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Note

THERMODYNAMIC ACID DISSOCIATION CONSTANTS OF PYRAZOLONES IN DIOXANE—WATER MIXTURES

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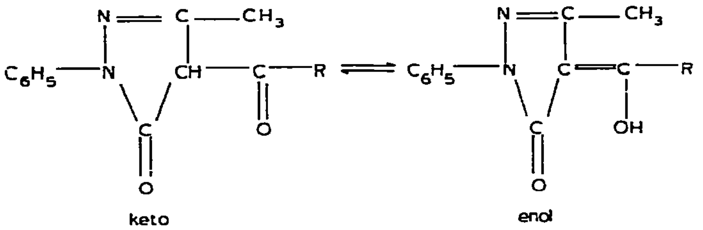
4-Aroylpyrazolones, represented by the general formula



where R = aroyl group, are versatile reagents in the field of analytical chemistry. Analytical applications of this family of compounds have been extensively examined in recent years [1—6]. A knowledge of their acid dissociation constants is of intrinsic importance in devising separative and analytical techniques. Moreover, these values are needed for evaluating the complexing ability of these ligands with metals. Additionally, the thermodynamic functions so derived greatly help in correlating as well as studying the metal—ligand reactions. No systematic investigation seems to have been made for determining the stabilities and structures of pyrazolones and their metal chelates. This prompted us to study in detail the proton dissociation reactions of 1-phenyl-3-methyl-4-benzoyl-pyrazolone-5 (PMBP) and its parent compound, namely 3-methyl-1-phenyl-pyrazolone-5 (MPP). An attempt has been made to arrive at theoretically comparable thermodynamic data.

The thermodynamic acid dissociation constant, TpK_a, of MPP in 20, 30 40 and 50 vol.% dioxane—water media at 25 and 35 ±0.01°C have been determined pH-metrically. Similar studies were also carried out with PMBP in 40, 45, 50, 60 and 70% (v/v) dioxane mixtures to assess the relative effect of benzoyl (C_6H_5CO—) substitution. No value for the thermodynamic equilibrium constant for enolization of both the reagents seems to have been reported so far.

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EXPERIMENTAL

"Reagent Grade" MPP was procured from B.D.H. PMBP was synthesized by the usual procedure reported in the literature [7] and recrystallized from chloroform to obtain yellow crystals of the enol form (m.p. 92°C; obtained: C = 73.10, H = 5.18; required for $C_{17}H_{14}N_2O_2$: C = 73.35, H = 5.03). All other chemicals were of A.R. or G.R. grade. An aqueous solution (10%) of tetramethylammonium hydroxide titrant was standardized against potassium hydrogen phthalate and diluted to 0.1 M, the proportions of dioxane and water being the same as used in preparing the titre solutions. B.D.H. Analar *p*-dioxane was purified as recommended [8].

pH-Metric titration

The titration procedure for determining TpK_a was essentially the same as that given by Albert and Serjeant [9]. Generally, 0.01 M solution of reagent was titrated without the addition of inert salt. Measurements of pH were made on a Beckmann Research pH meter which can be read to 0.002 unit of pH. The instrument was standardized against phthalate and borax buffers before and after each titration. Other details of the titration are given elsewhere [10].

Since these compounds are sparingly soluble in water, recourse to the use of mixed solvents had to be taken. These determinations have been restricted to 20, 30, 40, 45, 50, 60 and 70 vol.% dioxane—water mixtures. Determination of TpK_a has been accomplished by the pH titration method. The Van Uitert and Haas [11] relationship was used to obtain the hydrogen ion concentration from the values read on the pH meter (B)

$$-\log[H^+] = B + \log U_H^0 + \log Y_\pm \qquad (1)$$

Values of the correction factor, $\log U_H^0$, were obtained experimentally [12] and those of mean activity coefficients ($Y_\pm$) were computed by interpolation of the data given by Harned and Owen [13]. Here an assumption was made that the mean activity coefficients were the same on both the molal and molar scales.

The final expression for calculating the TpK_a of a monobasic acid, $HA \rightleftharpoons H^+ + A^-$, in aqueous dioxane medium is

$$TpK_a = B + \log U_H^0 + \log[(HA)/(A^-)] + \log 1/Y_\pm \qquad (2)$$

A correction for hydrolysis of the salt, which may be significant at the end of titration (i.e. at pH > 10) was applied by substituting $\log[(HA) + (OH^-)/(A^-) - (OH^-)]$ for $\log[(HA)/(A^-)]$ in eqn. (2). The standard free energy change, ΔG^0, was calculated from the equation

$$\Delta G^0 = 2.303\, RT\, TpK_a$$

and the standard enthalpy change was obtained by integration of the Van 't Hoff equation at two temperatures. The results are approximate because the heats of ionization vary with temperature, but for the small temperature interval used (10°C) ΔH^0 may be assumed constant [14]. The standard entropy change was calculated from ΔG^0 and ΔH^0.

RESULTS AND DISCUSSION

TpK_a values of MPP and PMBP in different aqueous dioxane media at 25 and 35°C are given in Tables 1 and 2, respectively. It is quite evident here that the TpK_a of these reagents in all media are consistently higher at 35°C as compared to 25°C. The average TpK_a generally falls within a spread of ±0.02 but not beyond ±0.03 in any case. The TpK_a values were plotted against mole fraction of dioxane (n_2) in Fig. 1 and the parameters derived from the empirical relations are detailed in Table 3. The empirical relationship between TpK_a and n_2 for both the pyrazolones was also computed by least squares analysis of the titration data (Table 3). Thermodynamic quantities ΔG^0, ΔH^0 and ΔS^0 for the acid dissociation were calculated following the temperature variation method (Table 4).

Titration of perchloric acid in the presence and absence of the pyrazolones proved that the protonation of these acids is negligible, as found by others [15]. Effect of dilution studied with slightly varying concentrations of these compounds was observed to be almost negligible, as the TpK_a values do not differ significantly.

Effect of temperature variation

The data given in Tables 1 and 2 show that the TpK_a values of both MPP and PMBP in all solvent media are higher at 35°C than at 25°C. Their temperature of maxima, $TpK_{a(max)}$, can be known if the TpK_a values are determined at several temperatures.

Effect of the medium

Considering the acid dissociation of pyrazolones involving a net increase of ions

$HA + H_2O \rightleftharpoons H_3O^+ + A^-$

a decrease in the dielectric constant of the reaction medium should obviously cause a decrease in the ionization constant (increase of TpK_a) of a weak acid dissolved in it. Data given in Tables 1 and 2 exactly support these conclusions. The relation between the dielectric constant of the medium and the ionization constants has been examined thoroughly in terms of primary and secondary medium effects [16,17].

According to Gurney [18] and others[19], the standard free energy change, ΔG^0, accompanying the proton transfer may be separated into electrostatic (ΔG^0_{el}) and chemical, i.e. specific solvent effect (ΔG^0_{chem}) parts. ΔG^0_{el} is conveniently estimated by the Born equation [20].

$$\Delta G^0_{el} = \frac{Ne^2}{2D}\left[\frac{1}{r^+} + \frac{1}{r^-}\right]$$

where r^+ and r^- denote the radii of the solvated ions, and for dilute solutions D represents the dielectric constant of the solvent [21,22]. Simplifying, we

TABLE 1

Thermodynamic ionization constants of MPP

Vol. % dioxane	Mole fraction of dioxane (n_2)	TpK_a at 25°C				TpK_a at 35°C			
		Found *	Calcd. **	Graphical	$\Delta \times 10^2$ (col. 3—col. 4)	Found *	Calcd. **	Graphical	$\Delta \times 10^2$ (col. 7 — col. 8)
1	2	3	4	5	6	7	8	9	10
20	0.050	7.62	7.58	7.61	+4	7.80	7.80	7.76	0
30	0.083	7.81	7.87	7.87	−6	8.01	8.09	8.02	−8
40	0.123	8.20	8.21	8.20	−1	8.32	8.45	8.35	−13
50	0.174	8.68	8.66	8.61	+2	8.81	8.91	8.76	−10
Total:					13				31
Ave. deviation:					3.25×10^{-2} ~0.03				7.75×10^{-2} ~0.08

* TpK_a obtained using all nine values of a set.

** Calculated values of TpK_a obtained by subjecting the experimental data to a least squares analysis.

TABLE 2

Thermodynamic ionization constants of PMBP

Vol. % dioxane	Mole fraction of dioxane (n_2)	TpK_a at 25°C				TpK_a at 35°C			
		Found *	Calcd. **	Graphical	$\Delta \times 10^2$ (col. 3—col. 4)	Found *	Calcd. **	Graphical	$\Delta \times 10^2$ (col. 7 — col. 8)
1	2	3	4	5	6	7	8	9	10
40	0.123	4.73	4.70	4.74	+3	4.99	4.93	5.00	+6
45	0.147	4.98	4.94	4.97	+4	5.14	5.18	5.23	−4
50	0.174	5.15	5.20	5.22	−5	5.46	5.47	5.48	−1
60	0.240	5.82	5.87	5.83	−5	6.10	6.15	6.10	−5
70	0.330	6.82	6.78	6.66	+4	7.12	7.09	6.94	+3
Total:					21				19
Ave. deviation					4.2×10^{-2} ~0.04				3.8×10^{-2} ~0.04

* TpK_a obtained using all nine values of a set.

** Calculated values of TpK_a obtained by subjecting the experimental data to a least squares analysis.

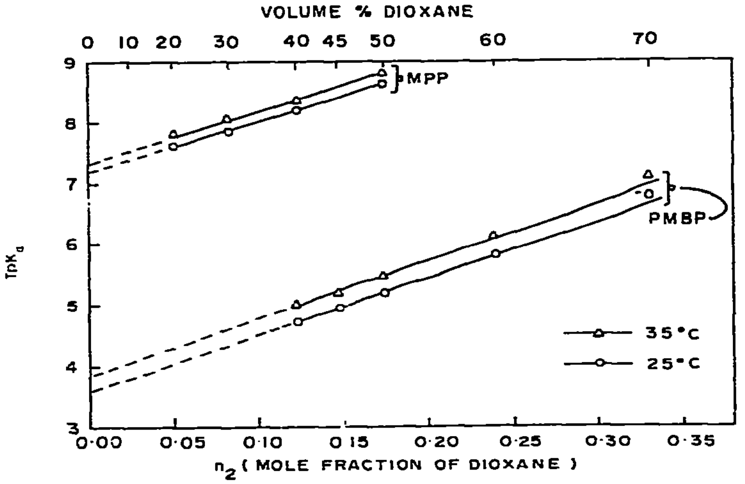

Fig. 1. Variation of TpK_a with mole fraction of dioxane (n_2).

obtain

$$pK_a = \frac{\Delta G^0_{\text{chem}}}{2.303RT} + \frac{Ne^2}{4.606RTD}\left[\frac{1}{r^+} + \frac{1}{r^-}\right]$$

Thus, a plot of pK_a vs. $1/D$ should yield a linear relationship and has been observed virtually to be the case in several instances [23,24], especially in the region of high dielectric constant ($D > 30$). At the same time, the departure from non-linearity is also equally frequent [10,25].

The TpK_a values of both MPP and PMBP increase as the proportion of the organic component in the medium increases. It is found that the plot of TpK_a against $1/D$ is linear only at the low percentage of dioxane but non-linear at higher concentrations (Fig. 2). Evidently this suggests that chemical factors (non-electrostatic) also significantly influence the acid dissociation of pyrazolones in dioxane—water media.

TABLE 3

Empirical relation between TpK_a and n_2 of dioxane

Pyrazolone	Temp. (°C)	$TpK_a = mn_2 + C$					
		Graphical		Least squares			
		m	*C*	*m*	*C*	*r* *	*b* *
MPP	25	8.13	7.20	8.71	7.14	+0.995	8.72
	35	8.14	7.35	8.19	7.35	+0.996	8.19
PMBP	25	9.29	3.60	10.06	3.46	+0.998	10.05
	35	9.38	3.85	10.41	3.65	+0.998	10.40

* *r* and *b* refer to the correlation coefficient and regression coefficient (actual slope), respectively.

TABLE 4

Free energy, enthalpy and entropy changes for ionization of pyrazolones *

Quantity **	Vol. % dioxane						
	20	30	40	45	50	60	70
MPP							
ΔG^0	10.41	10.66	11.18		11.85		
$-\Delta H^0 = 6.53$	11.00	11.29	11.74		12.43		
$-\Delta S^0$	56.78	57.64	59.39		61.63		
	56.89	57.81	59.25		61.50		
PMBP							
ΔG^0			6.45	6.79	7.02	7.95	9.30
$-\Delta H^0 = 11.89$			7.05	7.26	7.70	8.60	10.05
$-\Delta S^0$			61.50	62.64	63.41	66.50	71.05
			61.42	62.11	63.55	66.46	71.16

* First and second row values at 25 and 35°C, respectively.
** ΔG^0 and ΔH^0 in kcal mole^{-1} ; ΔS^0 in cal mole^{-1} K^{-1}.

On examining the variation of $T\text{p}K_a$ of both the ligands with mole fraction of dioxane, the difference in values in aqueous medium ($n_2 = 0$) and 70% aqueous dioxane ($n_2 = 0.33$) is of considerable magnitude, being around 2—3 $T\text{p}K_a$ units. When the $T\text{p}K_a$ values of MPP and PMBP are plotted against n_2, linear relationships are obtained (Fig. 1) with slopes equivalent to 8.5—10 which are as expected for weak acids [26]. Generally, maximum deviation in the experimental values of $T\text{p}K_a$ for these compounds from straight-line plot is of the order of 0.05 or nearly 0.5% in $T\text{p}K_a$. $T\text{p}K_a$ vs. n_2 data, subjected to least squares analysis, also confirm linear proportionality.

Furthermore, experimental data on $T\text{p}K_a$ measurements were analyzed

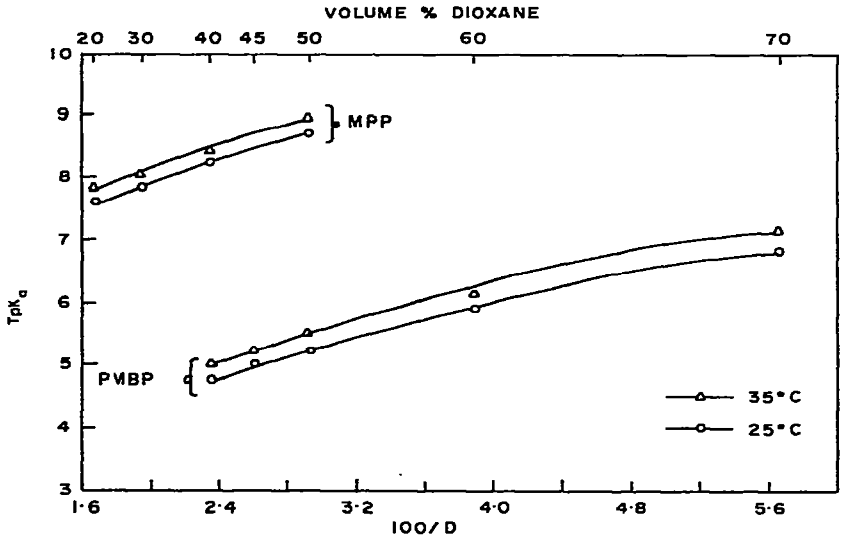

Fig. 2. Variation of $T\text{p}K_a$ with the dielectric constant of the medium.

statistically to see the goodness of fit by calculating the correlation coefficient, r, defined by

$$r = \Sigma(X - \bar{X})(Y - \bar{Y})/[\Sigma(X - \bar{X})^2 \cdot \Sigma(Y - \bar{Y})^2]^{1/2}$$

where $\bar{X}$ and $\bar{Y}$ are the mean values of $X(T\text{p}K_a)$ and $Y(n_2)$, respectively. A perfect linear relationship is undoubtedly shown between the two variables if r is equal to +1.0 [27]. Also, the regression coefficient or actual slope of the lines, b is easily deduced by

$$b = \Sigma(X - \bar{X})(Y - \bar{Y})/\Sigma(X - \bar{X})^2$$

Since the value of r is nearly +1.0 at 25 and 35°C for both MPP and PMBP Table 3), a striaght-line relationship between $T\text{p}K_a$ and n_2 is quite probable. This is in accordance with that noted with several carboxylic acids [13] as well as a number of β-diketones investigated in dioxane—water mixtures [10, 28—30]. Also, such behaviour is encountered in some other hydroorganic solvents, e.g. acetic, propionic, butyric and benzoic acids in methanol—water [31] and dimedone in ethanol—water systems [32].

Thermodynamic parameters for ionic equilibria

Values of $T\text{p}K_a$ have been determined with a precision of ±0.02 to ±0.03 and hence the error in ΔG^0 is estimated to be between ±0.03 and ±0.04 kcal mole^{-1}. The procedure employed here to evaluate ΔH^0 is subject to some error because the enthalpy change is small and $T\text{p}K_a$ values were not determined at several temperatures which would have allowed use of a more precise method [33]. However, the negative value of ΔH^0 found in dioxane—water solutions for both the pyrazolones indicates that their ionization at temperatures up to 35°C is exothermic. This may be attributed to the lower $T\text{p}K_a$ values of pyrazolones. This is in contrast to the behaviour observed with other β-diketones such as acetylacetone and 3-methylacetylacetone where the ΔH^0 for acid dissociation was observed to be positive [10]. Further, the change in ΔH^0 with change in medium is relatively small and within experimental error. For this reason, the plots of $T\text{p}K_a$ vs. n_2 had practically the same slopes at both the temperatures (Table 3). In other words, the two lines are parallel.

It is therefore justifiable to assume that ΔH^0 is independent of solvent composition over the range investigated. On this basis, a fresh value of ΔH^0 for MPP and PMBP was calculated. Numerically, this is equal to 42.06-times the difference in the intercepts of the parallel lines on the $T\text{p}K_a$ axis (Fig. 1) and it is these values that are given in Table 4.

Values of ΔS^0 at different percentages of dioxane are observed to be practically the same for MPP or PMBP, thereby indicating that it is independent of solvent composition. This is in agreement with our earlier observation, wherein the large negative value of entropy has been explained as arising due to ionization of the ligand since the sum total of the number of water molecules "bound" is more than the water molecules originally accompanying the undissociated pyrazolones.

Effect of substitution

The acid dissociation of substituted pyrazolone depends upon the nature of the substituent group attached to the functional —C = O group. TpK_a values of PMBP and its parent compound MPP determined in several dioxane—water mixtures show that TpK_a of the former is lower by several orders of magnitude as compared to the latter. This is what one would expect, as the introduction of the electronegative aroyl group ($C_6H_5C=O$—) enhances the acidic character of the hydroxyl group.

Pyrazolones in solution usually exist as equilibrium mixtures of the keto-enol forms. Therefore, TpK_a values presented in Tables 1 and 2 should in principle refer to both the processes of enolization and ionization of the pyrazolones [34].

The results of this investigation reveal that both MPP and PMBP are weak acids with pK_a values of the order of 7 and 3.5, respectively.

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