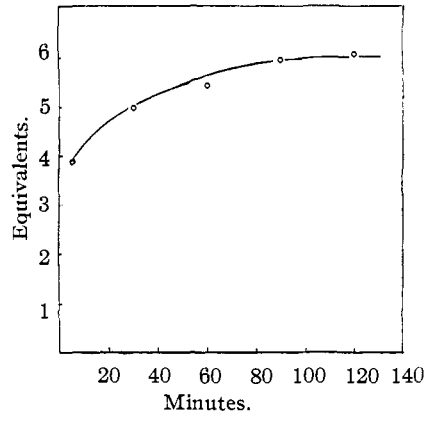


Fig. 4.—A curve showing the extent of reaction of succinic acid with lithium aluminum hydride. The reaction was carried out at reflux temperature with tetrahydrofuran as the solvent.

The primary drawback of the lithium aluminum hydride methods described here and by Higuchi, Lintner and Schleif[3] is that they cannot distinguish among the various functional types. Oxygen atoms, whether present as parts of peroxide, ketone, aldehyde, ester, lactone or various alcoholic groups are all stoichiometrically equivalent. On the other hand, the two atoms of oxygen in hydroperoxide or carboxylic acid groups are equivalent to three in any of the preceding compounds. Ether oxygens do not react. In absence of ether oxygen the general nature of the methods can be used for estimation of total bound oxygen content of a mixture containing oxygenated organic compounds since corrections can be applied for the non-conformity of carboxylic acids and hydroperoxides if these are present.

The indicators developed for the present analytical investigation may be of some value in organic synthesis utilizing lithium aluminum hydride. They can be used to indicate when a reacting mixture has consumed all of the hydride. They are also useful in determining the mole ratio of lithium aluminum hydride taken up in the manner illustrated by Fig. 4.

Acknowledgment.—This project was supported in part by the Research Committee of the Graduate School from funds supplied by the Wisconsin Alumni Research Foundation.

MADISON, WIS. RECEIVED NOVEMBER 20, 1950

(9) M. L. Moss, J. H. Elliott and R. Y. Hall, *Anal. Chem.*, **20**, 784 (1948).

(10) J. S. Fritz and N. S. Lisicki, Paper No. 25, Division of Analytical Chemistry, 118th Meeting, A. C. S., Sept., 1950.