Spectrophotometric Determination of the Acidity Constants of Some Oxime-Based α-Nucleophiles

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The acidity constants (pK_a) of oxime group containing nucleophiles like pralidoxime, butane 2,3-dione monoxime (BDMO), and some novel oxime-based functionalized nucleophiles, i.e., 3- and 4-hydroxyiminomethyl-1-alkylpyridinium bromides, have been determined spectrophotometrically at 27 °C in pure water and in a 50% (v/v) water−acetonitrile mixture, respectively. An effect of surfactant concentration on the pK_a of pralidoxime has also been studied. It has been found that the pK_a of pralidoxime was not affected by surfactant concentration.

Introduction

The extent of ionization of molecules in solution at different pH values is represented by an important parameter known as the acidity constant (pK_a).[1,2] The application of the acidity constants of an organic compound is very vast. The pK_a values play a fundamental role in biological systems and in many analytical procedures such as acid−base titration, solvent extraction, complex formation, and ion transport. It has already been established that acid−base properties affect the toxicity, chromatographic retention behavior, and pharmaceutical drug discovery developments. Much of the theoretical foundation of modern organic chemistry is based on the correlation between acid−base equilibrium and molecular structure.[3−5] Various methods are available for the determination of acidity constants such as potentiometric titration, spectrophotometry, and conductimetry. Of these, potentiometric titration[6] and spectrophotometric determination[7] are the most useful and widely used. The acidity constants of extremely acidic or basic compounds cannot be accurately determined by potentiometric titration because of their instability in an extreme pH range or because of the limitations of pH meters. Another essential requirement of this method is that the initial concentration of the samples must be accurately determined; i.e., the samples must be pure and dry. The spectrophotometric method has received widespread attention because it is very simple and rapid for the determination of acidity constants of organic compounds.

A substantial amount of work has been done in the field of (pK_a) determination spectrophotometrically. Alimasifar et al. have determined the acidity constants of some newly synthesized anthroquinones in a methanol−water medium.[8] Similarly, Niazi et al. have studied the pK_a of Alizarine Red S in aqueous and micellar media solutions.[9] Ghasemi et al.[10] have determined acidity constants of substituted resorcinol in binary aquo-organic mixtures. Over the past few years, we have been interested in the study of the catalytic efficiency of different α-nucleophiles for the hydrolysis of carboxylate and phosphate esters in self-organized systems.[11−16] In kinetic studies, the acidity constant (pK_a) of nucleophiles is very important. Therefore, we herein determine the acidity constants of simple and functionalized oxime-based reactivators. Oximates are α-nucleophiles (Scheme I), which bear one or more nonbonding electron pairs at the α position to the nucleophilic center. They exhibit enhanced reactivity compared with normal nucleophiles of similar basicity (the α-effect).[17−19]

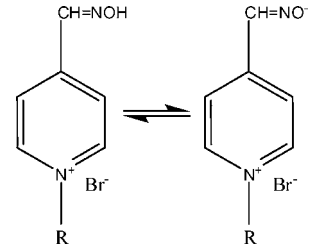

Figure 1. Schematic representation of the equilibrium between the forms of 4-hydroxyiminomethyl-1-alkyl pyridinium bromide.

Some oxime nucleophiles are also termed as reactivators of acetylcholinesterase (AChE). Acetylcholinesterase hydrolyzes the neurotransmitter acetylcholine (ACh) at cholinergic synapses. The inactivation of the AChE by organophosphorus could result in severe intoxification and death of the exposed individual. Compounds that are capable of dephosphorylating organophosphate-inhibited AChE and restoring its physiological activity are known as "acetylcholinesterase reactivators", and these are valuable antidotes with therapeutic efficacy against organophosphate toxicity.[20,21] To obtain guidelines for the evaluation of the effectiveness of acetylcholinesterase reactivators, knowledge of their acid−base properties is essential for understanding the biophysicochemical properties of the oxime-based functionalized surfactants, which are of considerable importance in their applied detoxification. The studied oximes have only one ionizable OH group (Figure 1), and hence, only one pK_a value is possible for these nucleophiles.

In addition, the resulting pK_a data obtained from the proposed spectrophotometric method were compared with a recognized method by use of the ACD/Laboratories Online (I -Lab) pK_a

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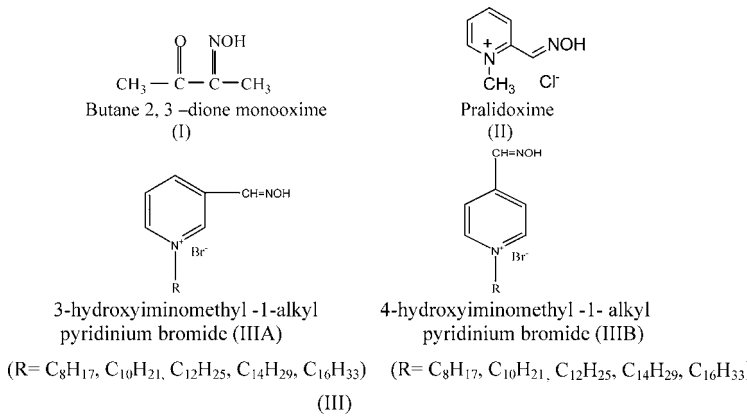
Scheme I



2008 software program. A good agreement is observed between the theoretical and experimental pK_a values.

Experimental Section

Apparatus. The spectrophotometric measurements were made using a Varian Cary 50 UV−visible spectrophotometer equipped with a peltier temperature controller unit and a computer connected to a spectrophotometer. All the spectrophotometric measurements were made at 27 °C ± 0.5 °C. Spectra were obtained between (200 and 400) nm. The pH of the solution was measured using a Systronics (Type-362) pH-meter containing a glass electrode and calibrated with at least two standard buffer solutions having pH 4.00 and 9.00.

Reagents. 3-Hydroxyiminomethyl-1-alkylpyridinium bromide series (IIIA) and 4-hydroxyiminomethyl-1-alkylpyridinium bromide series (IIIB) functionalized surfactants and pralidoxime were prepared in the laboratory of Dr. Kamil Kuca, Department of Toxicology, Faculty of Military Health Sciences, Czech Republic. Butane 2,3-dione monoxime (BDMO) and surfactant Triton-X 100 were procured from Sigma/Aldrich (St. Louis, Missouri, U.S.A). Cetyltriphenylphosphonium bromide ($CTPPh_3Br$) was obtained from the laboratory of Prof. R. M. Palepu, St. Francis Xavier University, Antigonish, Canada. 1-Decane sodium sulfonate (DSS) was purchased from S.D. Fine-chemicals (Mumbai, India). All reagents used were of analytical grade. Triply distilled water was used throughout.

Procedure. Solutions of simple oximes (pralidoxime, butane 2,3-dionemonoxime) were prepared in water, and solutions of oxime-based functionalized supernucleophiles were prepared in 50% (v/v) acetonitrile. An aliquot (3 mL) of a stock solution (5.0×10^{-4} M) of the oxime nucleophile was diluted with (25 mL) phosphate buffer solution of pH 6.1. The pH of this solution was adjusted to the desired value by the addition of dilute sodium hydroxide solution. After each pH adjustment, the solution was transferred into the cuvette, and the absorption spectra were recorded. Absorbances at selected wavelengths were obtained from the spectra.

Results and Discussion

(A) Theory and Calculation. The UV−absorption spectra of simple and functionalized oxime-based α-nucleophiles show mainly two bands (Figure 2). The shorter wavelength band, appearing at lower pH values, represents absorption by the nonionized species, whereas the longer wavelength band, observed at higher pH values, is due to the absorption by ionized species. On increasing the pH of the medium, the absorbance of the former band decreases, while that of the latter band increases, where an isosbestic point is achieved, denoting the existence of an equilibrium of the type

$$HA \rightleftharpoons H^+ + A^- \quad (1)$$

Then, the apparent acidity constant K_a of the acid HA is defined as the equilibrium constant.[22,23]

$$K_a = \frac{[H^+][A^-]}{[HA]} \quad (2)$$

By taking logarithms and rearranging, one can get the Henderson−Hasselbalch equation

$$pH = pK_a + \log\frac{[A^-]}{[HA]} \quad (3)$$

This equation can also be written as eq 4, and pK_a values were calculated based on three determinations around the point of half neutralization

$$pK_a = pK_{exp} - \log\frac{Abs_\Psi - Abs_{HOx}}{Abs_{Ox} - Abs_\Psi} \quad (4)$$

where Abs_Ψ is the absorbance of the partially ionized (at observed pH) form of the oxime; Abs_{HOx} is the absorbance of the unionized form of the oxime; and Abs_{Ox} is the absorbance of the completely ionized form of the oxime.

Table 1. Acidity Constants (pK_a) of Oxime Based Nucleophiles (1a) Pralidoxime and Butane 2,3-Dione Monoxime and (1b) (IIIA and IIIB) Series of Functionalized Surfactants Having Different Alkyl Chain Length (C_8, C_{10}, C_{12}, C_{14}, C_{16})

1a

	pK_a	
nucleophiles	observed value	literature value[21,22]
pralidoxime	7.8	8.1
BDMO	9.2	9.4

[Oxime], 5.3×10^{-5} M; Temperature, 27 °C

1b

	pK_a	
	experimental value	
functionalized surfactant	IIIA series	IIIA series
C_8	8.9	8.2
C_{10}	9.0	8.1
C_{12}	9.0	8.2
C_{14}	9.1	8.1
C_{16}	8.6	7.9

[Oxime], 5.3×10^{-5} M; temperature, 27 °C

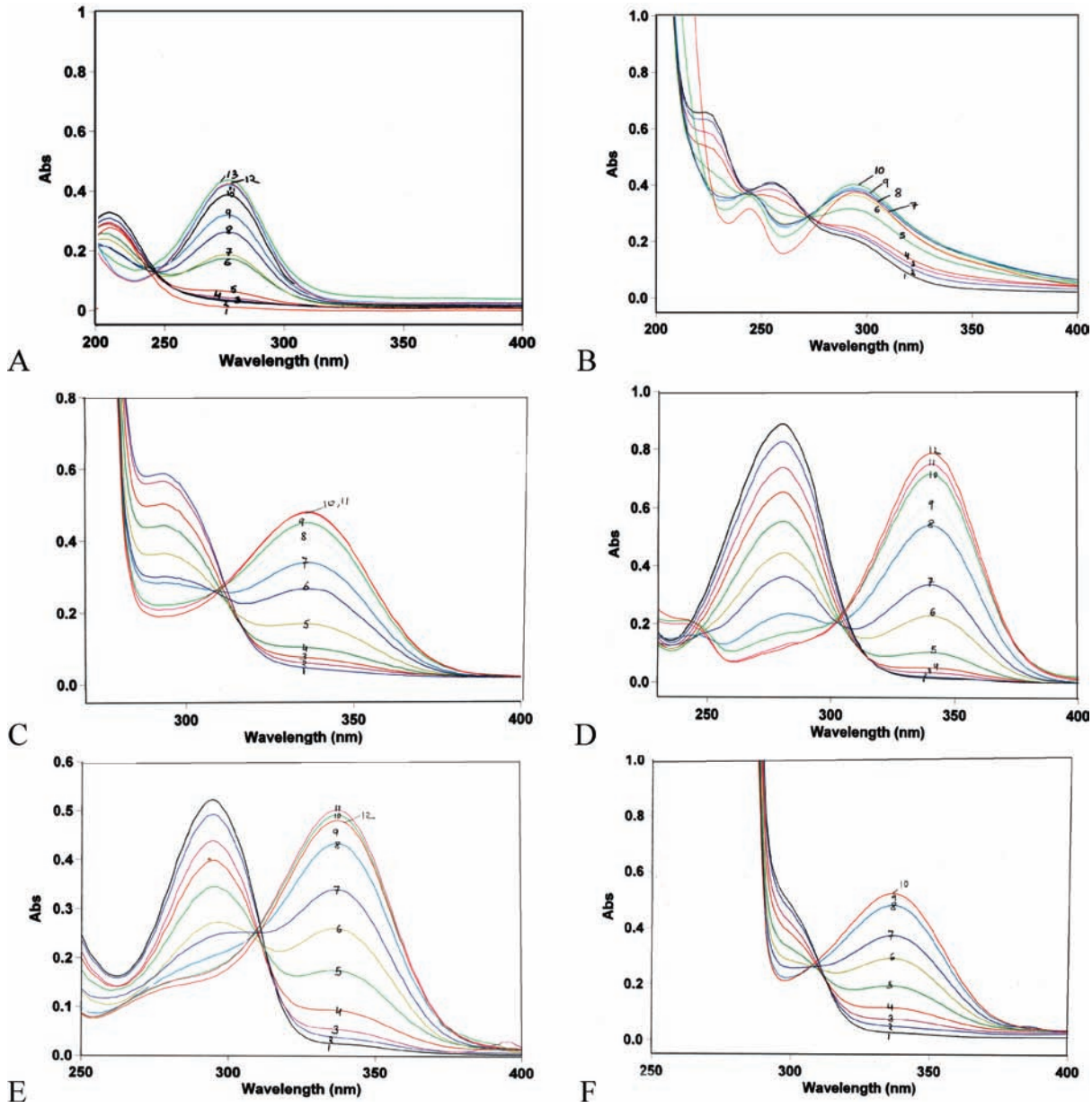


Figure 2. (A) Absorption spectra of butane 2,3-dione monoxime at different pH values. 5.3×10^{-5} M; in water, 27 °C. Run and pH: (1) 6.4; (2) 7.1; (3) 7.4; (4) 7.8; (5) 8.2; (6) 8.8; (7) 9.1; (8) 9.4; (9) 9.6; (10) 10.0; (11) 10.3; (12) 10.7; (13) 11.0. (B) Absorption spectra of 3- hydroxyiminomethyl-1-hexadecyl pyridinium bromide (IIIA series) at different pH values. 5.3×10^{-5} M; in 50% acetonitrile−water, 27 °C. Run and pH: (1) 7.2; (2) 7.5; (3) 7.8; (4) 8.3; (5) 8.9; (6) 9.4; (7) 9.6; (8) 9.8;(9) 10.0; (10) 10.5. (C) Absorption spectra of pralidoxime in the presence of $CTPPh_3Br$ (1.3 mM) at different pH values. 5.3×10^{-5} M; in water, 27 °C. Run and pH: (1) 6.2; (2) 6.5; (3) 6.8; (4) 7.1; (5) 7.5; (6) 7.9; (7) 8.2; (8) 8.5; (9) 8.8; (10) 9.1; (11) 9.6. (D) Absorption spectra of 4-hydroxyiminomethyl-1-dodecyl pyridinium bromide (IIIB series) at different pH values. 5.3×10^{-5} M; in 50% acetonitrile−water, 27 °C. Run and pH: (1) 6.2; (2) 6.5; (3) 6.8; (4) 7.1; (5) 7.5; (6) 7.9; (7) 8.2; (8) 8.6; (9) 8.9; (10) 9.2; (11) 9.6; (12) 10.0. (E) Absorption spectra of pralidoxime in the presence of DSS (1.2 mM) at different pH values. 5.3×10^{-5} M; in water, 27 °C. Run and pH: (1) 6.2; (2) 6.5; (3) 6.8; (4) 7.1; (5) 7.5; (6) 7.9; (7) 8.2; (8) 8.5; (9) 8.8; (10) 9.2; (11) 9.6; (12) 10.5. (F) Absorption spectra of pralidoxime in the presence of Triton-X 100 (1.1 Mm) at different pH values. 5.3×10^{-5} M; in water, 27 °C. Run and pH: (1) 6.2; (2) 6.5; (3) 6.8; (4) 7.1; (5) 7.5; (6) 7.9; (7) 8.2; (8) 8.5; (9) 8.8; (10) 9.7.

The results are shown in Tables 1a and 1b. The pK_a values of butane 2,3-dione monoxime and pralidoxime agree well with literature values.[24,25] Both these systems are taken as a reference, and the same methods have been used for the pK_a determination of functionalized α-nucleophiles. The absorption spectrum of oxime solutions was recorded in the range of (200 to 400) nm at different pH values. The acidity constants, pK_a, of the compounds are determined from the variation of the absorbance with pH, making use of three different spectrophotometric methods, namely, the half-curve height, isosbestic point, and limiting absorbance.[26]

The absorbances at 336 nm for pralidoxime, at 276 nm for BDMO, at 295 nm for 3-hydroxyiminomethyl-1-alkyl pyridinium bromide, and at 339 nm for 4-hydroxyiminomethyl-1-alkyl pyridinium bromide were plotted against the pH values of the buffer solutions. The sigmoidal curves obtained show typical dissociation thus confirming the establishment of an acid−base equilibrium in each case. Some representative curves are shown in Figures 3a and 3b.

(B) Effect of Surfactant Concentration on pK_a of Pralidoxime. Surfactants can affect the acid−base equilibrium of many substrates. One important property of micelles is their ability to solubilize a wide variety of compounds, which are insoluble or slightly soluble in water. Micelles can inhibit or accelerate reaction rates (by up to several orders of magnitude) and shift equilibria (acid−base).[27−30] Surfactants usually affect

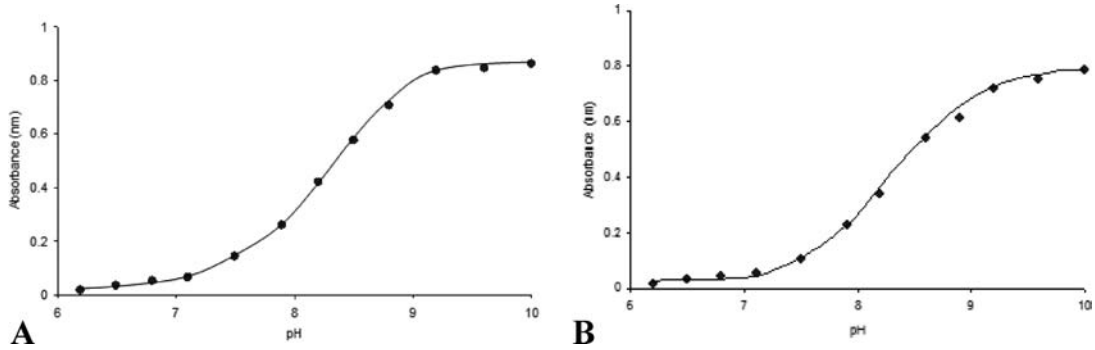
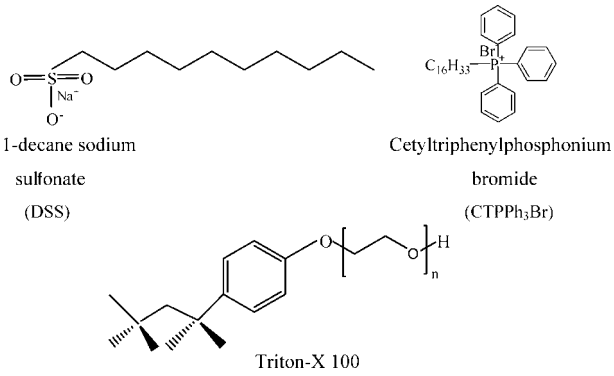


Figure 3. Plots between pH and absorbance for (a) 4-hydroxyiminomethyl-1-octyl pyridinium bromide at 339 nm and (b) 4-hydroxyiminomethyl-1-dodecyl pyridinium bromide at 339 nm.

Scheme II



spectral parameters: the intensity in the absorption band is increased, and shifts in the absorption maxima of reagents are observed.[31]

Micelles can influence the pK_a values of reagents due to the combination of electrostatic and microenvironmental effects of the micellar system.[32−34] It has been suggested that the effect of micellar systems on acid−base equilibria arises from an intrinsic factor (due to the energy difference between the aqueous and the nonpolar media) and a potential effect that is due to the electrically charged micellar surface.

In this investigation, the effect of nonionic (Triton-X 100), cationic ($CTPPh_3Br$), and anionic (DSS) surfactants (Scheme II) on the absorption spectra of pralidoxime at different pH values has been studied.

The pK_a of pralidoxime in different concentrations of each surfactant was determined at 27 °C. By changing the concentration [(0.0 to 1.3) mM] of the cationic surfactant $CTPPh_3Br$, the pK_a values of pralidoxime vary from 7.8 to 7.95. Similarly, with varying concentration of the anionic surfactant DSS and the nonionic surfactant Triton-X 100, (0.0 to 10.0) mM for DSS and (0.0 to 3.0) mM for Triton-X 100, the pK_a values of pralidoxime vary from 7.80 to 7.82 for DSS and 7.8 to 7.81 for Triton-X 100. It was found that the change in pK_a of pralidoxime was not very significant with a change in surfactant concentration.

Conclusion

The pK_a values of simple oxime nucleophiles (pralidoxime, butane 2,3-dione monoxime) and some novel oxime-based functionalized nucleophiles (3- and 4-hydroxyiminomethyl-1-alkylpyridinium bromide) have been determined spectrophotometrically. In this work, we also distinguish the behavior of acidity constants of pralidoxime in pure water, water−$CTPPh_3Br$, water−DSS, and water−Triton-X 100 systems at 27 °C studied by UV−visible spectrophotometry. Results show that the pK_a values of pralidoxime do not vary significantly with a change in surfactant concentration.

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