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THE IMPORTANCE OF INTERMOLECULAR EFFECTS IN PROTOMERIC EQUILIBRIA

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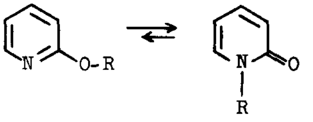
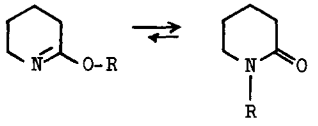
The recent estimate of the aromatic stabilization energy of 2-pyridone[1] (2) as 6.5 kcal/mol less than that of 2-hydroxypyridine (1) in an extension of the comparison previously used to estimate the same stabilization of N-methyl-2-pyridone[2] (6) as 6.3 ± 7.1 kcal/mol[3] less than that of 2-methoxypyridine (5) provides a use of protomeric equilibrium constants which should be valuable in evaluation of the thermodynamic consequences of aromaticity in other heteroaromatic isomer pairs. Both values are based on a comparison of the energy differences of the equilibria of the heteroaromatic isomers 1-2 and 5-6 with the nonaromatic isomers 3-4 and 7-8, respectively. The close correspondence between the estimated relative stabilization energies for 2 and 6 might be considered surprising, since the value for 6 was obtained by extrapolation to the gas phase and includes estimates of differences in zero point energies, while the value for 2 was obtained for dilute solutions in water. However, our previous concern that protomeric equilibria in solution could be dominated by intermolecular effects[2,4] has been suggested to be unjustified for dilute aqueous solutions.[1] The purpose of this communication is to reaffirm our position that intermolecular solvent effects must be considered and/or corrected for if protomeric equilibria are to be considered applicable to relative chemical binding energies and to show that the agreement between the results for 2 and 6 probably stems from a compensating cancellation of enthalpy effects.



1, R = H   2, R = H

5, R = CH_3 6, R = CH_3



3, R = H   4, R = H

7, R = CH_3 8, R = CH_3

That an equilibrium in solution does not give direct information about the equilibrium between isolated, unperturbed molecules is well recognized[5] and may be readily shown for equilibria between the isomeric molecules **A** and **B**, as shown in the thermodynamic cycle in Figure 1. The equilibrium of interest for evaluating the difference in energy of the isomers independent of their environment is shown at the top of the figure as a hypothetical equilibrium in the vapor phase. Protomeric equilibria are usually measured in dilute solutions and involve for each isomer solute solvent complexes, shown in Figure 1 for convenience to involve the same number, $\tilde{n}$, of solvent molecules, **S**. The relationship between the equilibrium enthalpy in solution and the equilibrium enthalpy in the gas phase is given by Eq. 1, from which it can

$$\Delta H^{\circ}_{eq(vapor)} = \Delta H^{\circ}_{eq(soln)} - (\Delta H_{vap_{\mathbf{A}}} - \Delta H_{vap_{\mathbf{B}}}) - (\Delta\bar{H}_{soln_{\mathbf{B}}} - \Delta\bar{H}_{soln_{\mathbf{A}}}) \qquad \text{(Eq. 1)}$$

readily be seen that the enthalpy in the vapor phase would be equivalent to that in solution for an isomerization only if there is mutual cancellation in or of the last two sets of enthalpies. Although such a result is not impossible, Eq. 1 suggests that in most cases solution phase enthalpies will not be equivalent to gas phase enthalpies.

$$\begin{tikzcd}
\mathbf{A}_{(v)} \arrow[rr, dashed, shift left, "\Delta H^{\circ}_{eq(vapor)}"] \arrow[d, shift left] & & \mathbf{B}_{(v)} \arrow[ll, dashed, shift left] \arrow[d, shift left, "\Delta H_{vap_{\mathbf{B}}}"] \\
\tilde{n}\mathbf{S} + \mathbf{A}_{(l)} \arrow[u, shift left, "\Delta H_{vap_{\mathbf{A}}}"] \arrow[d, shift left] & & \mathbf{B}_{(l)} + \tilde{n}\mathbf{S} \arrow[u, shift left] \arrow[d, shift left, "\Delta\bar{H}_{soln_{\mathbf{B}}}"] \\
\mathbf{A}\tilde{n}\mathbf{S} \arrow[u, shift left, "\Delta\bar{H}_{soln_{\mathbf{A}}}"] \arrow[rr, shift left] & & \mathbf{B}\tilde{n}\mathbf{S} \arrow[ll, shift left, "\Delta H^{\circ}_{eq(soln)}"] \arrow[u, shift left]
\end{tikzcd}$$

Figure 1. Equilibrium of Isomeric Molecules **A** and **B**

Specific application of this analysis to the case in question suggests that the equilibria for **1** and **2** in solution and in the vapor state will not be the same. For example, the strong tendency of 2-pyridone to dimerize in nonpolar media[6] has been taken to indicate that specific and strong interactions will exist between **2** and solvent molecules.[2,7] In view of the different structures of **1** and **2**, it seems unlikely that these isomers would have equal and therefore compensating heats of solution in water, and accordingly the third term in Eq. 1 would have a significant value. Moreover, the above assumption of an equal average number of solvent molecules involved in the array of solute solvent complexes might not be correct and could contribute further to differences in solvation enthalpies. The differences in the heats of vaporization can be evaluated if **5** and **6** are considered suitable models for **1** and **2**. In that case, the previously estimated[2] $\Delta\Delta H_{vap}$ $(\Delta H_{vap_{\mathbf{6}}} - \Delta H_{vap_{\mathbf{5}}})$ of 4.4 kcal/mol is a reasonable estimate for the corresponding term in Eq. 1 and clearly demonstrates that large differences may be expected for solution and gas phase enthalpies.

The correspondence of the estimates of stabilization energies for **2** and **6** relative to **1** and **5**, respectively, seems to result from a compensation of differences in enthalpies of solvation and vaporization arising from the comparison of the equilibria **1**-**2** and **3**-**4** and not because intermolecular effects are negligible. The compensation of enthalpies can be most easily seen by inspection of the difference of enthalpy differences between the equilibrium reactions **1**-**2** and **3**-**4** in the vapor state, $\Delta\Delta H^{o}_{rxn(vapor)}$ $(\Delta H_{rxn(vapor)\mathbf{1}\text{-}\mathbf{2}} - \Delta H_{rxn(vapor)\mathbf{3}\text{-}\mathbf{4}})$, shown in Eq. 2.

$$\Delta\Delta H_{rxn(vapor)} = \Delta\Delta H_{rxn(soln)} - (\Delta H_{vap_{\mathbf{1}}} - \Delta H_{vap_{\mathbf{2}}}) - (\Delta H_{vap_{\mathbf{5}}} - \Delta H_{vap_{\mathbf{6}}}) - (\Delta\bar{H}_{soln_{\mathbf{1}}} - \Delta\bar{H}_{soln_{\mathbf{2}}}) - (\Delta\bar{H}_{soln_{\mathbf{5}}} - \Delta\bar{H}_{soln_{\mathbf{6}}}) \quad \text{(Eq. 2)}$$

Rough mutual cancellation of the differences in the heats of vaporization and solution of **1** and **2**, the second and fourth terms, by the same differences for **5** and **6**, the third and fifth terms, would not be surprising in view of the similar functionalities involved.

Protomeric equilibria in solution are of considerable interest in their own right; however, a given protomeric equilibrium should not be used for deductions about differences in stabilities of isolated, unperturbed molecules. We reiterate that for one reaction, equilibria measured in or extrapolated to the gas phase are preferred for obtaining information about relative chemical binding energies.[2,5] On the other hand, in comparisons of a series of equilibria in which differences in enthalpies of solvation and vaporization are compensated, as shown by Eq. 2, protomeric equilibria can be useful in obtaining fundamental information about chemical bonding. This cancellation of interaction factors by comparisons of related systems may be considered an example of the extrathermodynamic relationships which have been discussed in general form.[8]

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References

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2. P. Beak, J. Bonham, and J. T. Lee, Jr., *J. Amer. Chem. Soc.*, **90**, 1569 (1968).
3. The large errors result from cumulative errors in the estimates of differences in zero point energies and intermolecular effects between the isomers. The apparent error limits are considerably lower if these effects are neglected. Kinetic energy differences were estimated to be negligible.[2]
4. The intermolecular effect was specified to include solvent effects; see ref. 2, footnote 7.
5. (a) J. E. Leffler and E. Grunwald, "Rates and Equilibria of Organic Compounds," John Wiley and Sons, Inc., New York, N. Y., 1963, Chap. 2; (b) K. B. Wiberg, "Physical Organic Chemistry," John Wiley and Sons, Inc., New York, N. Y., 1964, p 255; (c) J. A. Larsen, P. A. Bovis, M. W. Grant, and C. A. Lane, *J. Amer. Chem. Soc.*, **93**, 2067 (1971); (d) F. E. Rogers and R. J. Rapiejko, *ibid.*, **93**, 4596 (1971) and references cited therein.
6. M. H. Krackov, C. Milee, and H. G. Mauther, *ibid.*, **87**, 892 (1965); G. G. Hammes and H. O. Spivey, *ibid.*, **88**, 1621 (1966).
7. That the magnitude of the heat of solvation for **2** might be large is indicated by the enthalpy transfer of -7.8 kcal/mol for N-methylacetamide from carbon tetrachloride to water; G. C. Kresheck and I. M. Klotz, *Biochemistry*, **8**, 8 (1969). The values of interest, however, are the differences in the heats of solvation of **1** and **2**.
8. Reference 5a, Chap. 6.