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HEATS OF SOLUTION AND TAUTOMERIC EQUILIBRIUM CONSTANTS. THE 2-PYRIDONE: 2-HYDROXYPYRIDINE EQUILIBRIUM IN NON-AQUEOUS MEDIA[1]

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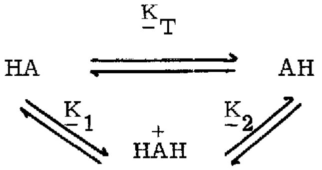
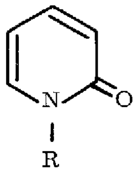
We wish to point out that heat of solution data provide a useful method for estimating $\Delta\underline{H}^{o}$ for tautomeric processes in non-aqueous solvents, and we illustrate the approach by its application to the 2-pyridone: 2-hydroxypyridine equilibrium ($\underline{1} \rightleftharpoons \underline{2}$).

Scheme 1.

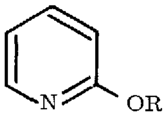


$$\underline{K}_T = \underline{K}_1\underline{K}_2$$

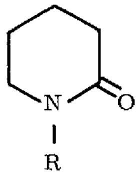
Protomeric equilibrium constants, $\underline{K}_T$, can be determined quantitatively in the aqueous phase using the basicity method, Scheme 1.[2] $\underline{K}_1$ and $\underline{K}_2$ are evaluated from basicity measurements of 'fixed' model compounds which normally are alkyl derivatives of the prototropic species. Because of difficulties inherent in obtaining $p\underline{K}_a$ data for compounds in non-aqueous solutions, $\underline{K}_T$ values in these media have usually been determined by UV spectroscopic comparison of mobile and model systems.[2] However the UV method is limited to those equilibria which contain spectroscopically detectable concentrations of each tautomer.



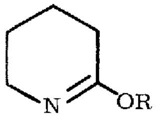
$\underline{1}$ R = H
$\underline{3}$ R = Me



$\underline{2}$ R = H
$\underline{4}$ R = Me



$\underline{5}$ R = H
$\underline{7}$ R = Me



$\underline{6}$ R = H
$\underline{8}$ R = Me

$$\Delta \underline{H}^{o}_{\underline{1} \rightleftharpoons \underline{2}(H_2O)} = \Delta \underline{H}^{o}_{\underline{3}(\mathrm{protonation})} - \Delta \underline{H}^{o}_{\underline{4}(\mathrm{protonation})} \ldots\ldots\ldots\ldots\ldots\ldots \quad (1)$$

$$\Delta \underline{H}^{o}_{\underline{1} \rightleftharpoons \underline{2}(\mathrm{solv.})} = \Delta \underline{H}^{o}_{\underline{1} \rightleftharpoons \underline{2}(H_2O)} - \Delta\Delta \underline{H}^{o}_{\underline{3}(\mathrm{solv.} - H_2O)} + \Delta\Delta \underline{H}^{o}_{\underline{4}(\mathrm{solv.} - H_2O)} \ldots \quad (2)$$

From Scheme 1 it follows that the enthalpy of the equilibrium $\underline{1} \rightleftharpoons \underline{2}$ in water, $\Delta \underline{H}^{o}_{\underline{1} \rightleftharpoons \underline{2}(H_2O)}$ can be estimated by eqn. (1) in which $\Delta \underline{H}^{o}_{(\mathrm{protonation})}$ refers to heat of protonation of the model (numbered) in aqueous solution. Inherent in this approach is the assumption that differential solvation of the cations of $\underline{3}$ and $\underline{4}$ is compensated for by differences in solvation between $\underline{1}$ and $\underline{3}$, and between $\underline{2}$ and $\underline{4}$ Substitution of data from the Table into eqn (1) indicates that $\underline{1}$ predominates over $\underline{2}$ with $\Delta \underline{H}^{o}_{\underline{1} \rightleftharpoons \underline{2}(H_2O)} = 3.4$ kcal mole^{-1}: cf. $\Delta \underline{G}^{o}_{293^{o}K} = 4.0$ kcal mole^{-1} from basicity measurements.[3] For the equilibrium in the solvents benzene and cyclohexane, equation (2) now gives $\Delta \underline{H}^{o}_{\underline{1} \rightleftharpoons \underline{2}(C_6H_6)} = 0.21$ kcal mole^{-1} and $\Delta \underline{H}^{o}_{\underline{1} \rightleftharpoons \underline{2}(C_6H_{12})} = -1.1$ kcal mole^{-1} respectively.

TABLE

HEAT OF SOLUTION AND PROTONATION DATA AT 25.00 ± 0.05 °C (KCAL MOLE^{-1})[a]

Compound	$\Delta \underline{H}^{o}_{(H_2O)}$	$\Delta \underline{H}^{o}_{(\mathrm{protonation})}$	$\Delta \underline{H}^{o}_{(C_6H_6)}$	$\Delta \underline{H}^{o}_{(C_6H_{12})}$	$\Delta\Delta \underline{H}^{o}_{C_6H_{12}-H_2O)}$
$\underline{3}$	-3.19 ± 0.04	-0.23 ± 0.12	0.75 ± 0.03	3.5 ± 0.5	6.7 ± 0.5
$\underline{4}$	-0.65 ± 0.03	-3.63 ± 0.08	0.09_5 ± 0.02	1.52 ± 0.07	2.2 ± 0.1
$\underline{7}$	-5.55 ± 0.06	—	—	2.79 ± 0.06	8.3 ± 0.1
$\underline{8}$	-4.0 ± 0.3	—	—	0.97 ± 0.03	5.0 ± 0.3

[a] Measurements were made using the LKB 8700 Precision Calorimetry systems Enthalpies of solution were determined by the ampoule technique. Enthalpies of protonation (using $HClO_4$) were measured by titration calorimetry, with the titrant delivered from a Metrohm Dosimat automatic titrator.

Our data are less complete for the piperidone - hydroxytetrahydropyridine equilibrium $\underline{5} \rightleftharpoons \underline{6}$. For aliphatic amide-imidol equilibria, basicity measurements indicate that the amide form is favoured by $\Delta \underline{G}^{o}_{298^{o}K} = 10.6$ kcal mole^{-1} in aqueous solution,[4] and the present results suggest that in going from water to cyclohexane the equilibrium will be swung towards the imidol form by a factor of 3.3 ± 0.4 kcal mole^{-1} in $\Delta \underline{H}^{o}$.

These results suggest that the predominance of the oxo-forms 1 and 5 in aqueous solution diminishes considerably in solvents of lower polarity, as previously shown for substituted pyridones.[5] The predicted predominance of 2-hydroxypyridine 2 over 2-pyridone 1 in cyclohexane corresponds well with recent investigations of the equilibrium in the gas phase which show from mass spectrometry[6,7] and IR studies[8] a predominance of 2-hydroxypyridine, quantitatively assessed from UV measurements[9] as K_T = 2.5 ± 1.5 in favour of 2 at 120 - 140°C. Photoelectron spectral measurements[10] also agree with this finding. However, a recent UV study in one of our departments,[11] while confirming the sensitivity of the equilibrium $1 \rightleftharpoons 2$ to solvent polarity, finds $\Delta G^{o}_{293^{o}K}$ = 0.3 kcal mole^{-1} in favour of 1 in cyclohexane. We believe that this difference probably arises from association phenomena occurring for the mobile system, which is highly dimerised in non-polar solvents.[12]

Recently some of us have used the difference in ΔG^{o} values for $1 \rightleftharpoons 2$ and $5 \rightleftharpoons 6$ for estimating aromatic resonance energy differences between 1 and 2,[4] and the approach has been applied to related systems.[4, 13] The use of prototropic tautomerism for this purpose had previously been criticised by Beak et al.[14] who favoured the more rigorous approach using gas phase equilibrations of corresponding alkyl derivatives. However, Beak and Woods[15] subsequently acknowledged the validity of using data for pairs of protomeric equilibria e.g. $1 \rightleftharpoons 2$, and $5 \rightleftharpoons 6$, as long as enthalpies of solvation and vaporisation for the two series cancel. We believe that the differences in $\Delta\Delta H^{o}_{(C_6H_{12}—H_2O)}$ values for 3 and 4 = 4.5 ± 0.6, and for 7 and 8 = 3.3 ± 0.4 kcal mole^{-1} are sufficiently similar to go some way towards meeting this requirement.

Conclusion. The present method should be generally useful for the study of highly biased equilibria in non-aqueous solvents and also for the investigation of equilibria where the spectral absorptions of the species do not differ significantly.

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