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Effects of Added Dimethylsulfoxide on pK$_a$ Values of Uncharged Organic Acids and pH Values of Aqueous Buffers.

Pasupati Mukerjee* **and J. Donald Ostrow#**

*School of Pharmacy, University of Wisconsin, Madison, WI, 53706 USA

#Gastrointestinal/Liver Department, Academic Medical Center, 1105 AZ Amsterdam, The Netherlands

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Abstract: Recent studies of pK$_a$ values of carboxylic acids in $(CD_3)_2SO$-aq. buffer mixtures, using ^{13}COOH-NMR, conflict with our new data and other reports, which show that the pK$_a$ of uncharged carboxylic acids and pH values of anionic buffers increase dramatically with increasing vol% DMSO.

Introduction

pK$_a$ values of a number of acetic acid and propionic acid derivatives in mixtures of $(CD_3)_2SO$ and water, up to 64 vol% $(CD_3)_2SO$, have been published recently from Lightner's laboratory.[1-4] The ionization of the acids with 99% ^{13}C-enrichment of -COOH carbons was monitored by ^{13}C-NMR. For some acids, due to their poor water-solubility, titrations were performed only at high concentrations of added $(CD_3)_2SO$ and their pK$_a$ values in water were determined by an extrapolation procedure. The extrapolation utilized a reported pattern of a linear variation of pK$_a$ of several soluble acids against log vol% $(CD_3)_2SO$, and assumed the pK$_a$ value in water, i.e. 0 vol% of $(CD_3)_2SO$, could be obtained when log vol% $(CD_3)_2SO$ had a value of zero.[1-3]

These recent papers describe large and puzzling discrepancies from the extensively reported pK$_a$ values of similar carboxylic acids in dimethylsulfoxide (DMSO)[5-9] and its mixtures with water.[10-16] The recent pK$_a$ values differ in both the magnitude and the pattern of variation of pK$_a$ with DMSO concentration. For example, a number of studies have shown that pK$_a$ values increase roughly linearly with the mole fraction, N, of DMSO,[11,12,14,15] so that $\Delta pK_a = AN$, where A is a constant and ΔpK_a is the increase in pK$_a$ when DMSO is added. It is unlikely that the use of $(CD_3)_2SO$ instead of $(CH_3)_2SO$ (DMSO), or the enrichment of the carboxylic groups with ^{13}C, can account for these differences. We, therefore, present an account of these discrepancies, as well as our own studies, with emphasis on the effects of added DMSO on the pH of the aqueous buffers which were used in the recent papers,[1-4] in order to examine the statement "Added $(CD_3)_2SO$ did not alter buffer pH...".[2]

Materials and Methods

All chemicals were obtained from Merck, Darmstadt, Germany. Dimethylsulfoxide (Merck "Uvasol", no. 102950), was spectroscopic grade and 99.8% pure, containing less than 0.1% water. All other reagents were of extra pure or analytical quality. Double-distilled water, prepared from water passed previously through charcoal and deionizing columns, was used throughout. Mixtures of 0.1 mol/L aqueous buffers with DMSO were prepared both by simple mixing (leading to a progressive decline in buffer strength as DMSO concentration increased), or by adding one-tenth volume of 1.0 mol/L buffer to the appropriate volumes of DMSO and water to yield 0.1 mol/L final buffer concentration

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over the entire range of DMSO concentrations. The vol% DMSO was calculated from the volumes of DMSO and buffer which were mixed, ignoring the small decrease in total volume that results from such mixing.[10]

pH values were determined in duplicate to the nearest 0.01 unit at 20°C using a pHI-10 meter (#123132, Beckman, Fullerton, CA, USA) and a single-probe, combination test-tube electrode (Beckman #39845), constructed with epoxy and filled with 4 M KCl saturated with AgCl. Before each series of measurements, the electrode was standardized with buffer standards at pH 4.01 and 7.00 (Radiometer, Villeurbanne, France) and readings were taken only when a steady pH value was attained (usually within 15 seconds). After exposure to a series of DMSO - water systems containing up to 74 vol% DMSO, the rinsed electrode gave readings within ± 0.03 pH units of the initial standard pH values.

Results and Discussion

Figure 1 shows the apparent pH values (pH_a), read off the pH meter, of solutions of 0.0001 M $HClO_4$ and 0.10 M Tris-HCl, acetate and phosphate buffers, plotted against the vol% DMSO. In Figs. 1 (and 2), vertical dashed lines represent the DMSO concentrations used in the recent papers.[1-4] At 74 vol%, the highest DMSO concentration we tested, the pH_a values increased by 0.84, 1.08 and 3.48 for $HClO_4$, Tris and acetate respectively. Phosphate buffers showed even more pronounced increases up to 35 vol% DMSO, but were only partially soluble at or above 45 vol% DMSO. Similar increases in pH_a were seen when the buffer strengths were diluted by the added DMSO (not shown).

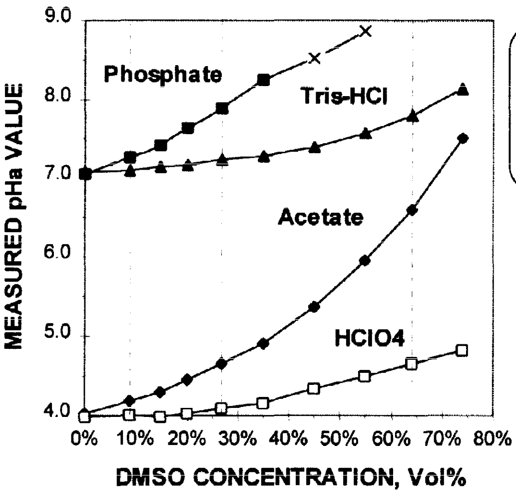


FIG 1

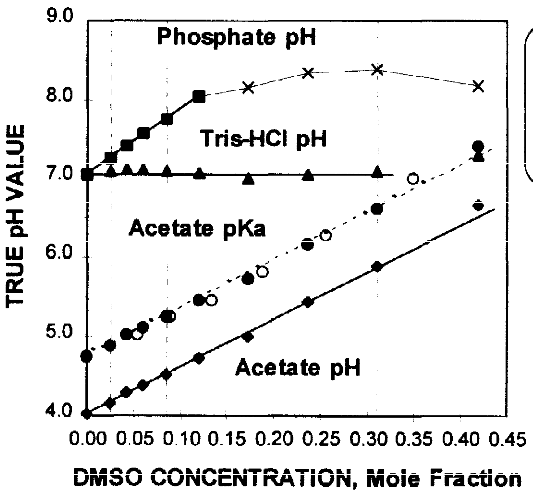


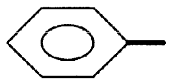
FIG 2

The significant increases in pH_a values (ΔpH_a) for the dilute solution of the strong acid, $HClO_4$, reflect changes in the standard potentials of the glass electrode system, not the activity of H^+, which can be assumed to be effectively constant. Thus, the ΔpH_a values of $HClO_4$ can be used to calibrate the effects of mixing DMSO with water.[13,17] Subtracting these ΔpH_a values from the pH_a values of the buffer systems, we obtain the true pH values of the buffers, which are plotted in Fig. 2 against the mole fraction (N) of DMSO. The pH of the Tris-HCl buffer changed little with added DMSO up to N = 0.31, but the pH values of the acetate and phosphate buffers increased linearly and steeply with N. The data for acetate and phosphate buffers contradict the statement in the recent papers that "Added $(CD_3)_2SO$ did not alter buffer pH...." .[2] These results also point out the need to properly calibrate the glass electrodes in non-aqueous media,[7-17] which was apparently not done in the recent papers.[1-4]

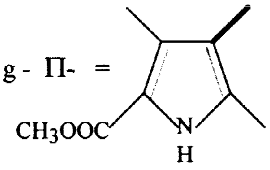
Serious discrepancies between the recent papers[1-4] and previous work[10,12,13,15] are also evident in the reported ΔpK_a estimates for a number of carboxylic acids (Table 1). The ΔpK_a values for N = 0.31 were calculated from interpolation of published data, or from experimental ΔpK_a values at N = 0.48, using the established relationship, $\Delta pK_a = AN$.[11,12,14,15] For three similar unsubstituted carboxylic acids (acetic, propionic and butyric) and two substituted acids (phenyl-acetic, and 3-hydroxybutyric), the ΔpK_a values in $(CH_3)_2SO$ at N = 0.31 are in the range of 1.95 to 2.42. In contrast, the recent pK_a values in $(CD_3)_2SO$-water mixtures at N = 0.31[1-3] lead to far lower ΔpK_a values (0.04 to 0.19) for phenylacetic acid and two aromatic 3-substituted propionic acids. At N = 0.31, four different 3-substituted propionic acid derivatives, including the two in Table 1, were reported to have pK_a values of 4.72 - 4.83,[1-3] some 2.5 units lower than the value of 7.26 estimated for propionic acid itself in DMSO (Table 1). Phenylacetic acid shows an equally marked contrast between the estimated pK_a value in DMSO (6.43) and that recently reported in $(CD_3)_2SO$ (4.35),[1] each at N = 0.31.

Table 1: pK_a and ΔpK_a of Organic Acids & Water	**pK_a in water**	**ΔpK_a [a] in DMSO, N = 0.48**	**ΔpK_a [a] in DMSO, N = 0.31**	**ΔpK_a [a] in $(CD_3)_2SO$, N = 0.31**
CH_3-COOH	4.76 [18]	3.26 [10] 3.24 [12]	1.95 [10,b] 2.09 [12,c]	
CH_3-CH_2-COOH	4.87 [18]	3.70 [13]	2.39 [c]	
CH_3-CH_2-CH_2-COOH	4.82 [18]	3.74 [13]	2.42 [c]	
Φ-CH_2-COOH [f]	4.31 [18]	3.29 [13]	2.12 [c]	0.04 [d] 0.19 [e]
CH_3-CH(OH)-CH_2-COOH	4.55 [13]	3.37 [13]	2.18 [c]	
Φ-CH_2-CH_2-COOH [f]	4.66 [18]			0.06 [d] 0.13 [e]
Π-CH_2-CH_2-COOH [g]	4.69 [3]			0.12 [3]
H_2O (pK_w)	14.00 [12]	4.38 [12]	2.83 [12,b]	

f - Φ- =



g - Π- =



a- ΔpK_a = pK_a at N mol% DMSO or $(CD_3)_2SO$ minus pK_a in water (N = 0).

b - Interpolated from pK_a data bracketing N = 0.31.

c - Calculated from ΔpK_a (DMSO at N = 0.48) using the equation $\Delta pK_a = AN$.

d - From reference [1], ΔpK_a calculated using pK_a (water) from reference [18].

e - From reference [1], ΔpK_a = calculated from pK_a (water) reported in reference [1].

pK_a values of acetic acid (HA) can be estimated from the pH values (Fig. 2). Following established principles[19-21] using activities (a), concentrations (c) and activity coefficients (γ), and assuming γ_{HA} is unity,[19] we have:

$$K_a = a_{H^+} . a_{A^-} / a_{HA} = (a_{H^+} . c_{A^-} . \gamma_{A^-}) / c_{HA} \qquad (1)$$

From the expressions for γ_{A^-}[19-21] and the dielectric constants of DMSO-water mixtures,[10] we find that the variation of $\log \gamma_{A^-}$ is less than 0.01 unit, effectively negligible. Since the ratio c_{A^-}/c_{HA} is kept constant and $pH = -\log a_{H^+}$, then (pK_a - pH) is a constant, whose value in our work, 0.73, was obtained from pK_a and pH values in water; thus, pK_a = pH + 0.73. Fig. 2 shows that these pK_a values (●) and Morel's[10] data (O), plotted against N, agree within 0.05 and are

described well by the same straight line. Similarly, the pH values of the Tris-HCl buffer (Fig. 2) imply only a small effect of added DMSO on the pK_a of Tris, in agreement with a prior report.[16]

To summarize, in sharp contrast to recent work,[1-4] our data show that added DMSO: (a) strongly affects the pH values of acetate and phosphate buffers; (b) produces profound changes in the pK_a of a typical carboxylic acid, acetic acid; and (c) results in a linear variation of pK_a with N (Fig. 2). We believe the reported lack of pH change[2] and the anomalously small changes in pK_a with added $(CD_3)_2SO$,[1-4] may be interrelated. The relations may be complex, however. At N = 0.31, the apparent pK_a values reported, 4.35 to 4.85,[1-4] fall in the pH range 3.2 - 6.8 (aqueous) covered by the acetate buffers used. However, Tris buffers above pH 6.8 and HCl with or without acetic acid below pH 3.2, were used also. The effects of DMSO on these systems are very different (Fig. 1 & 2).

Finally, we note that many factors affect ΔpK_a values,[5-9,12] including intramolecular interactions of a carboxyl group. For example, the pK_a values of benzoic, salicylic and 2-6-dihydroxybenzoic acids in pure DMSO[6] are 11.1, 6.8 and 3.1 respectively and 4.2, 3.0 and 1.1 in water.[18] These lead to very different and unpredictable ΔpK_a values (at N = 1) of 6.9, 3,8 and 2.0 respectively. The ΔpK_a of benzoic acid cannot, therefore, be used to model the ΔpK_a of the other two acids at any N. Thus, with respect to the recent work,[1-4] even accurately determined pK_a values of soluble simple carboxylic acids in DMSO-water mixtures may be unreliable for determining the pK_a in water of poorly-soluble carboxylic acids, such as mesobilirubin, which show complex intramolecular interactions of the carboxyl group(s).

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