# A Student-Designed Analytical Laboratory Method

## Titrations and Indicator Ranges in Mixed Aqueous-Organic Solvents

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The use of pH indicators for endpoint determination in aqueous acid–base titrations provide a colorful and inexpensive analytical method; however, many acids and bases that are used in the pharmaceutical industry are only sparingly soluble in water; e. g., lidocaine, lidocaine hydrochloride, salicylic acid, benzoic acid, and procaine (*1*). Such acids and bases can be examined in mixed aqueous-organic solvents, organic-surfactant systems, and in nonaqueous solvents. The question addressed in this student-designed laboratory experiment is, "Can common pH indicators be used in mixed solvents and if so are the color changes and pH ranges the same as in water?" Over the last decade, numerous acid–base titrations experiments have appeared in *this Journal* (*2–4*), but to our knowledge none address this issue. Harris and Kratochvil's and Sawyer, Heineman and Beebe's laboratory manuals each contain an acid–base titration in a purely nonaqueous media, but both are "canned" experiments that do not allow for student design. Harris and Kratochvil's experiment, "Nonaqueous Photometric Titration: Determination of Oxine with *p*-Toluene-sulfonic Acid", requires that a spectrophotometer be available plus it uses 100% acetonitrile which is more expensive than a mixed aqueous-organic solvent system that is no greater than 50% organic by weight (*5*). Sawyer, Heineman, and Beebe's experiment, "Acid–Base Titrations in Nonaqueous Media: Titrations of Nicotine", analyzes a toxin, nicotine, as well as using toxic glacial acetic acid. Several special safety precautions are necessary to perform this experiment; e. g., wear plastic gloves, work in a hood, explosion possibility, etc. Also the electrode can be damaged if left in the glacial acetic acid for more than 20 minutes (*6*), and pure nonaqueous solvents of low dielectric constant present problems like homoconjugation that complicate the analysis. Our experiment allows for student design, is inexpensive, poses no abnormal health risks and does not require special safety precautions. It allows students to work in teams to design a new analysis method to address the concerns associated with titrating sparingly soluble acids and/or bases with common pH indicators. High school teachers to college professors can employ this experiment with the proper amount of instruction and direction by the laboratory supervisor. As educators we realize the importance of teaching students not only how to use the appara-

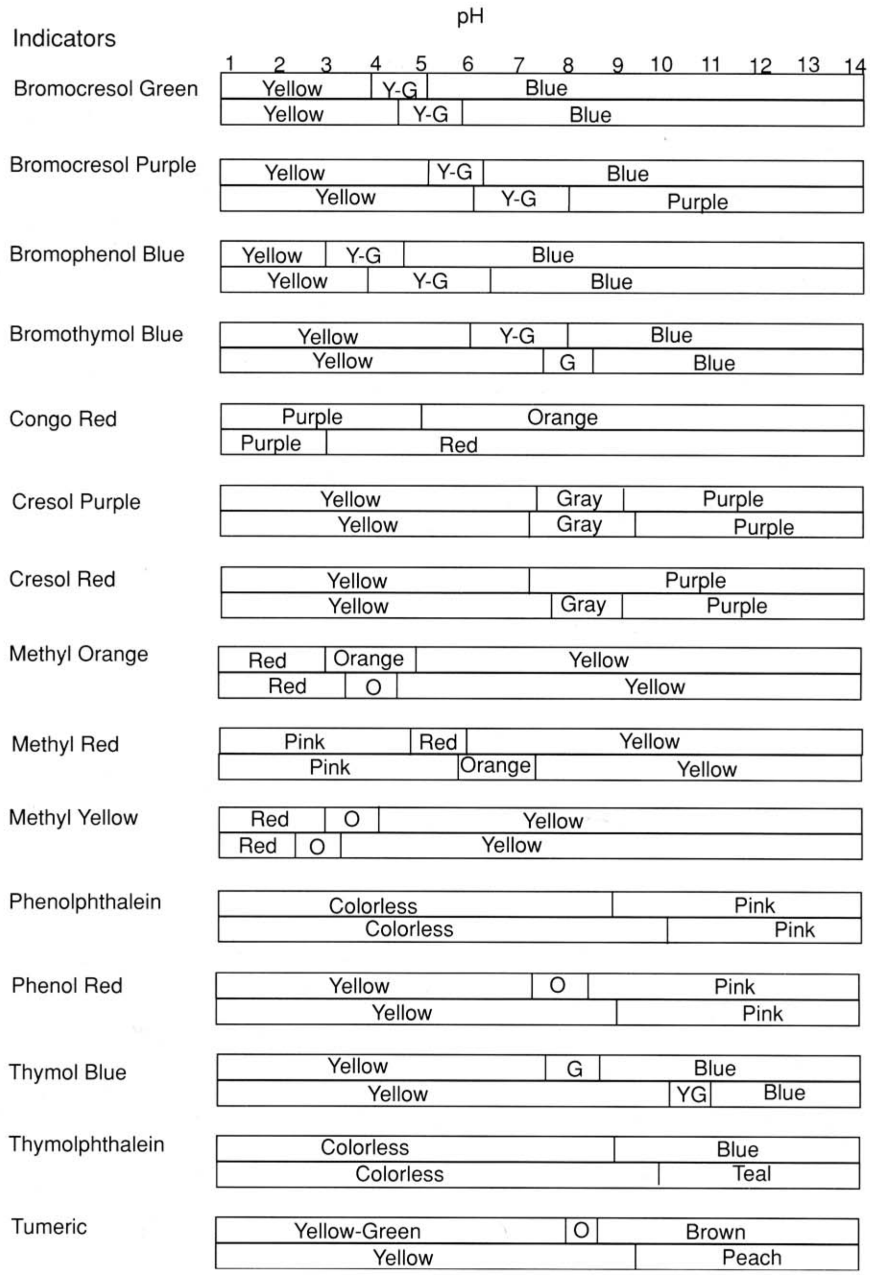


Figure 1. Typical student data for the color changes and pH ranges of common indicators. The top color bar for each indicator is for water. The bottom color bar for each indicator is for the mixed aqueous-methanol solvent system (50 % methanol by weight) (Y-G or YG = yellow-green, R = red, GR = gray, O = orange and G = green).

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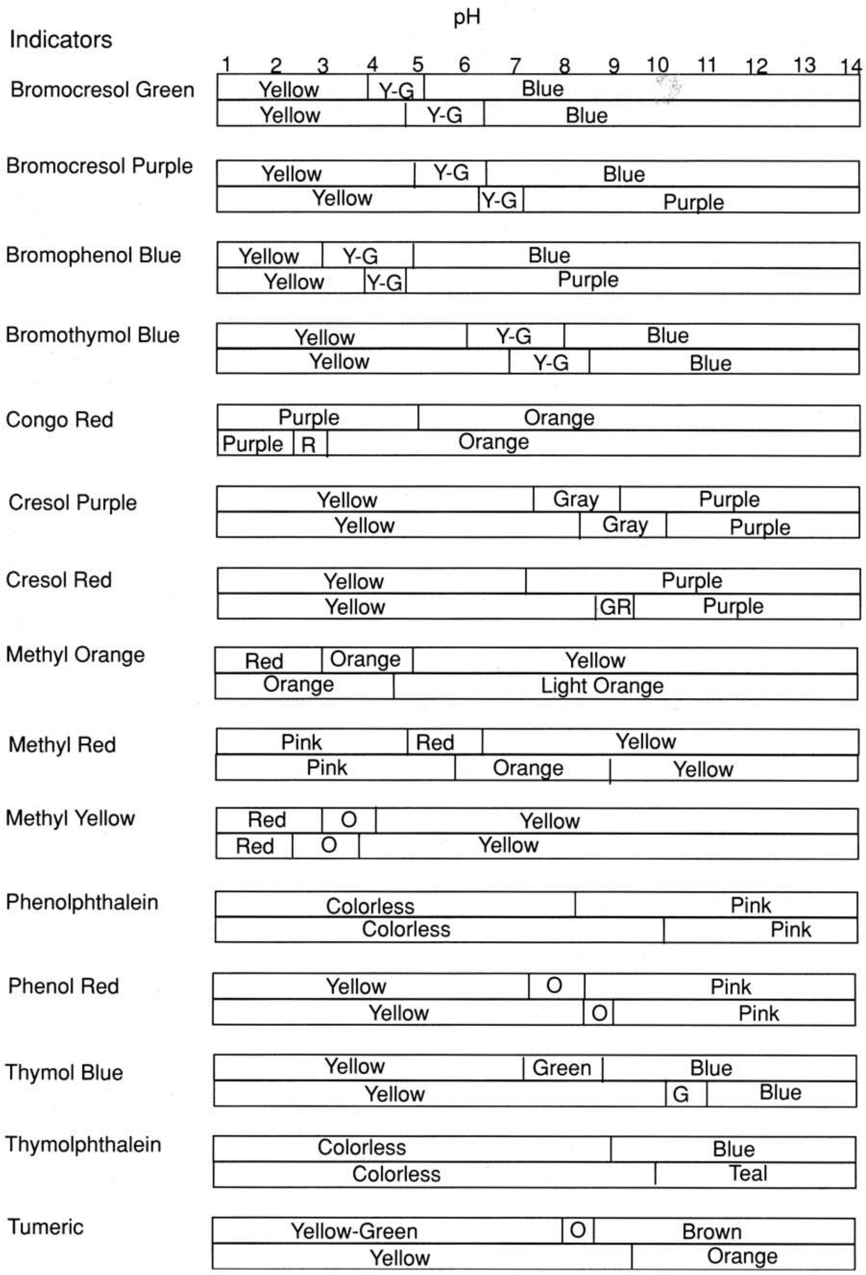


Figure 2. Typical student data for the color changes and pH ranges of common indicators. The top color bar for each indicator is for water. The bottom color bar for each indicator is for the mixed aqueous-acetonitrile solvent system (30% acetonitrile by weight) (Y-G or YG = yellow-green, O = orange and G = green).

tus and how to follow procedures, but also how to approach "real-world" problems utilizing the knowledge they have learned in the classroom. This lab serves that purpose because it uses the ideas that are familiar even at the high school level. It serves as a learning tool because it is designed to ensure success and build confidence in one's ability to design an approach to solve "real-world" problems.

Acid–base titrations provide a convenient means to analyze many unknown mixtures. Water has an autoprotolysis constant of $K_w = 10^{-14}$ and hence a pH range from 0–14, but nonaqueous solvents or mixed aqueous-organic solvents have pH ranges that may be larger or smaller than the normal 0–14 range. For example, the pH range of methanol with an autoprotolysis constant of $K_s=10^{-16.7}$ is 0–16.7 and acetonitrile has a $K_s=10^{-28.6}$ and a pH range of 0–28.6 (*7*). Various percent mixtures of water/methanol would have pH ranges somewhere in between 0–16.7. Fortunately, it is not necessary to know the autoprotolysis constant or the pH ranges for mixed aqueous-organic solvents as the pH can be calculated directly via

$$\mathrm{pH_x} = \mathrm{pH_s} - (E_x - E_s)/S \qquad (1)$$

where $\mathrm{pH_x}$ is the pH of the sample (x), $\mathrm{pH_s}$ is the pH of the standard (s), $E_x$ the millivolt value of the sample as read by the pH meter, $E_s$ the millivolt value of the standard as read by the pH meter, and $S$ the slope, normally 59.16 mV/pH unit at 25 °C. This form of eq 1 refers to a pH meter equipped with a combination glass electrode (*8–10*). The millivolt setting is used because a greater than the normal pH range may be encountered. Many digital meters are capable of displaying –19.99 to 19.99 pH. In other meters, such as analog meters, the scale is limited. The millivolt range of most pH meters provides a greater range, such as 1400 mV, then the pH range of 0–14 that is 414 mV at 25 °C. The pH value can be calculated comparing the millivolt values obtained in the standards with the millivolt values obtained in a sample (*8*). Standard pH values in mixed aqueous-organic solvents of varying composition are readily available in the literature (*11, 12*). For example, a 0.05 *m* potassium hydrogen phthalate reference buffer solution in a mixed aqueous-methanol system (50% methanol by weight) has a pH of 5.131 at 25 °C (*11*).

## Experimental Measurements

Students or instructors can prepare the pH indicators according to the *CRC Handbook of Chemistry and Physics* (*13*). We suggest that the students work in pairs to facilitate discussion when problems arise and that two lab periods be allotted for this experiment. The aqueous range of the pH indicators can be found in the "CRC", or the students can use a pH meter equipped with a combination glass electrode that has been calibrated with a standard buffer solution to find the ranges via titration with 0.01 M hydrochloric acid (HCl) and/or 0.01 M sodium or potassium hydroxide (NaOH or KOH). We report the use of a mixed aqueous-methanol system (50% methanol by weight) and a mixed aqueous-acetonitrile system (30% acetonitrile by weight). For the mixed aqueous-methanol system a 0.05 molal potassium hydrogen phthalate (KHP) buffer solution should be prepared in the mixed solvent. It will have a pH = 5.131 at 25 °C (*11*). For the mixed aqueous-acetonitrile system a 0.05 molal KHP buffer solution should be prepared in the mixed solvent. It will have a pH = 4.985 at 25 °C (*12*). There are several other standards for various mixed aqueous-organic solvent systems listed in the literature (*12*). After taking the KHP standard's reading in millivolts, the pH ranges and color changes in the mixed aqueous-organic solvents can be found by utilizing a pH meter. The millivolt readings can be converted easily to pH via eq 1. When finding the mixed aqueous-organic solvent pH range and color changes one must remember to prepare the 0.01 M HCl and the 0.01 M NaOH or KOH

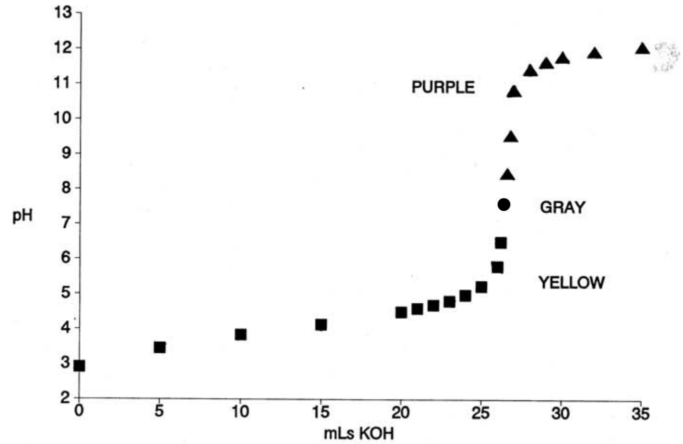


Figure 3. Titration of salicylic acid with potassium hydroxide in the mixed aqueous-methanol solvent system (50% methanol by weight). The different symbols represent the color changes for the pH indicator *m*-cresol purple (squares = yellow, circles = gray and triangles = purple).

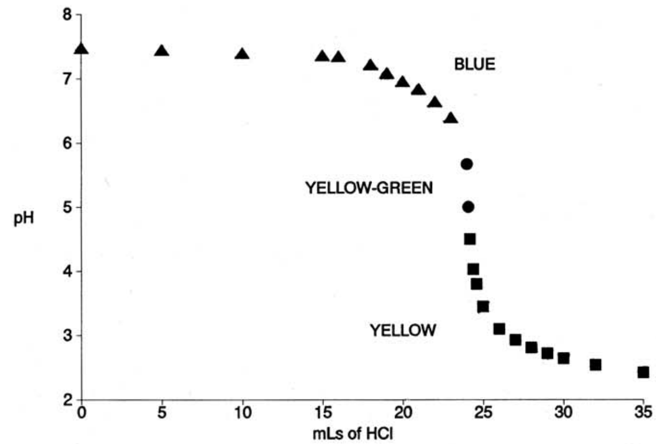


Figure 5. Titration of lidocaine with hydrochloric acid in the mixed aqueous-methanol solvent system (50% methanol by weight). The different symbols represent the color changes for the pH indicator bromocresol green ( squares = yellow, circles = yellow-green and triangles = blue).

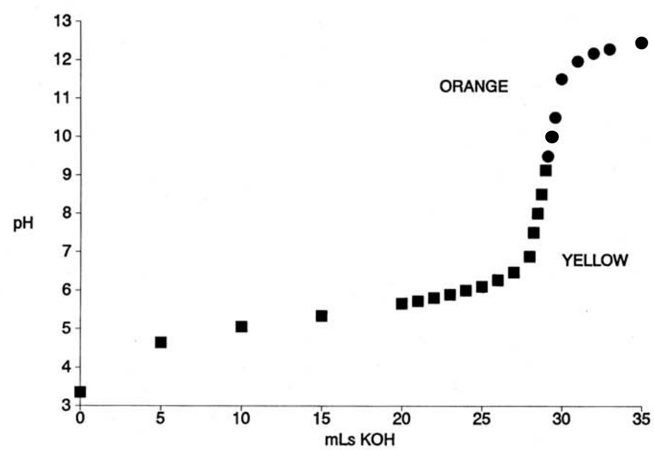


Figure 4. Titration of *o*-toluic acid with potassium hydroxide in the mixed aqueous-acetonitrile solvent system (30% acetonitrile by weight). The different symbols represent the color changes for the pH indicator tumeric (squares = yellow and circles = orange).

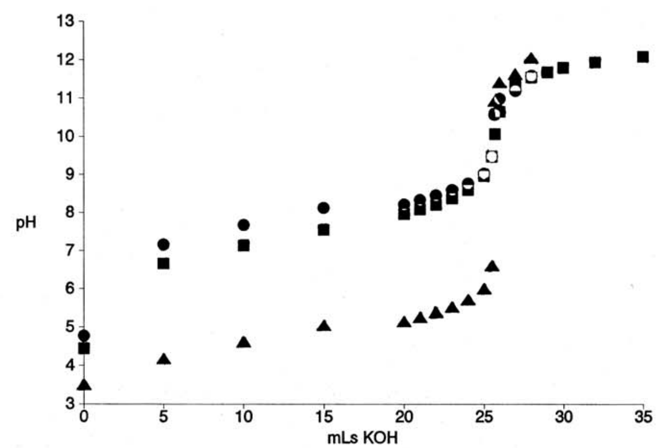


Figure 6. Titration of lidocaine hydrochloride with potassium hydroxide in various solvent systems. The circles represent a two-phase surfactant system of aqueous-organic cetylpyridinium chloride. The squares represent a mixed aqueous-methanol solvent system (50% methanol by weight). The triangles represent an equal volume of dichloromethane and the surfactant cetylpyridinium chloride.

solutions in the mixed aqueous-organic solvent of interest. Each group of students should prepare a 0.01 M solution of a sparingly water soluble acid and base for titration in the mixed solvent system being examined. Acids such as salicylic acid, *o*-toluic acid, benzoic acid or lidocaine hydrochloride will work, and bases as lidocaine, sodium benzoate or sodium salicylate (those acids listed here will go to their basic form by the addition of excess base and vice versa). Students should plot the titration curve and choose one or two appropriate indicators and carry out the titration in them. A plot of the titration curve will demonstrate whether they have chosen wisely. According to Williams and Howell (*14*) visual enhancement of titration endpoints can be achieved by carrying out the titrations in polystyrene foam coffee cups. We have found that the mixed aqueous-organic solvents do not affect the integrity of the cups. We recommend them because they are inexpensive, they protect the electrode from accidental damage, and they can be reused upon rinsing. More advanced students also can be asked to calculate the titration error involved with their choices of indicators (*15*).

## Discussion

Typical student data illustrating the pH indicators' color changes and pH ranges in water and in the mixed aqueous-methanol system are shown in Figure 1. Note that the indicators' pH ranges and/or color changes are rarely the same in the mixed aqueous-organic solvents. A similar chart could be prepared by the student to aid in their indicator selection for the acid and base samples. Also note that some transition colors were not apparent in both solvents. For example, the tumeric indicator has an aqueous color transition of yellow-green to orange to brown, but in the mixed aqueous-methanol system only a yellow to pale orange transition is seen. The indicator *m*-cresol red illustrates that we all perceive colors differently as most students thought the basic region of the *m*-cresol red indicator was more purple than red. Figure 2 is typical data for the pH indicators in water and in the mixed aqueous-acetonitrile system. Once again the color changes and pH ranges differ in the two solvents. Comparing Figure 1 and Figure 2 we also note that the two mixed aqueous-organic systems differ on their pH ranges and color changes as expected. Figure 3 is the titration curve of salicylic acid titrated with KOH in the mixed aqueous-methanol system. The color changes and pH ranges for *m*-cresol purple are depicted. This indicator choice was appropriate because the color change occurs at or near the "true" equivalence point. The titration curve of *o*-toluic acid titrated with KOH in the mixed aqueous-acetonitrile system with tumeric as the indicator, and that of lidocaine titrated with hydrochloric acid in the aqueous-methanol system with bromocresol green as the indicator are shown in Figures 4 and 5, respectively. Lidocaine or lidocaine hydrochloride cannot be titrated in water because it is not soluble and will crystallize out of solution. Figure 6 shows the improvements that can be made in the titration curves by changing the solvent system. The titration of lidocaine hydrochloride in the mixed aqueous-methanol system has slightly improved the titration curve and hence endpoint detection over the two-phase surfactant system of aqueous-organic cetylpyridinium chloride, and the water solubility problems have been eliminated in both cases. The titration lidocaine hydrochloride in equal volumes of dichloromethane and the surfactant cetylpyridinium chloride is clearly the best in this case (see Ref. *16* for experimental details). Another interesting approach to this experiment would be to examine the edible acid/base indicators' color changes and pH ranges, such as red cabbage and grape juice, in the mixed aqueous-organic solvent systems. Mebane and Rybolt report their aqueous pH ranges and color changes as well as the preparative methods for several common and not so common edible pH indicators (*17*).

This laboratory experiment is inexpensive and uses virtually no equipment other than a buret and a pH meter, and it can be performed at almost any level with the correct amount of direction from the instructor. Students will not only learn how to approach problems, but also they will gain exposure to a little-known area of chemistry-pharmaceutics. They will learn how to test their hypothesis that pH indicators do/do not change their ranges and color transitions in solvent systems other than water, and they will have used that knowledge to approach the problem of acid–base titrations of sparingly water soluble samples. Also a note for the instructor, the students will not be able to merely look up the pH indicator ranges and color changes for the mixed aqueous-organic solvent systems as in the case of aqueous systems because they are not currently available in the literature.

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