

Potentiometric Determination of Ionisation Constants of 3,5-Disubstituted Isoxazoles

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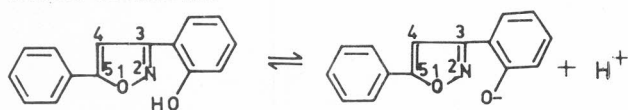
The ionisation constants of 3-(2'-hydroxyphenyl)-5-phenylisoxazole (OHPPI), 3-(2'-hydroxyphenyl)-5-(*p*-methoxyphenyl)isoxazole, (OHPMPI), 3-(2'-hydroxyphenyl)-5-(*p*-chlorophenyl)isoxazole (OHPCPI), 3-(2'-hydroxy-5'-chlorophenyl)-5-phenylisoxazole (OHCPI), and 3-(2'-hydroxy-5'-methylphenyl)-5-phenylisoxazole (OHMPPI) have been evaluated potentiometrically at different temperatures, ionic strengths and in solutions of varying dielectric constants. The order of ionisation constants is: OHMPPI > OHPMPI > OHPPI > OHPCPI > OHCPI.

In continuation of our earlier work^{1,2}, we report in this note the ionisation constants of 3-(2'-hydroxyphenyl)-5-phenylisoxazole (OHPPI), 3-(2'-hydroxyphenyl)-5-(*p*-chlorophenyl)isoxazole (OHPCPI), 3-(2'-hydroxyphenyl)-5-(*p*-methoxyphenyl)isoxazole (OHPMPI), 3-(2'-hydroxy-5'-chlorophenyl)-5-phenylisoxazole (OHCPI) and 3-(2'-hydroxy-5'-methylphenyl)-5-phenylisoxazole (OHMPPI), determined potentiometrically at different temperatures, ionic strengths and in solutions of varying dielectric constants.

The ligands OHPPI, OHPMPI, OHPCPI, OHCPI and OHMPPI were prepared by the literature method³ and recrystallised from ethanol. The purities of the compounds were checked by TLC and melting point determinations. All the solvents used were of AR grade and were fractionally distilled before use.

The experimental method consists of *pH*-metric titrations of (i) nitric acid and (ii) nitric acid + ligand against sodium hydroxide. Appropriate quantities of KNO₃ were added to maintain the required ionic strength. An Elico digital *pH*-meter model LI-120 with glass and calomel electrodes (accuracy ± 0.01 unit) was used for *pH*-measurements. Toshniwal high precision constant temperature bath with an accuracy of $\pm 0.1^\circ\text{C}$ was used to maintain the experimental temperature. The *pH*-values in all aquo-organic mixtures were corrected using the method of Van Uitert and Haas⁴. Volume correction was applied by the method suggested by Rao and Mathur⁵.

The ligand 3-(*o*-hydroxyphenyl)-5-phenylisoxazole ionises as follows:



The ionisation constants (pK_a) were calculated using Irving and Rossotti method⁶. The ionisation constants of these ligands were obtained at $\bar{n}_H=0.5$ and point-wise calculations. The average ionisation constant values of different isoxazoles are, OHCPI (9.40); OHPCPI (9.80); OHPPI (10.25); OHPMPI (10.30); OHMPPI (10.70) and *ortho*-hydroxyacetophenone oxime (11.86). The uncertainty in the pK_a values is of the order of ± 0.02 .

The pK_a values of isoxazoles follow the order: OHMPPI > OHPMPI > OHPPI > OHPCPI > OHCPI. The lower value of OHCPI as compared to that of OHPPI is due to the presence of electron withdrawing group e.g., -Cl, at *para*-position to the hydroxyl group in the 3-phenyl moiety of the former. The increase in pK_a value from 10.25 to 10.70 in case of OHMPPI is ascribed to the inductive effect of methyl group. The presence of Cl in the 5-position causes the electron deficiency on the nitrogen atom thereby facilitating the hydrogen bond present between N of the isoxazole moiety and H of the OH group to become weaker as compared to that in the unsubstituted compound. This helps in easy liberation of protons in solution thereby decreasing the pK_a value of the compound from 10.25 to 9.80, while -OCH₃, being an electron repelling group, enhances the electron density on the nitrogen atom. This results in strong hydrogen bonding thereby increasing the pK_a value of the compound to 10.30.

Isoxazoles having N and O as donor atoms are similar to oximes and form six-membered rings. Therefore, an attempt has been made to compare the pK_a values of isoxazoles with those of oximes. The decrease in acidity of isoxazoles as compared to that of oximes may be due to lower electron density on the nitrogen of isoxazole ring. The oxygen in isoxazole makes a lone pair available to aromatic sextet of the ring and thus acquires a partial positive charge. The isoxazole ring nitrogen, which is adjacent to this electron deficient oxygen, in turn, is partially depleted of its electrons. This phenomenon results in weaker hydrogen bonding in isoxazoles as compared to that in oximes.

Effect of ionic strength on the ionisation constant

The ionisation constants of OHPPI and OHPCPI were determined at different ionic strengths in 75% (v/v) methanol-water mixture at 35°C and the values are presented in Table I. Brønsted⁷ related the thermodynamic ionisation constant, (pK_a^0) with the ionisation constant (pK_a) in a given solvent at a given

Table 1—Ionisation Constants and Thermodynamic Parameters of Substituted 3-(*o*-Hydroxyphenyl)-5-phenylisoxazole at Different Ionic Strengths

Ligand (medium)	pK_a at $\mu =$					ΔG kJ mol ⁻¹	ΔH kJ mol ⁻¹	ΔS JK ⁻¹ mol ⁻¹
	0.00	0.02	0.05	0.07	0.10			
OHPPI (75% methanol-water)	10.84	10.58	10.40	10.35	10.25	60.67	45.81	-43.09
OHPCPI (75% methanol-water)	10.22	10.00	9.90	9.85	9.80	57.74	27.19	-99.16
OHPCPI (50% methanol-water)	10.77	10.50	10.30	10.25	10.09	—	—	—
OHMPPI (75% methanol-water)	—	—	—	—	—	60.67	58.78	-6.28

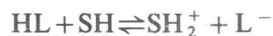
temperature with the ionic strength (μ) of the medium by the equation:

$$pK_a = pK_a^\circ - A\Delta Z^2 \sqrt{\mu}$$

where A is a constant and ΔZ^2 is the difference of the squares of the charges of the products and reactants. A plot of pK_a versus $\sqrt{\mu}$ was linear with a slope equal to $A\Delta Z^2$ and the intercept equal to pK_a° . The value of ΔZ^2 was obtained and is found to be 1.80 (calc. 2.00). To improve the ΔZ^2 value, modified form of Debye-Hückel equation⁸ was used. The value of ΔZ^2 thus obtained is 2.10 which is nearer to the calculated value (2.00).

Effect of temperature on ionisation constant

The thermodynamic parameters, ΔH , ΔG and ΔS were calculated by determining the ionisation constants at different temperatures in the range 25-45°C in 75% (v/v) methanol-water mixture and at constant ionic strength using Vant Hoff's method⁹. The thermodynamic parameters obtained for the presently studied isoxazoles are listed in Table 1. The accuracy was found to be ± 2.5 kJ mol⁻¹ in ΔH and ΔG values and ± 5.0 JK⁻¹ mol⁻¹ in ΔS values. The negative entropy values obtained in the present system can be explained as follows:



$$\begin{aligned} \Delta S &= (S_{SH_2^+} + S_{L^-}) - (S_{HL} + S_{SH}) + \Delta S_{\text{sol-sol-int.}} \\ &= (S_{SH_2^+} - S_{SH}) + (S_{L^-} - S_{HL}) + \Delta S_{\text{sol-sol-int.}} \\ &= X + Y + \Delta S_{\text{sol-sol-int.}} \end{aligned}$$

In the above equations, the first term is negative since SH_2^+ ion is highly solvated resulting in the decrease of

entropy with respect to SH. Similarly, the second term is also negative leading to overall negative values. $\Delta S_{(\text{sol-sol-int.})}$ will depend on the mol fraction of the organic component and its ability to stabilise or destabilise the structure of water molecules. Similar observations were earlier made for chalcones¹⁰ and phenols¹¹.

Effect of dielectric constant on the ionisation constant

The effect of dielectric constant on the ionisation process of OHPPI was studied by determining the pK_a values in solutions of different dielectric constants and different proportions of methanol-water, acetone-water and dioxane-water mixtures and the values were compared with the literature values. The validity of Born's, equation was verified by plotting pK_a versus $1/D$.

References

- Vithal Rao D, Krishnamoorti A & Lingaiah P, *Indian J Chem*, **16A** (1978) 722.
- Vithal Rao D & Lingaiah P, *J Indian chem Soc*, **LVI** (1979) 1251.
- Murthy A K, Rao K S R K M & Rao N V S, *J Indian chem Soc*, **49** (1972) 1025.
- Van Uitert L G & Haas L G, *J Am chem Soc*, **75** (1953) 451.
- Rao Balachandra U & Mathur H B, *Indian J Chem*, **7** (1969) 1234.
- Irving H M & Rossotti H S, *J chem Soc*, (1954) 2904.
- Amis E S, *Solvent effects on reaction sites and mechanism* (Academic Press, New York), 1966, p. 24.
- Robinson R A & Stokes R M, *Electrolytical solutions* (Butterworths, London), **229** (1955) 230.
- Botton P D, *J chem Educ*, **47** (1970) 638.
- Jagannadha Swamy S & Lingaiah P, *Indian J Chem*, **21** (1982) 209.
- Hazra D K & Lahiri S C, *Indian J Chem*, **10** (1972) 753.