# Partition Coefficients of Some Heterocyclic N-Bases and N-Oxides Between Aqueous and Benzene Phases and pKa Values of N-Oxides Conjugate Acids

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**The distribution ratios of some heterocyclic N-oxides and N-bases between aqueous and benzene phases have been determined. Such ratios appear to be independent of the total base concentration over the range investigated. The partition of an N-oxide into benzene is about 1000 times less than its analogous N-base. The pKa values of the heterocyclic N-oxides conjugate acids have been determined by the partition technique.**

The partition coefficients (*P*) between aqueous and organic phases and the acid dissociation constants (expressed as p*K*a values) are characteristic and very valuable constants in the study of the solution chemistry of organic ligands and of their metal complexes. Such data are of special importance when studying the adducts of neutral metal chelates with such organic bases by the solvent extraction technique. The role of the formation of such adducts with heterocyclic N-bases *(1, 4)* or with N-oxides *(2)* in the synergistic enhancement of the extraction coefficient of metal ions from aqueous solutions has been the subject of many studies. Scattered values of *P* and p*K*a of the heterocyclic N-bases are available in the literature. However, values of the partition coefficients of the heterocyclic N-oxides are not reported and no systematic work on the determination of the p*K*a values of methyl-substituted pyridine N-oxides is reported and the values reported by different authors are inconsistent. The object of the present investigation is to determine p*K*a values and the partition coefficients of some heterocyclic N-oxides and of their analogous N-bases. The N-oxides investigated are pyridine N-oxide (PO), 2-methyl (2MPO), 3-methyl (3MPO), 4-methyl (4MPO), and 2,6-dimethylpyridine N-oxide (2,6DMPO). The N-bases investigated are similarly pyridine (Py), 2-methyl (2MP), 3-methyl (3MP), 4-methyl (4MP), and 2,6-dimethylpyridine (2,6DMP).

## Experimental

***Determination of distribution ratios of N-oxides.*** 4-Methylpyridine N-oxide was purified by recrystallization from benzene. All other N-oxides were purified by distillation under vacuum immediately before use. Analytical reagent benzene was used without further purification. Stock solutions were prepared by weighing and other solutions were prepared by dilution. The ultraviolet spectra of these bases in benzene were determined, after appropriate dilution, using the Unicam S.P.500 spectrophotometer and matched silica cells. Maximum absorption occurred at wavelengths ($\lambda_{max}$) in the region 271-281 nm, and Beer's law was checked in each case and the molar extinction coefficient ($\epsilon_{max}$) was thereby calculated. Ten milliliters of the benzene solution of the N-oxide was equilibrated with 10 ml of $10^{-4}M$ HCl solution (preequilibrated with benzene) by shaking the two phases for 2 hr in a glass-stoppered centrifuge tube of ca. 30-ml capacity at room temperature (25° ± 1°C). This aqueous phase was chosen since in such a medium the N-oxides are unprotonated and the electrolyte concentration is very small. After equilibration the two phases were separated by centrifugation, and an aliquot of the benzene phase was withdrawn and the absorbance was determined, after the necessary dilution, at the predetermined $\lambda_{max}$. Thus from the previously determined $\epsilon_{max}$, the total concentration of the base in the benzene phase was calculated. Its concentration in the aqueous phase was then calculated by difference and the distribution ratio was calculated.

***Determination of distribution ratio of N-bases.*** A 0.1*M* solution of the base in benzene (preequilibrated with 0.1*M* aqueous NaOH) was prepared by weighing, and from it a solution of 0.04*M* was prepared by dilution. Ten milliliters of the benzene solution of the base was equilibrated in the same way discussed above with 10 ml of the 0.1*M* NaOH solution (preequilibrated with benzene). Five milliliters of the aqueous phase was then withdrawn and diluted with 5 ml of 1*M* HCl. It was then shaken with 10 ml of chloroform to free it from any dissolved benzene. This process was repeated three times and then the absorbance of the aqueous phase at the predetermined $\lambda_{max}$ was determined after the appropriate dilution. The total concentration of the base in the aqueous phase was calculated using its value of $\epsilon_{max}$ previously determined for solutions of known concentrations of the base in an equivolume mixture of 0.1*M* NaOH and 1*M* HCl. Each solution was washed three times with chloroform prior to absorbance measurements. The concentration of the base in the benzene phase was then calculated by difference.

## Results and Discussion

The stoichiometric distribution ratio ($D = \Sigma[B]_{org}/\Sigma[B]_{aq}$) of each of the heterocyclic N-oxides was determined between benzene and $10^{-4}M$ HCl solution as a function of the initial total concentration, $[B]^0_{tot}$, of the base in benzene. Each determination was repeated at least three times and reproducibility was better than 2%. The results are given in Table I together with the values of $\lambda_{max}$ and $\epsilon_{max}$ for these bases in benzene preequilibrated with $10^{-4}M$ HCl solution. For each N-oxide, the variation of the distribution ratio, *D*, with $[B]^0_{tot}$ does not show any trend and such variation could easily be attributed to experimental errors. These results seem to indicate that Nernst distribution law is applicable over this range of $[B]^0_{tot}$. The average distribution ratio ($\bar{D}$) for each N-oxide has thus been calculated. If the ratio between the activity coefficients of the N-oxide in the organic and aqueous phases can be assumed to be unity within this range of $[B]^0_{tot}$ then the average distribution ratio ($\bar{D}$) can be equated to the thermodynamic partition coefficient (*P*).

The stoichiometric distribution ratio (*D*) of each of the heterocyclic N-bases has been determined between benzene and 0.1*M* NaOH at a fixed $[B]^0_{tot}$ value of 0.04*M*. The results are given in Table II together with the values of $\lambda_{max}$ and $\epsilon_{max}$ of these bases in an equivolume mixture of 0.1*M* NaOH and 1*M* HCl solutions.

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**Table I. Distribution Ratios of Heterocyclic N-Oxides Between $10^{-4}M$ HCl Aqueous Phase and Benzene at 25° ± 1°C**

| Base | $\lambda_{max}$ (nm) in benzene | $\xi_{max}$ | $[B]^0_{tot}$, $M$ | $D \times 10^3$ | $\bar{D}(P)$ |
|---|---|---|---|---|---|
| PO | 279 | 14,200 ± 200 | 0.016 | 2.52 | $(2.57 \pm 0.08) \times 10^{-3}$ |
| | | | 0.048 | 2.65 | |
| | | | 0.080 | 2.66 | |
| | | | 0.160 | 2.51 | |
| | | | 0.240 | 2.49 | |
| 2MPO | 278 | 11,450 ± 150 | 0.0016 | 14.2 | $(14.6 \pm 0.3) \times 10^{-3}$ |
| | | | 0.0032 | 14.6 | |
| | | | 0.0080 | 14.8 | |
| | | | 0.0400 | 14.8 | |
| 3MPO | 280 | 13,030 ± 120 | 0.008 | 6.76 | $(6.77 \pm 0.17) \times 10^{-3}$ |
| | | | 0.010 | 6.96 | |
| | | | 0.040 | 6.83 | |
| | | | 0.080 | 6.54 | |
| 4MPO | 281 | 14,900 ± 200 | 0.004 | 3.39 | $(3.35 \pm 0.12) \times 10^{-3}$ |
| | | | 0.008 | 3.50 | |
| | | | 0.010 | 3.39 | |
| | | | 0.040 | 3.18 | |
| | | | 0.080 | 3.44 | |
| | | | 0.100 | 3.19 | |
| 2,6DMPO | 277 | 8,500 ± 140 | 0.001 | 99.7 | $(100 \pm 3) \times 10^{-3}$ |
| | | | 0.004 | 100.0 | |
| | | | 0.008 | 101.0 | |
| | | | 0.080 | 99.0 | |

In general, the partition coefficients of the pyridine N-oxides are about 1000 times less than those of their analogous pyridine N-bases. This could be attributed to the fact that the N-oxide oxygen atom readily forms hydrogen bonds and that pyridine N-oxides are strongly hydrogen bonded in aqueous solutions. This will no doubt increase the preferential partition of these bases toward the aqueous phase. The partition results also indicate that both basicity of the ligand and the number and position of the methyl substituents play an important role in ascertaining the value of the partition coefficient of the base.

For the determination of the p*K*a values of the N-oxide conjugate acids, the following method was used. The distribution ratio ($D$) of the N-oxide between an aqueous HCl solution of a known initial total concentration, $[H^+]^0_{tot}$, and benzene (preequilibrated with the same aqueous phase) was determined as a function of $[H^+]^0_{tot}$ in the range 0.01–0.15$M$. At least 10 measurements were made within this range. The initial total concentration, $[B]^0_{tot}$, of the N-oxide was kept constant throughout each series of determination and at a value in the range 0.008–0.03$M$ depending on the particular N-oxide. The stoichiometric distribution coefficient, $D$, thus determined is given by

$$D = \frac{[B]_{org}}{[B] + [HB^+]} \qquad (1)$$

or

$$D = \frac{P}{1 + [H^+]/Ka} \qquad (2)$$

where $P$ is the partition coefficient of the N-oxide, $[H^+]$ is the free hydrogen ion concentration in the aqueous phase after extraction, and

$$Ka = [H^+][B]/[HB^+] \qquad (3)$$

Also

$$[H^+]^0_{tot} = [H^+] + [HB^+] \qquad (4)$$

and

$$[B]^0_{tot} = [B]_{org} + [B] + [HB^+] \qquad (5)$$

From Equations 1, 3, 4, and 5 we obtain

$$[H^+]^0_{tot} = [H^+] + \frac{[B]^0_{tot}\,[H^+]}{(1 + D)(Ka + [H^+])} \qquad (6)$$

Equations 2 and 6 were solved for each set of data using a computer program and the iteration technique. Thus values of $P$ and $Ka$ were calculated (Table III). As can be seen from the standard deviation in the calculated values of p*K*a, the fit of the experimental data to Equation 2 is excellent. The values of the partition coefficients ($P$) thus calculated are in good agreement with those determined separately and as given in Table I which indicate that the partition coefficient of the N-oxide does not vary appreciably with the ionic strength of the aqueous phase in the range $\mu$ = 0.01–0.15. This is a further indication

**Table II. Distribution Ratios of Heterocyclic N-Bases Between 0.1$M$ NaOH Aqueous Phase and Benzene at 25° ± 1°C $[B]^0_{tot} = 0.04M$**

| Base | $\lambda_{max}$ (nm)[a] | $\xi_{max}$[a] | $D$ | p*K*a[b] |
|---|---|---|---|---|
| Py | 255 | 5887 ± 50 | 3.5 | 5.44 |
| 2MP | 262 | 6963 ± 50 | 9.1 | 6.21 |
| 3MP | 262 | 5710 ± 50 | 11.9 | 5.88 |
| 4MP | 252 | 7093 ± 50 | 14.5 | 6.24 |
| 2,4DMP | 259 | 5746 ± 50 | 22.7 | — |
| 2,6DMP | 270 | 8493 ± 50 | 22.3 | 6.89 |

[a] Determined in 0.45$M$ HCl and after washing its aqueous solution with chloroform. [b] Ref. 7.

Table III. Acid Dissociation Constants (p*K*a) of Heterocyclic N-Oxides Conjugate Acids at 25° ± 1°C

| Base | $[B]^0_{tot}$, *M* | p*K*a Found | p*K*a Reported | *P* |
|---|---|---|---|---|
| PO | 0.04 | 0.55 ± 0.01 | 0.79[a], 0.56[b] | $2.4 \times 10^{-3}$ |
| 2MPO | 0.04 | 1.10 ± 0.02 | 1.02[c] | $14.3 \times 10^{-3}$ |
| 3MPO | 0.04 | 1.00 ± 0.01 | 1.08[a] | $6.7 \times 10^{-3}$ |
| 4MPO | 0.04 | 1.32 ± 0.02 | 1.29[a] | $3.3 \times 10^{-3}$ |
| 2,6DMPO | 0.008 | 1.41 ± 0.01 | 1.44[c] | $100.0 \times 10^{-3}$ |

[a] Ref. 5. [b] Ref. 6. [c] Ref. 4.

that the average distribution ratios ($\bar{D}$) given in Table I may be equated to the thermodynamic partition coefficients (*P*).

The p*K*a values of the pyridine N-oxides thus obtained are compared in Table II with the reported values.

The results obtained show that the p*K*a values of the pyridine N-oxides follow the same order as those of the corresponding pyridines—i.e., PO < 3MPO < 2MPO < 4MPO < 2,6DMPO.

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Received for review July 25, 1972. Accepted November 20, 1972.

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# Enthalpy and Entropy of Dilution of Tetraethanolammonium Bromide

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**The excess enthalpy of aqueous solutions of tetraethanolammonium bromide has been measured from 0.025–3.0*m* at 25°C. The excess entropy has been calculated from the enthalpy and Gibbs free energy. Unlike tetrapropylammonium bromide, tetraethanolammonium bromide has low values of excess enthalpy and entropy.**

A large body of evidence has accumulated indicating that the interaction of the surface of a molecule with a solvent has a profound influence on the thermodynamic and kinetic properties of solutions *(4–6, 17–19)*. In spite of a large amount of work in the area, we still cannot predict the way in which a change in the surface properties of a molecule affects its solution properties. Recent advances in statistical mechanics allow the calculation of the properties of a solution up to moderate concentrations (~1*m*) from a knowledge of the law of force between two solute molecules in an infinitely dilute solution *(8)*.

Recently, Ramanathan and Friedman *(15)* have reversed this procedure to find out what laws of force are needed to explain experimental data. In this way, quantitative information on the way solute solvation influences the attractive and repulsive forces between solutes is derived. Measurements on tetraethanolammonium bromide [tetrakis(2-hydroxyethyl)ammonium bromide] are of particular interest because previous results on the free energy *(19)*, volumes *(19)*, conductance *(6)*, viscosity *(5)*, partial molal heat capacity *(19)*, volume of mixing with other electrolytes *(18)*, salting out coefficients *(17)*, and heats of transfer *(19)* have indicated that the substitution of a terminal hydroxy group for a terminal methyl group in the tetrapropylammonium ion results in a drastic change of properties. The present data show how this change in the surface of the molecule affects the enthalpy and entropy of aqueous solutions.

## Experimental

Since the experimental details have been described *(3)*, only a brief description is given here.

The tetraethanolammonium bromide was prepared by the method of Wen and Saito *(19)* as modified by Evans et al. *(6)*. A mixture of 248 grams of triethanolamine (1.6 moles), 100 grams of 2-bromoethanol (0.8 mole), and 300 ml of methanol was refluxed for 24 hr. After titration with concentrated aqueous hydrobromic acid to pH 3, the mixture was cooled and the triethanolamine hydrobromide removed by filtration. The filtrate was evaporated. The resulting oil was cooled slowly with occasional stirring until it crystallized and the crystals of tetraethanolammonium bromide were removed by filtration.

A saturated solution of tetraethanolammonium bromide in methanol was cooled to −20°C, and the much less soluble crystals of the hydrobromide were filtered off. This was done two times. The filtrate was evaporated to dryness.

The tetraethanolammonium bromide was first precipitated three times from warm methanol by adding fourfold excess of ethanol and cooling. Then the sample was recrystallized four times from ethanol. Since tetraethanolammonium bromide is hygroscopic, all recrystallizations were performed in a dry box. The crystals were dried in an Abderhalden drying pistol at 56°C for 24 hr.

The solutions of tetraethanolammonium bromide were prepared in a dry box. Each sample was weighed out separately and used the same day. There was no appreciable weight gain of the solid tetraethanolammonium bromide in the dry box.

## Analysis

The tetraethanolammonium bromide sample was analyzed for bromide and triethanolamine hydrobromide. The bromide ion was determined gravimetrically by precipitation as AgBr. The results were 29.10 and 29.09% bromide. The calculated value was 29.15% bromide.

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