

Effect of solvent composition on the acidity of phenols in dimethyl sulfoxide – water mixtures

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ABSTRACT: The effect of solvent composition on the acidity of substituted phenols in DMSO–H₂O systems was examined. It is shown that in DMSO–H₂O mixtures with up to 35 mol% DMSO there is a linear relationship between the p*K*_a values of monosubstituted phenols in the binary solvent mixtures of different compositions and the corresponding p*K*_a values in water. This leads to an equation relating the slope and intercept terms, p*K*_a(DMSO–H₂O) = slope[p*K*_a(H₂O)] + intercept. The basis of this relationship in the Kirkwood–Westheimer equation is examined. The significance of a possible ‘supersolvent’ is discussed. The applicability of the relationships derived herein to other rate–equilibria relationships and solvent mixtures is considered. © 1998 John Wiley & Sons, Ltd.

KEYWORDS: phenols; acidity; solvent composition; supersolvent

INTRODUCTION

Although the properties of binary solvent mixtures have been studied for many years, their continued relevance cannot be overstated.^{1–3} This sub-discipline of physical organic chemistry is constantly evolving and being applied not only in traditional studies, such as the solvent effect on enzyme activity,⁴ but also in emerging fields such as supercritical fluids.⁵ One of our ongoing interests has been the study of the effect of solvent composition on the nucleophilic reactivity of substituted phenoxide anions with various substrates in binary mixtures of dimethyl sulfoxide (DMSO) and water,^{6–8} a solvent system which has been intensely studied. Unfortunately, comprehensive sets of p*K*_a values for organic acids in aqueous binary solvent are not always available. The need for more comprehensive sets of p*K*_a values for organic acids in various solvent mixtures prompted our exploration of the factors governing the extent to which the p*K*_a values of typical organic acids vary in aqueous binary solvent mixtures.

The focus here was on exploring correlations that would permit the prediction of p*K*_a values of substituted phenols in DMSO–H₂O mixtures and extend currently available data.^{7,9,10} We use the empirical models of

Poh^{11,12} and Halle *et al.*,¹³ who related empirical linear free energy relationships to the Kirkwood–Westheimer equation.¹⁴ A general expression is obtained which predicts the p*K*_a value of a phenol in DMSO–H₂O mixtures in the water-rich region (≤35.5% DMSO) given its p*K*_a value in water.

EXPERIMENTAL

The p*K*_a values of the phenols in 59.3 mol% DMSO were determined as described previously.^{7,9} The results, together with previously determined values in 48.6, 35.5, 19.5 and 9.7 mol% DMSO, are collated in Table 1.^{9,10}

RESULTS AND DISCUSSION

p*K*_a relationships

In the 1970s, Poh^{11,12} proposed two different methods for predicting p*K*_a values of organic acids in various solvent systems. In his first method Poh used the sphere-in-contact model developed by Born¹⁵ to derive the equation:

$$pK_0(\text{sol})_A = [(pK_0(\text{sol})_B - pK_0(\text{H}_2\text{O})_B) + pK_0(\text{H}_2\text{O})_A] \quad (1)$$

which applies to two unsubstituted carboxylic acids

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Table 1. pK_a values of phenols in DMSO–H₂O mixtures^{7,9}

Phenol		H ₂ O	9.7% DMSO	19.5% DMSO	35.5% DMSO	48.6% DMSO	59.3% DMSO ^a
2-CN	Experimental	7.22	7.54	7.97	8.88	9.53	9.71
	Calculated		7.48	7.83	8.37		
	Difference		-0.06	-0.14	-0.51		
3,4,5-Cl ₃	Experimental	7.68	7.85	8.01	8.77	9.43	9.96
	Calculated		8.00	8.41	9.05		
	Difference		0.15	0.40	0.28		
4-CN	Experimental	7.80	8.17	8.45	9.31	10.22	10.44
	Calculated		8.14	8.56	9.23		
	Difference		-0.03	0.11	-0.08		
3,5-Cl ₂	Experimental	8.03	8.27	8.53	9.38	10.08	10.59
	Calculated		8.40	8.85	9.57		
	Difference		0.13	0.32	0.19		
2,4-Cl ₂	Experimental	7.65	8.01	8.31	9.08	10.17	10.67
	Calculated		7.97	8.38	9.01		
	Difference		-0.04	0.07	-0.07		
3,4-Cl ₂	Experimental	8.51	8.78	9.10	10.08	10.67	11.41
	Calculated		8.94	9.46	10.27		
	Difference		0.16	0.36	0.19		
2-Br	Experimental	8.45	8.96	9.64	10.57	11.37	11.68
	Calculated		8.88	9.38	10.19		
	Difference		-0.08	-0.26	-0.38		
Phenol	Experimental	9.88	10.62	11.21	12.44	13.59	13.95
	Calculated		10.49	11.18	12.30		
	Difference		-0.13	-0.03	-0.14		
3-CH ₃ O	Experimental	9.65	10.35	11.05	12.24	13.11	13.68
	Calculated		10.23	10.90	11.96		
	Difference		-0.12	-0.15	-0.28		
4-Cl	Experimental	9.35	9.85	10.18	11.52	12.45	12.91
	Calculated		9.89	10.52	11.52		
	Difference		-0.04	0.34	0.00		
4-CH ₃ O	Experimental	10.27	10.70	11.47	12.90	13.97	14.53
	Calculated		10.93	11.67	12.88		
	Difference		0.23	0.20	-0.02		

^a This work.

(denoted A and B) in two different solvents, one of which is typically H₂O.

The requirement of this model is that all carboxylic acids experience the same relative change in pK_a upon transfer from a given solvent to a second solvent.¹⁶ Clearly, this is not the case for phenols in DMSO–H₂O mixtures: the change in pK_a value of phenols upon changing the DMSO content in the solvent is strongly dependent upon the pK_a value of the phenol in H₂O. Poh showed that Eqn(1) is only modestly successful for carboxylic acids, with an average error of 0.43 pK_a units for the systems investigated. This first model of Poh is thus inappropriate for the study of the pK_a values of phenols in DMSO–H₂O mixtures.

One shortcoming of Poh's first method is that specific solute–solvent interactions are excluded. He addressed this problem with his second method¹² by comparing the empirical Hammett–Taft relationship:^{17–20}

$$\log(K_a/K_0) = \rho^* \sigma^* \quad (2)$$

which implicitly accounts for all experimental variables, to the Kirkwood–Westheimer cavity¹⁴ model:

$$\log(K_a/K_0) = e\mu \cos \phi / 2.303k_B T D_E l^2 \quad (3)$$

The K_a and K_0 values in Eqn (2) represent the dissociation constants of the substituted and unsubstituted acids, respectively, σ^* is the substituent constant and ρ^* is the reaction constant. For systems where resonance effects are important, σ^* can be replaced by the appropriate substituent constant (σ^- , for example).

In the Kirkwood–Westheimer equation [Eqn (3)], e is the electronic charge, μ is the bond dipole moment, ϕ is the angle between the dipole axis and the line joining the reaction site to the midpoint of the dipole axis, D_E is the effective dielectric constant (which is used to make allowances for deviations in the local dielectric constant of the solvent around the solute molecules from its macroscopic value, ϵ_r), k_B is the Boltzmann constant, T is the absolute temperature, and l is the distance between the reaction site and the midpoint of the dipole. It is noted that this model does not account for specific interactions such as hydrogen bonding.

The following equation is obtained from Eqns (2) and

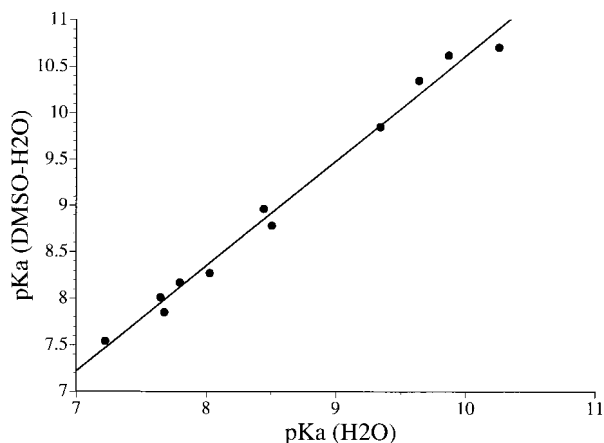


Figure 1. Plots of the pK_a values of phenols in 9.7 mol% DMSO vs pK_a values in H_2O

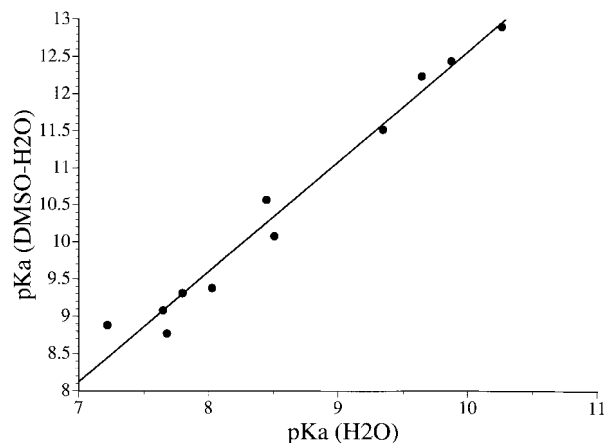


Figure 3. Plots of the pK_a values of phenols in 35.5 mol% DMSO vs pK_a values in H_2O

(3) if the solvents have no effect on μ , and if the ionized molecule has a reasonably fixed geometry (e.g. phenols):

$$\rho_s/\rho_w = (D_E)_W/(D_E)_S \quad (4)$$

In solvents in which hydrogen bonding effects are important, ρ_s/ρ_w values were found to be significantly different to the values that can be calculated from Eqns (3) and (4). To account for these discrepancies, a hydrogen bonding factor, F_{HB} , was introduced, such that

$$\rho_s/\rho_w = F_{HB}(D_E)_W/(D_E)_S \quad (5)$$

Halle *et al.*¹³ used a similar approach to model the acidities of organic acids in DMSO– H_2O mixtures. It was shown that

$$(pK_a)_S = [(\rho)_S/(\rho)_W](pK_a)_W - [(\rho)_S/(\rho)_W](pK_0)_W + (pK_0)_S \quad (6)$$

Combining the approaches of Poh¹² and Halle *et al.*¹³ and simplifying leads to

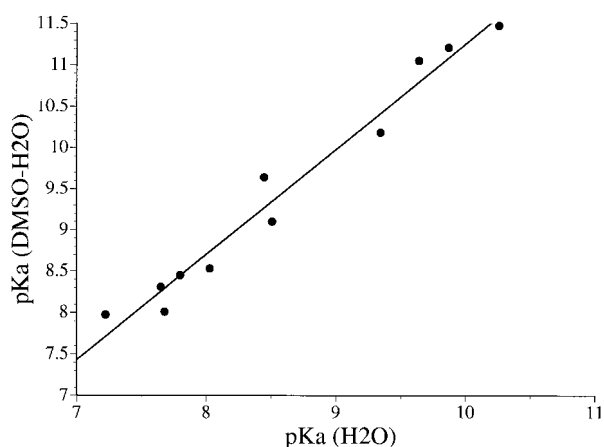


Figure 2. Plots of the pK_a values of phenols in 19.5 mol% DMSO vs pK_a values in H_2O

$$(pK_a)_S = F_{HB}[(D_E)_W/(D_E)_S](pK_a)_W + \text{constant} \quad (7)$$

which predicts that a plot of pK_a values in a mixed solvent against pK_a values in H_2O will be linear.

The validity of the Eqn (7) can be tested using the pK_a values of phenols in DMSO– H_2O mixtures. Plots of pK_a values of substituted phenols in DMSO– H_2O mixtures against their pK_a values in H_2O , using the data in Table 1,^{7,9,10} are shown in Figs. 1–5. The solvent mixtures used in these studies were 30, 50, 70, 80 and 85 vol.%. In the present work, we chose to use mole % DMSO rather than volume % DMSO because mole % has a readily understood physical significance and because mole % DMSO values do not vary with temperature. Thus, 30, 50, 70, 80 and 85 vol.% correspond to 9.7, 19.5, 35.5, 48.6 and 59.3 mol%, respectively.

Each of Figs 1–5 is described by a simple equation of the form $y = mx + b$, where x is the pK_a value of the phenol in H_2O and y is the pK_a at a given DMSO– H_2O composition. For these specific solvent mixtures, the pK_a

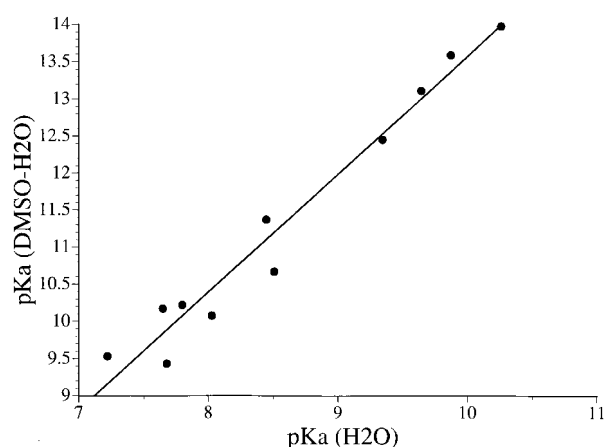


Figure 4. Plots of the pK_a values of phenols in 48.6 mol% DMSO vs pK_a values in H_2O

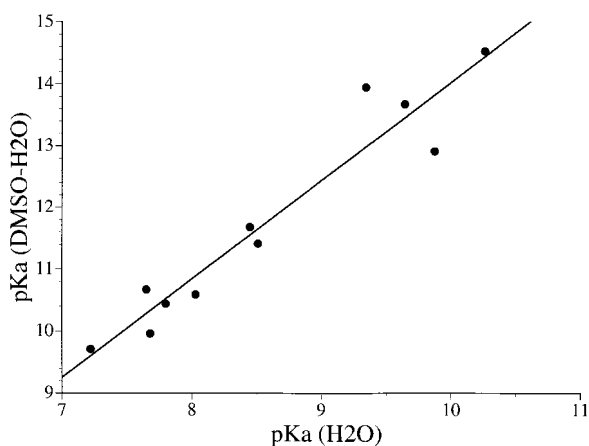


Figure 5. Plots of the pK_a values of phenols in 59.3 mol% DMSO vs pK_a values in H_2O

values can be fitted to the following set of equations:

$$pK_a(9.7 \text{ mol\% DMSO}) = 1.13 pK_a(H_2O) - 0.659 (r^2 = 0.998) \quad (8)$$

$$pK_a(19.5 \text{ mol\% DMSO}) = 1.27 pK_a(H_2O) - 1.45 (r^2 = 0.970) \quad (9)$$

$$pK_a(35.5 \text{ mol\% DMSO}) = 1.47 pK_a(H_2O) - 2.23 (r^2 = 0.975) \quad (10)$$

$$pK_a(48.6 \text{ mol\% DMSO}) = 1.58 pK_a(H_2O) - 2.27 (r^2 = 0.963) \quad (11)$$

$$pK_a(59.3 \text{ mol\% DMSO}) = 1.59 pK_a(H_2O) - 1.86 (r^2 = 0.922) \quad (12)$$

One of the motivations of these investigations was the desire to obtain a general expression, valid for any solvent composition, which can predict pK_a values of substituted phenols in binary solvent mixtures. Since the plots in Figs 1–5 are all linear, it seemed reasonable that a universal expression may exist for all solvent compositions if a relationship can be found between the ‘slope’ term, $F_{HB}[(D_E)_W/(D_E)_S]$, and the ‘intercept’ term and solvent composition, i.e.

$$pK_a(\text{DMSO}-H_2O) = \text{slope}[pK_a(H_2O)] + \text{intercept} \quad (13)$$

Plots of the slope terms against solvent composition and intercept terms against solvent composition were therefore constructed (Figs 5 and 6 respectively) and were found to be reasonably linear up to approximately 35.5 mol% DMSO. In these water-rich solvent compositions, the slope terms and intercept terms can be described by

$$\text{slope} = 1.36\chi + 1.00 (r^2 = 0.999) \quad (14)$$

$$\text{intercept} = -6.33\chi - 0.061 (r^2 = 0.987) \quad (15)$$

where χ represents the mole fraction of DMSO ($0.01 \times \text{mol\% DMSO}$). Substituting Eqns, (14) and (9) into Eqn, (13) yields

$$pK_a(\text{DMSO}-H_2O) = [(1.36\chi + 1.00)pK_a(H_2O)] - 6.33\chi - 0.061 \quad (16)$$

which predicts the pK_a value of any phenol in DMSO– H_2O mixtures in the H_2O -rich region (DMSO < 35.5 mol%), given the pK_a value in H_2O . The validity of Eqn (16) for media up to 35.5 mol% DMSO is demonstrated by comparison of the experimental values to the calculated values, as shown in Table 1. There is excellent agreement between the empirically and experimentally determined values with the average absolute error being only 0.17 pK_a units.

The finding in this work of an equation that predicts the pK_a value of phenols in DMSO– H_2O mixtures based on the pK_a value in water looks toward extension to other ionization equilibria (carboxylic acids, anilinium ions, etc.), i.e. whether these processes will be subject to similar behavior. It is planned to undertake such studies in the future.

Some further comments are necessary concerning the 35.5 mol% DMSO composition as the limit of the applicability of Eqn (16). Figures 6 and 7 show that as the DMSO-rich region is approached (>35.5 mol% DMSO), curvature sets in: neither the ‘slope’ terms nor the ‘intercept’ terms are linear outside the water-rich region. At present, a physical description of why the slope varies in a non-linear way (or even why it varies in a linear way in the water-rich region) is not fully apparent. However, it is not surprising that there is a progressive change of behavior between the water-rich region and the DMSO-

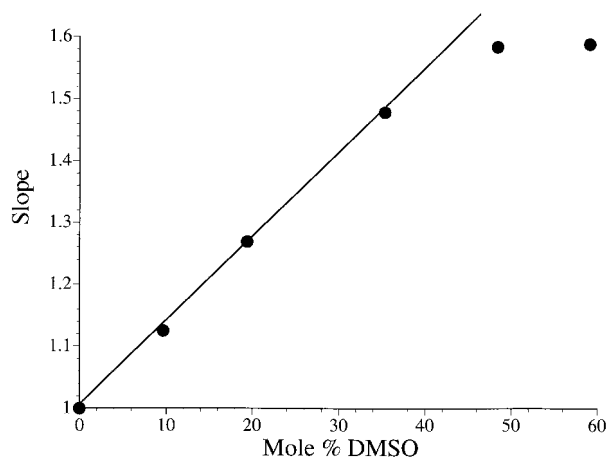


Figure 6. Dependence on the solvent composition of the ‘slope’ term of the $pK_a(\text{DMSO}-H_2O)$ vs $pK_a(H_2O)$ plots

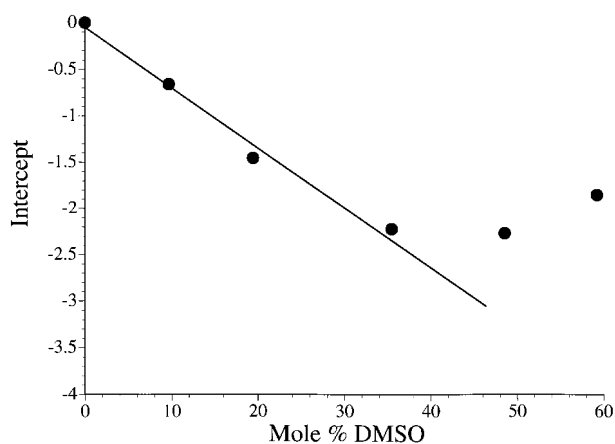


Figure 7. Dependence on the solvent composition of the 'intercept term' of the $pK_a(\text{DMSO-H}_2\text{O})$ vs $pK_a(\text{H}_2\text{O})$ plots

rich region. DMSO and H_2O are known to have a very strong tendency to form aggregated complexes. The 2:1 complex (33.3 mol% DMSO) is particularly stable. Evidence for this phenomenon is that many physical properties of $\text{DMSO-H}_2\text{O}$ are known to exhibit extrema at 33.3 mol% DMSO, including heat of mixing,²¹ viscosity, density,²² energy-volume coefficient,²³ partial molal entropy, the heat of solution of hydrogen²⁴, freezing point²⁵ and adiabatic compressibility.²⁶

Turning to the behavior in DMSO-rich mixtures, much fewer data are available here concerning equilibrium processes, but a number of kinetic studies of nucleophilic processes, e.g. reactions of phenoxide anions with carbon,^{6a,b} sulfur^{6d} and phosphorus^{6e,f} esters, have been reported. In these instances a smooth dependence of the $\log(\text{rate})$ on mol% DMSO has been found, which does not correlate, however, with solvent composition in the water-rich region. Again, this break in the observed behavior occurs around 35 mol% DMSO, thus providing further evidence for the key significance of this solvent composition in discussions of reactivity relationships in $\text{DMSO-H}_2\text{O}$ mixtures.

Supersolvent

An interesting phenomenon was discovered during the development of this model. Extrapolation of the plots of pK_a vs solvent composition into the hypothetical region of negative DMSO content shows that the plots may intersect at a fixed point of approximately -90 mol% DMSO and $pK_a = 3$ (Fig. 8). At this hypothetical solvent composition, which we have called 'supersolvent,' all phenols have the same pK_a value, regardless of substituent. Although the common intercept point may in fact be fortuitous, and other lines may be drawn such that no common intercept point occurs, we nonetheless believe that this phenomenon is interesting and worthy of discussion.

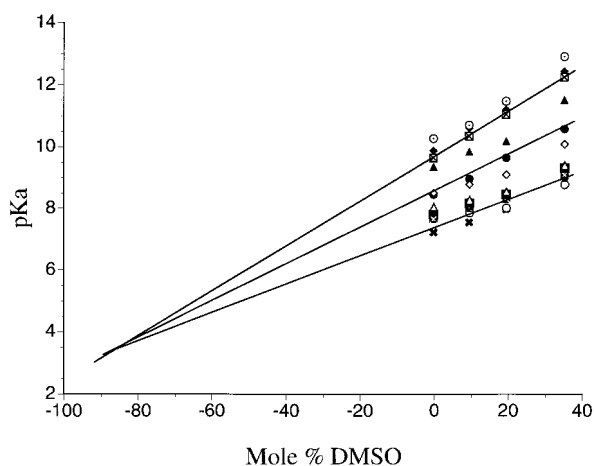


Figure 8. 'Supersolvent' plot. Plots of the pK_a values of phenols in $\text{DMSO-H}_2\text{O}$ mixtures vs mol% DMSO, with plots extended into the region of imaginary solvent composition, to show the common intersection point

The question that the supersolvent poses is, 'what is the physical property of the solvent which causes all phenols to have the same acidity?' In other words, all phenols have the same pK_a value as the reference phenol in that solvent. This idea is represented by the equation

$$(pK_a)_s = (pK_0)_s \quad (17)$$

Examination of Eqns (4) and (6) shows that for the relationship in Eqn (17) to be true, $[(D)_E]_W/(D)_E)_S$ must be zero, which holds when $(D)_E)_S$ the effective dielectric constant, is infinitely large. Under these conditions, an electronic effect exerted by the substituent plays no role in the ionization of the organic acid: the solvent does all of the work.

Applicability to other rate-equilibria relationships and solvent mixtures

The linear relationship that we have observed between pK_a values of substituted phenols in $\text{DMSO-H}_2\text{O}$ mixtures and the corresponding pK_a values in H_2O [Figs 1-5 and Eq (16)] will be of value in the main because of its predictive capability. A partial survey indicates that other properties, such as ionizations of different classes of organic acids and bases, as well as reaction rates, show in many cases (e.g. proton transfer from carbon acids,²⁷ heats of transfer²⁸ and anionic σ -complex formation^{28,29}) similar behavior. Moreover, available evidence shows that this type of behavior persists in mixtures of DMSO with common alcohols.^{29,30}

A theoretical basis of the relationship [Eqn (16)] is at present only imperfectly understood. A primary condition is clearly that plots of the given property (e.g. pK_a) are a linear function of mol% DMSO in the H_2O -rich region. The classical instance of this is the plot of the H_+ acidity function^{31,32} versus mol% DMSO, which after an

almost linear portion in the H₂O-rich region displays a sharply upward deviation in the DMSO-rich region. This is generally accounted for in terms of a combination of factors: strong H-bonding between H₂O and DMSO molecules and the progressive desolvation of OH⁻ with decreasing H₂O content.^{32,33} A similar reasoning may be used in accounting for the increasing values of the slope parameters in the pK_a (DMSO–H₂O) vs pK_a(H₂O) plots as the pK_a of the phenol increases [Eqns (8)–(12)]. Here, also, the corresponding individual plots of pK_a vs mol% DMSO show an increasing upward deviation in the DMSO-rich region. A plausible explanation is that with relatively strongly acidic phenols where the negative charge on the conjugate base is delocalized over the benzene ring as well as residing in part on the anionic oxygen, efficient solvation can persist in the DMSO-rich region since DMSO is known to interact efficiently with charge dispersed species through dipole–dipole interactions. On the other hand, in the case of weakly acidic phenols with less charge dispersal in the corresponding anions, solvation through H-bonding with H₂O molecules will be the predominant stabilization mechanism, and in the DMSO-rich media where this stabilization is not available, substituents on the benzene ring will assume a correspondingly greater role. This in turn will be reflected in a greater sensitivity of the pK_a to medium effect (mol% DMSO) changes; hence the increasing slope parameters in Eqns (8)–(12).

Although the perhaps unique properties of DMSO and its mixtures with water and alcohols have been of immense value in both mechanistic and synthetic chemistry,² adequate theoretical treatments of these (and by and large other) mixed solvents have yet to be published, to the authors' knowledge. Hence the empirical relationships observed here, and that can be anticipated from the present study, will continue to be used as a predictive tool in organic chemistry.

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