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THERMODYNAMIC PROTON–LIGAND DISSOCIATION CONSTANTS OF SUBSTITUTED 3-HYDROXY-4-PYRONES IN DIOXANE–WATER MIXTURES

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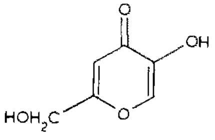
ABSTRACT

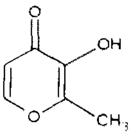
Thermodynamic proton–ligand dissociation constants $\mathrm{T}pK_a$ were determined pH-metrically in 10–50 vol.% dioxane–water mixtures at 25 and $35 \pm 0.1\,^{\circ}\mathrm{C}$ for two substituted 3-hydroxy-4-pyrones (3-hydroxy-2-methyl-4-pyrone (maltol) and 3-hydroxy-5-(hydroxymethyl)-4-pyrone (kojic acid). Extrapolation and least-squares methods were used to obtain $\mathrm{T}pK_a$ in pure water (0%). Both of the 3-hydroxy-4-pyrones are monoprotic and they are very weak acids. The $\mathrm{T}pK_a$ values do not vary linearly with the reciprocal of the dielectric constant of the medium, but a plot dioxane of mole fraction n_2 vs. $\mathrm{T}pK_a$ is linear at a given temperature. The "true constant" K_a^t and solvation number n (in the expression $(\mathrm{H}^+)(\mathrm{A}^-)/(\mathrm{HA}) = K_a^t(\mathrm{S})^n = K_a^*$) for these compounds were evaluated by analysing the experimental data mathematically. Values of the changes in standard free energy, enthalpy and entropy associated with the dissociation were calculated. The effects of temperature, medium and substituent are briefly discussed.

INTRODUCTION

Among the substituted pyrones, kojic acid (I) and maltol (II) possess remarkable medicinal [1] and analytical potential. Kojic acid has been proposed for the spectrophotometric determination of iron in ores [2] and as an indicator for complexometric titration of iron(III) [3]. It has also been used as an antibiotic [4] and in the synthesis of a large number of un-



(I)



(II)

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saturated alcohols and triols on an industrial scale [5]. Murkami [6] and Murkami and Mera [7] have shown that kojic acid behaves as tropolone and its metal complexes are of relatively higher stability owing to the formation of a stable five-membered chelate ring with hydrogen. Likewise maltol gives analytically suitable coloured complexes with iron(III), molybdenum(VI), vanadium(V), uranium(VI) and germanium [8–12]. Surprisingly, no data seem to be available on their thermodynamic proton–ligand dissociation constants. Stoichiometric dissociation constants for both the compounds have, however, been reported by several workers [13–17]. Thermodynamic constants are of greater value than the stoichiometric constants because the former refer to the interaction among the species in the pure solvent; that is, each ion is completely free from the effect of others except the solvent molecules. Thermodynamic functions ($\Delta G^{\ominus}$, $\Delta H^{\ominus}$, $\Delta S^{\ominus}$) associated with the dissociation of these compounds are computed following the standard equations. Values of solvation number and true dissociation constants are also evaluated.

Kojic acid is sparingly soluble in water and hence recourse to the use of dioxane–water mixed media had to be taken for $\mathrm{Tp}K_a$ determination. In addition, the determination of dissociation constants in binary mixed media provides useful data for the theoretical understanding of the dissociation process in a system where two dipoles, e.g. dioxane and water in our case, as well as the anion compete for the proton. It also serves the purpose of providing buffers for the calibration of pH-meters in these systems. The dioxane–water system is a good model because it covers a very wide range of dielectric constant (from 78 for pure water to 2.2 for pure dioxane) and it consists of a polar, hydrogen-bonding component and a relatively non-polar component.

EXPERIMENTAL

Apparatus

A Beckman Research pH-meter with a glass combination electrode was used for pH measurements; it can read up to ±0.002 pH units. It was standardized with phthalate and borax buffers before and after each titration. A constant temperature was maintained (to an accuracy of ±0.1° C) by circulating water through a double-walled reaction vessel; a Colora K-4661 (F.R.G.) thermostat was used.

Reagents

Kojic acid and maltol, both obtained from Koch Light, U.S.A., were used as received. *p*-Dioxane was purified as recommended [18]. Tetramethylammonium hydroxide (TMAH) (0.1 M) (AnalaR) was used as titrant. It was standardized against potassium hydrogen phthalate. All other chemicals were of AnalaR or G.R. grade.

pH-titration procedure

The titration procedure for determining the dissociation constants was essentially the same as outlined by Albert and Serjeant [19]. In general, 0.01 M reagent solution was titrated without the addition of inert salt.

Reagent solution (0.5 mM) in the appropriate dioxane–water solution was introduced into a thermostatted (25.0 or $35.0 \pm 0.1°C$) titration vessel equipped with a magnetic stirring bar, a glass combination electrode and a microburette of capacity 5.0 ml. This initial volume was taken to allow for the change in total volume of the solution on titrant addition [20]. For practical purposes, the error caused by volume correction is almost negligible (less than 0.01 pH unit for the central five readings of the titration set, with a maximum error of 0.018 pH unit [21]). After 10 min, the titration was initiated by addition of a 0.50 ml aliquot of 0.10 M TMAH and the highest stable pH value was recorded. Further titrant additions were made in the same fashion. The titrations were repeated and the values were reproducible to within ± 0.01 pH unit.

CALCULATIONS

Two methods, non-logarithmic (N) and logarithmic (L) were used to calculate the dissociation constants.

Non-logarithmic method

The dissociation cosntant of an acid in an aqueous medium is given as

$$K_a = \{[H^+][A^-]/[HA]\} \tag{1}$$

Also, we know that

$$[HA] = [C_a] - [A^-] \tag{2}$$

where C_a is the total concentration of the acid. Substituting the value of [HA] from eqn. (2)

$$[A^-] = -1/K_a([A^-][H^+]) + C_a \tag{3}$$

which is a straight line equation with a slope equal to the negative inverse of the dissociation constant and an intercept equal to the total concentration of the acid ($x = [A^-][H^+]$ and $y = [A^-]$). The least-squares method was used to evaluate the slope and intercept of the above equation. Values of $[A^-]$

and $[H^+]$ were obtained analytically. The relationship of Van Uitert and Haas [21] was used to evaluate the hydrogen ion concentration from the values read on the pH-meter (B).

$$-\lg[H^+] = B + \lg U_H^{\ominus} - \lg 1/\gamma\pm$$

Values of the correction factor $\lg U_H^{\ominus}$ were obtained experimentally [22] and those of the mean activity coefficients $\gamma\pm$ were computed by interpolation of the data given by Harned and Owen [23], assuming that the mean activity coefficients are the same on both the molal and molar scales. The dissociation constants thus obtained were converted to thermodynamic values using the appropriate activity coefficients $\gamma\pm$.

Logarithmic method

Values of $\mathrm{T}pK_a$ in aqueous dioxane media were calculated using the equation

$$\mathrm{T}pK_a = B + \lg U_H^{\ominus} + \lg([HA]/[A^-]) + \lg 1/\gamma\pm \quad (4)$$

Details relating to the logarithmic (L) method of computation are essentially the same as given elsewhere [24].

The thermodynamic functions ($\Delta G^{\ominus}$, $\Delta H^{\ominus}$, $\Delta S^{\ominus}$) associated with the acid dissociation were calculated using the standard equations

$$\Delta G^{\ominus}(25\,^{\circ}\mathrm{C}) = 1.3646\ pK_a(25\,^{\circ}\mathrm{C})(\mathrm{kcal}) \quad (5)$$

$$\Delta G^{\ominus}(35\,^{\circ}\mathrm{C}) = 1.4103\ pK_a(35\,^{\circ}\mathrm{C})(\mathrm{kcal}) \quad (6)$$

$$\Delta H^{\ominus} = 42.06[pK_a(25\,^{\circ}\mathrm{C}) - pK_a(35\,^{\circ}\mathrm{C})](\mathrm{kcal}) \quad (7)$$

$$-\Delta S^{\ominus}(25\,^{\circ}\mathrm{C}) = 3.353[\Delta G^{\ominus}(25\,^{\circ}\mathrm{C}) - \Delta H^{\ominus}](\mathrm{cal}) \quad (8)$$

$$-\Delta S^{\ominus}(35\,^{\circ}\mathrm{C}) = 3.2446[\Delta G^{\ominus}(35\,^{\circ}\mathrm{C}) - \Delta H^{\ominus}](\mathrm{cal}) \quad (9)$$

RESULTS

The $\mathrm{T}pK_a$ values obtained using the logarithmic method usually show either an upward or a downward trend as the titration progresses. This is probably caused by an impurity in the substance undergoing determination so that not so much of it is present as thought. This can easily be overcome by the use of the non-logarithmic method as is evident from eqn. (3). The thermodynamic proton–ligand dissociation constants $\mathrm{T}pK_a$ for the two substituted pyrones in various dioxane–water mixtures at 25 and 35 °C are summarized in Table 1 as calculated by both methods. The $\mathrm{T}pK_a$ values obtained using the non-logarithmic (N) and logarithmic (L) methods are in fair agreement. However, the $\mathrm{T}pK_a$ values obtained using the non-logarith-

TABLE 1

Thermodynamic ionization constants TpK_a of kojic acid and maltol

Ligand	Temp. (°C)	Solvent medium (vol.% dioxane)				
		10	20	30	40	50
		$n_2 = 0.023$	$n_2 = 0.050$	$n_2 = 0.083$	$n_2 = 0.123$	$n_2 = 0.174$
Kojic acid	25	7.91	8.26	8.69	9.06	9.72
		(7.94)	(8.28)	(8.64)	(9.05)	(9.74)
	35	7.93	8.26	8.64	9.11	9.75
		(7.90)	(8.22)	(8.62)	(9.06)	(9.77)
Maltol	25	8.81	9.18	9.59	10.02	10.71
		(8.82)	(9.12)	(9.53)	(10.01)	(10.74)
	35	8.69	9.03	9.46	9.97	10.61
		(8.69)	(9.01)	(9.45)	(9.93)	(10.66)

Values in parentheses were calculated using the logarithmic (L) method. The average TpK_a value generally has a spread of ±0.03 unit (not beyond ±0.04 unit in any case).

mic method are used for all other detailed calculations owing to their better accuracy.

The TpK_a values of maltol increase slightly with an increase in temperature, while no significant differences are observed in the TpK_a values found for kojic acid at the two temperatures. The TpK_a values are plotted against $1/D_s - 1/D_w$ (D_s = dielectric constant of the solvent, D_w = dielectric con-

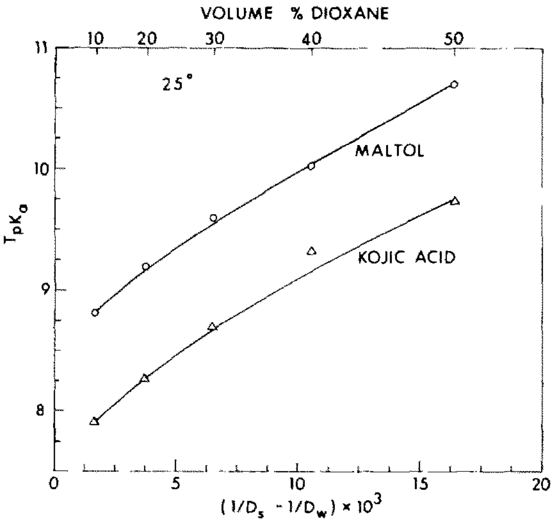

Fig. 1. Variation in TpK_a with dielectric constant D of the medium (temperature, 25 °C).

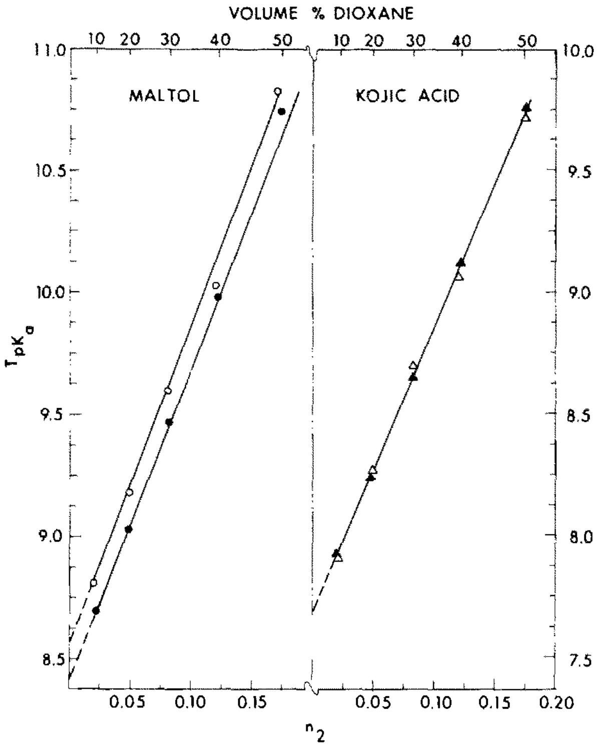

Fig. 2. Variation in TpK_a with n_2 (mole fraction of dioxane).

stant of water) (Fig. 1) and the mole fraction of dioxane n_2 (Fig. 2). The empirical relations derived therefrom are given in Table 2. Such relations between TpK_a and n_2 were also calculated by subjecting the TpK_a data to least-square analysis (Table 2). Table 3 shows the thermodynamic functions computed using the temperature variation method.

TABLE 2

Empirical relationship between TpK_a and mole fraction of dioxane n_2

Ligand	Temp. (°C)	TpK_a = $mn_2 + c$				
		Graphical		Least-squares		
		m	*c*	*m*	*c*	*r*
Kojic acid	25	11.60	7.70	11.80	7.66	0.998
	35	11.60	7.70	12.02	7.65	0.999
Maltol	25	12.50	8.55	12.33	8.54	0.999
	35	12.85	8.41	12.76	8.40	1.000

r is the correlation coefficient.

TABLE 3

Standard free energy, enthalpy and entropy changes for dissociation of kojic acid and maltol

Thermodynamic function		Solvent medium (vol.% dioxane)				
		10	20	30	40	50
Kojic acid						
$\Delta G^\ominus$	25°C	10.79	11.27	11.86	12.37	13.27
$\Delta G^\ominus$	35°C	11.18	11.64	12.19	12.85	13.75
Maltol						
$\Delta G^\ominus$	25°C	12.03	12.52	13.09	13.67	14.61
$\Delta G^\ominus$	35°C	12.25	12.74	13.34	14.07	14.96
$\Delta H^\ominus$		7.36				
$-\Delta S^\ominus$	25°C	15.65	17.31	19.21	21.17	24.30
$-\Delta S^\ominus$	35°C	15.88	17.45	19.42	21.76	24.68

$\Delta H^\ominus$ and $\Delta G^\ominus$ are in kcal mol^{-1}; $\Delta S^\ominus$ is in cal mol^{-1} K^{-1}.

DISCUSSION

Effect of solvent on dissociation equilibria

In an aqueous dioxane solvent, the proton–ligand dissociation may be influenced by different solvent characteristics. These effects can be due to: (i) the dielectric constant of the mixed solvent, (ii) the change in the hydrogen bonding in water in the presence of organic solvent, and (iii) proton solvation of the organic solvent.

Bates et al. [25] and Rorabecher et al. [26] have explained the change in TpK_a with solvent composition by considering both electrostatic and non-electrostatic effects. They have concluded that the non-electrostatic phenomenon becomes increasingly important in solvents containing relatively higher concentrations of the organic solvent (os).

Protonation is viewed [26] as a two-step process,

$$H^+ + A^{-b} \overset{K_{os}}{=} \underset{\text{solvent separated ion pair}}{H^+ \ldots A^{-b}} \overset{K_{H-A}}{=} HA^{+1-b} \tag{10}$$

where

$$K_H = K_{os} K_{H-A} \tag{11}$$

The values of K_{os} representing the diffusion controlled equilibrium constant for ion pair formation, can be calculated from Fouss' equation [27]

$$K_{os} = (4/3)\pi a^3 N_A 10^{-3} \exp\left[-\left(Z_H Z_A e_0^2\right)/DaRT\right] \tag{12}$$

where a represents the distance of closest approach between the solvated proton and the base in the ion pair. Other terms have their usual meaning. The term K_{H-A} in eqn. (10) denotes the proton jump equilibrium occurring within the ion pair; this is presumably a non-electrostatic term dependent primarily on the relative basicity of the solvent molecules separating the solvated proton and base species in the ion pair. It also appears that the non-electrostatic part of the interaction is related to the proton acceptance property of the medium and the proton solvation of the organic solvent. Taking the logarithm of eqn. (11) and including the Fouss expression for K_{os} we have

$$\lg K_{H} = \lg(4/3)\pi N_A 10^{-3} + 3 \lg a + \lg K_{H-A} - \left[Z_H Z_A e_0^2/2.303RTa\right](1/D) \quad (13)$$

It can be seen that with decreasing dielectric constant D of the medium, $\lg K_H$ (TpK_a) increases as shown for the compounds in Table 1. The variation in pK_a with D_s in the solvent mixtures is given by the equation [27]

$$pK_a = \left(\Delta G^{\ominus}_{\text{nonel}}/2.303\ RT\right) - \left(Ne^2/4.606RT\right)(1/D_s - 1/D_w)(1/r^+ + 1/r^-) \quad (14)$$

Conventionally, pK_a is plotted against $1/D_s$. Both types of relationship, i.e. linear for water-rich media [28,29] and non-linear [30] have been reported. The plots of TpK_a as a function of $1/D_s - 1/D_w$ for maltol and kojic acid do not obey a strict linear relationship and their curvature varies (Fig. 1). For brevity, plots at 25 °C only are shown in Fig. 1. If there is no change in solvation of an acid and its anion in a binary mixed solvent, such a plot should give a straight line. The TpK_a values of both the compounds, when plotted against $1/D_s - 1/D_w$, show curvature. This deviation from linearity particularly at higher concentration of dioxane can be attributed to the two non-electrostatic factors described below.

(a) Dioxane is a non-polar basic solvent. Although intermolecular interactions between dioxane molecules are weak, interactions between molecules of dioxane and water are rather strong due to the basicity of the ether oxygen atoms of dioxane. Consequently, dioxane can form hydrogen bonds with water and hence dioxane–water mixtures are miscible at any composition. As dioxane associates with water molecules in an aqueous dioxane solution, hydrogen bonds between water molecules which originally exist in pure water are partly replaced with those between dioxane and water molecules in the mixture. However, since dioxane has very poor acidity, the dioxane molecules cannot interact with the oxygen atom of water molecules. As a result, dioxane breaks up the water structure. According to Braude and Stern [31], the tetrahedral lattice structure of water gradually breaks down with the addition of organic solvent, and owing to the denser packing and the smaller extent of hydrogen bonding between water molecules, the stability of the hydroxonium ion increases and the proton-donating property of the medium falls. This may imply that the proton-accepting property of the solvent increases. Hence, the pK_a of the ligand will tend to decrease.

(b) When the amount of organic solvent becomes sufficiently large in a water–organic mixture, proton solvation of the organic solvent molecules take place. Thus increasing proton solvation by the organic solvent decreases the K_a value of the ligand and vice versa.

Mole fraction of dioxane

A consideration of the direct participation of the solvent in the acid dissociation should lead to a better understanding of the composition of the solvent as well as of the solvates [32]. For example, such a participation is essential as can be seen from straight line plots of pK_a vs. n_2 in several instances [33].

When the mole fraction of dioxane is altered, an appreciable change in the TpK_a values is evident for both the compounds. Thus on plotting TpK_a vs. n_2, linear relationships are obtained (Fig. 2). The experimental values of TpK_a show a maximum deviation from linearity of the order of approximately ±0.04 in TpK_a. The fit was judged by calculating the correlation coefficient r [24]. Linear proportionality between the two variables is quite evident from the values of r which are approximately unity (Table 2) in all cases. A similar behaviour has been found for other mixed solvents, e.g. acetic, propionic, butyric and benzoic acids in methanol–water mixtures [34] and dimedone in ethanol–water [35].

Evaluation of pK_a and n

The acid dissociation constant K_a^t of an acid HA in a mixed medium can be expressed as

$$n\mathrm{S} + \mathrm{HA} \overset{K_a^t}{=} x\mathrm{SH}^+ + y\mathrm{SA}^- \tag{15}$$

where n is the total of x plus y moles of solvent S, aqueous dioxane being the medium in the present study.
Hence,

$$(x\mathrm{SH}^+)(y\mathrm{SA}^-)/(\mathrm{S})^n(\mathrm{HA}) = K_a^t \tag{16}$$

where the parentheses denote activity. Equation (16) is usually written as

$$(\mathrm{H}^+)(\mathrm{A}^-)/(\mathrm{HA}) = K_a^t(\mathrm{S})^n = K_a^* \tag{17}$$

where it is understood that the ions are solvated and K_a^* includes the solvent term $(\mathrm{S})^n$. By taking logarithms of eqn. (17), we obtain

$$\lg K_a^* = \lg K_a^t + n \lg(\mathrm{S})$$

or

$$\mathrm{p}K_a^* = \mathrm{p}K_a^t - n \lg(\mathrm{S}) \tag{18}$$

TABLE 4

Calculation of "true ionization constant" pK_a^t for kojic acid and maltol

Dioxane (vol.%)	pK_a^* (found)		lg(S)		pK_a^t		pK_a (calc.)		pK_a (graph)	
	25°C	35°C	25°C	35°C	25°C	35°C	25°C	35°C	25°C	35°C
10	7.91	7.93	1.694	1.693	18.00	18.16	7.91	7.90	7.91	7.92
	8.81	8.69			19.23	19.55	8.81	8.67	8.87	8.69
20	8.26	8.26	1.635	1.634	18.00	18.13	8.26	8.26	8.26	8.26
	9.18	9.03			19.35	19.51	9.17	9.05	9.18	9.04
30	8.69	8.64	1.568	1.567	18.03	18.11	8.66	8.67	8.69	8.64
	9.59	9.46			19.35	19.52	9.59	9.48	9.58	9.46
40	9.06	9.11	1.490	1.488	17.94	18.10	9.12	9.14	9.10	9.11
	10.07	9.97			19.29	19.52	10.07	9.98	10.08	9.98
50	9.72	9.75	1.394	1.392	18.02	18.17	9.70	9.72	9.72	9.74
	10.71	10.61			19.38	19.54	10.67	10.60	10.70	10.60

First row, kojic acid, second row, maltol. Kojic acid: at 25°C, $n = 6.22 \pm 0.03$ (calc.); 6.22 (graph); p$K_a^t = 19.35 \pm 0.03$; 19.37 (graph); at 35°C, $n = 6.41 \pm 0.03$ (calc.); 6.40 (graph); p$K_a^t = 19.53 \pm 0.03$; 19.56 (graph). Maltol: at 25°C, $n = 5.96 \pm 0.04$ (calc.); 6.00 (graph); p$K_a^t = 18.00 \pm 0.02$; 18.10 (graph); at 35°C, $n = 6.04 \pm 0.03$ (calc.); 6.06 (graph); p$K_a^t = 18.13 \pm 0.03$; 18.27 (graph).

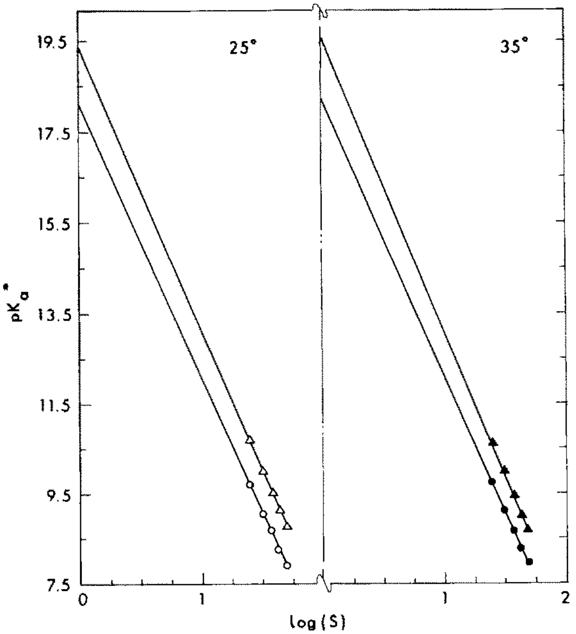

Fig. 3. Plots of pK_a^* vs. lg (S).

Since pK_a^* (defined in eqn. (18)) is the thermodynamic constant, pK_a^t thus evaluated should be a true constant independent of the media, provided that the assumptions for S and n are correct.

Finally the solvation number n can be computed from the following equation derived from eqn. (18)

$$n = \left[pK_{a_2}^* - pK_{a_1}^*\right] / \left[\lg(S_1) - \lg(S_2)\right]$$

The pK_a^* and n values listed in Table 4 were computed from the least-squares fitting of eqn. (18) and from the plot of pK_a^* (or TpK_a) against lg(S) (Fig. 3). Slight deviations of the graphical values from the experimental values can be seen. It is interesting that there is excellent agreement between the two sets of values of TpK_a calculated independently via eqns. (3) and (18).

Thermodynamic functions

The TpK_a values were determined with a precision of ± 0.02 to ± 0.03 and hence the error in $\Delta G^{\ominus}$ is estimated to be between ± 0.03 and ± 0.04 kcal mol^{-1}. The procedure followed here to evaluate $\Delta H^{\ominus}$ is subject to some error because the enthalpy change is small and values were not obtained at different temperatures which would have allowed the use of a more precise method [36]. However, the positive value of enthalpy obtained for maltol indicates that its dissociation is accompanied by the liberation of heat and the process is endothermic. The dissociation of kojic acid did not show any significant difference in dissociation constant on changing the temperature from 25 °C to 35 °C, and thus no value of $\Delta H^{\ominus}$ could be computed. Furthermore, the change in $\Delta H^{\ominus}$ with change in medium is relatively small and negligible within the experimental error. It is because of this that the slopes of the straight lines in the plots of TpK_a vs. n_2 (Fig. 2) are approximately the same at both the temperatures (Table 2), and the two lines are almost parallel. It is therefore justifiable to assume that $\Delta H^{\ominus}$ is independent of solvent media over the range investigated. On this basis, a fresh value of $\Delta H^{\ominus}$ was calculated. Numerically, this is equal to 42.06 times the difference in the intercepts of the parallel lines on the TpK_a axis (Fig. 2); this value is given in Table 4. The slightly decreasing trend in $\Delta S^{\ominus}$ with increasing dioxane content indicates that the dissociation process of the compounds is primarily an entropy controlled process. Since the dissociation diminishes, the entropy of the system also decreases. The same is favoured in higher dielectric solvents, i.e. at lower values of n_2. The fairly large negative values of entropy encountered here can be explained as being due to the dissociation of the ligand, since the sum total of the "bound" water molecules is more than the total number of water molecules originally accompanying the undissociated reagents. These facts are thus in accordance with the assumption that the decrease in the dissociation constant in dioxane–water mixtures is chiefly due to statistical effects. It is interesting to note that $\Delta G^{\ominus}$ becomes increasingly positive with an increase in dioxane content in the case of protonation processes such as $HA = H^+ + A^-$. This cannot be correlated with the change in water structure, i.e. the structure of water is diminished by the addition of dioxane or by an increase in basicity of the solvent; however, the results can be explained in terms of ionic solvation and a consequent change in entropy and enthalpy values. This also shows that the dielectric constant is not the only factor affecting the dissociation, the main factor being solute–solvent interactions [37,38].

Substituent effects

The presence of the electron-repelling $-CH_3$ group in the near vicinity of the ionizable –OH group in maltol produces the positive inductive effect which is responsible for the increased density of electrons at the ionizable site; this results in a lowering of the dissociation (or increase in $\mathrm{T}pK_a$) of this compound as compared with kojic acid.

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