

# Energies and Alkylations of Tautomeric Heterocyclic Compounds: Old Problems—New Answers

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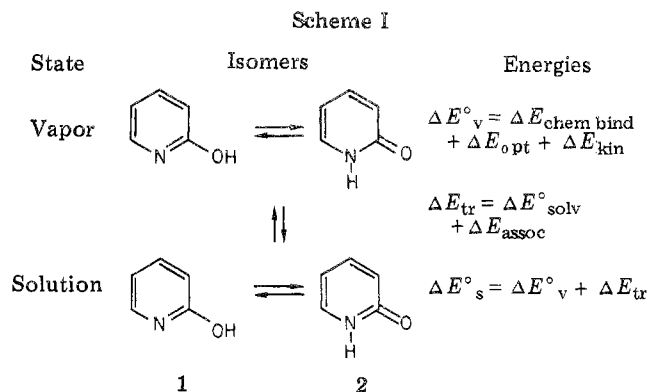
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Received November 4, 1976

Studies of tautomeric equilibria were important in the early development of quantitative concepts of chemical bonding, and much of our current knowledge of structure–stability relationships is derived from these studies.<sup>1,2</sup> The energy difference between isomers still provides one of the best measures of relative chemical binding energies. Investigations of classic tautomerism, in which isomers in rapid equilibrium differ in the binding site of a proton, have been most extensive in the last 25 years in heterocyclic chemistry. The myriad of structural types of continuing interest in this area, in combination with the availability of reliable physical methods, have led to reports of solution tautomeric equilibrium constants for a large number of systems.<sup>5,6</sup> Use of this information has been widespread. For example, the position of amide–imidic acid equilibria of uracil is considered relevant to theories of genetic mutation and for testing quantum mechanical calculations.

As recently as 3 years ago the area of protomeric heterocyclic equilibria appeared to be rather thoroughly explored and settled. Work to be discussed in this Account suggests, however, that neither previous experiments nor theory has generally given reliable information about the difference in chemical binding energies of tautomers. For example the long-accepted idea that 2-pyridone is more stable than 2-hydroxypyridone<sup>1a,4b,5a,5b</sup> has recently been shown to result from differences in solvation between the two isomers. In fact, 2-hydroxypyridine has a slightly lower free energy in the vapor, and there is no significant difference in the fundamental stabilities of the tautomers. Similar large reversals in the position of tautomeric equilibria have been observed on transfer of other systems from solution to vapor. Analysis of the effects underlying these changes suggests that the dependence of tautomer energy on molecular environment will prove to be general. The equilibria discussed in this Account have been investigated many times by a variety of methods; the recent results, however, are new and often opposite in direction to those determined by previous work.

The fundamental energetic considerations which are pertinent to protomeric tautomerism in solution are illustrated in Scheme I for 2-hydroxypyridine (1)–2-pyridone (2) as the prototypical case. The energy difference between 1 and 2 observed in solution ( $\Delta E^\circ_s$ ) is related to that in the vapor ( $\Delta E^\circ_v$ ) by an energy of transfer term ( $\Delta E_{tr}$ ) which results from differences in the energies of solvation ( $\Delta E^\circ_{solv}$ ) and/or association ( $\Delta E^\circ_{assoc}$ ) of the isomers. The energy difference of



monomeric species in the vapor includes differences in kinetic energies ( $\Delta E_{kin}$ ) and zero-point vibrational energies ( $\Delta E_{opt}$ ), as well as the difference in chemical binding energies ( $\Delta E_{chem\ bind}$ ). It is, of course, the latter term that is relevant to chemical bonding theory.<sup>7</sup> In order to properly understand the position of protomeric equilibrium for 1–2, consideration of all these energy terms is necessary.

**Solution Studies.** It is well known that the position of protomeric equilibria can be affected by changes in the solvent.<sup>5</sup> For example, the equilibrium between 6-chloro-2-hydroxypyridine and 6-chloro-2-pyridone shifts from 14% of the hydroxy tautomer in water to 97% of that isomer in dioxane, a free-energy change ( $\Delta\Delta G^\circ$ ) of ca. 2 kcal/mol.<sup>8–10</sup>

(1) (a) G. W. Wheland, "Advanced Organic Chemistry", Wiley, New York, N.Y., 1949, pp 580–646; (b) C. K. Ingold, "Structure and Mechanism in Organic Chemistry", Cornell University Press, Ithaca, N.Y., 1953, pp 530–601; (c) J. Hine, "Structural Effects on Equilibria in Organic Chemistry", Wiley, New York, N.Y., 1975, pp 270–280.

(2) Historically, the idea of a mobile equilibrium was extended to ring–chain and valence tautomerism.<sup>9</sup> Many rearrangements of current interest, e.g., fluxional behavior, electrocyclizations, and sigmatropic reactions, may be considered to arise from an extension of interest in valence tautomerism beyond concern about the ground states of isomers to bonding in the transition states between them.<sup>4</sup>

(3) P. R. Jones, *Chem. Rev.*, **63**, 461 (1963); L. A. Paquette, *Angew. Chem., Int. Ed. Engl.*, **10**, 11 (1971); E. Vogel and H. Günther, *ibid.*, **6**, 385 (1967); G. Schroder, J. F. M. Oth, and R. Merengi, *ibid.*, **4**, 752 (1965).

(4) (a) J. March, "Advanced Organic Chemistry", McGraw-Hill, New York, N.Y., 1968, pp 625–636; (b) W. J. LeNoble, "Highlights of Organic Chemistry", Marcel Dekker, New York, N.Y., 1974, pp 393–425, 460–537; (c) R. B. Woodward and R. Hoffmann, "The Conservation of Orbital Symmetry", Verlag Chemie, Weinheim/Bergstr., West Germany.

(5) (a) A. R. Katritzky and J. M. Lagowski, *Adv. Heterocycl. Chem.*, **1**, 2 (1963); (b) A. Albert, "Heterocyclic Chemistry", Athlone Press, London, 1968; (c) J. Elguero, C. Marzin, A. R. Katritzky, and P. Linda, *Adv. Heterocycl. Chem. Suppl.*, No. 1 (1975).

(6) The first specific suggestion of tautomerism was apparently made for amide–imidic acid isomerization of isatin by A. Baeyer in 1882 as part of his classic work on the structure and synthesis of indigo: A. Baeyer and S. Oekonomides, *Ber.*, **15**, 2093 (1882).

(7) (a) L. P. Hammett, "Physical Organic Chemistry", McGraw-Hill, New York, N.Y., 1940, Chapter 3; (b) K. B. Wiberg, "Physical Organic Chemistry", Wiley, New York, N.Y., 1964, Chapter 2; (c) J. E. Leffler and E. Grunwald, "Rates and Equilibria of Organic Reactions", Wiley, New York, N.Y., 1963, Chapters 1–5.

After receiving a bachelor's degree in the East (Harvard), Peter Beak has remained in the Midwest for a doctoral degree (Iowa State) and independent research (Illinois). His collaborators comprise an adventuresome research group whose interests include the discovery and use of novel reactions as well as the elucidation of structure–stability relationships.

Table I  
Equilibrium Constants for Scheme II

| Protomers | Solvent                | Equilibrium constants |         |               |                          |                                       |
|-----------|------------------------|-----------------------|---------|---------------|--------------------------|---------------------------------------|
|           |                        | $K_T$                 | $K_1^a$ | $K_2$         | $K_3$                    | $K_4$                                 |
| 1-2       | Decane,<br>cyclohexane | 1.6                   | 2.6     | $b$           | $b$                      | $5.6 \times 10^6 \pm 1.7 \times 10^6$ |
| 3-4       | Cyclohexane            | 0.09                  | 0.008   | $c$           | $c$                      | $9.4 \times 10^5 \pm 10^5$            |
|           | Chloroform             | 2.6                   | 6.8     | $c$           | $c$                      | $2.7 \times 10^3 \pm 5 \times 10^2$   |
| 5-6       | Chloroform             | 2.2                   | 4.8     | $4.3 \pm 1.5$ | $7 \times 10^3 \pm 10^3$ | $7 \times 10^3 \pm 10^3$              |

<sup>a</sup>  $K_1 = (K_T \text{ monomer})^2$ . <sup>b</sup> The hydroxypyridine dimer was not detected. <sup>c</sup> The mercaptopyridine dimer was not detected.

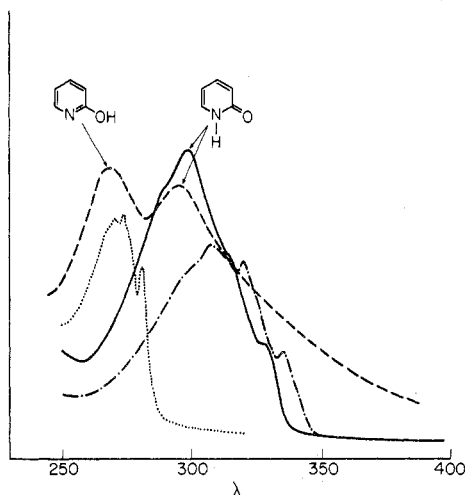
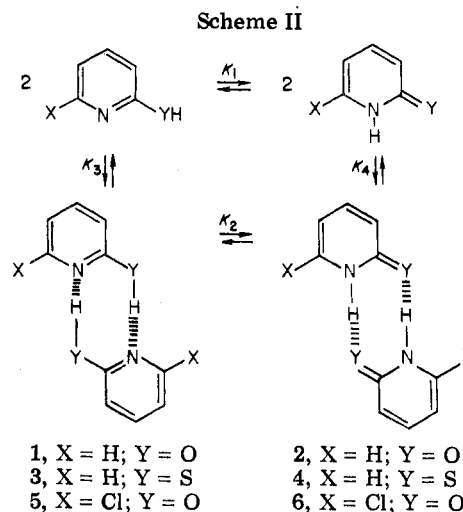


Figure 1. Ultraviolet spectra of (a) 2-hydroxypyridine-2-pyridone in decane at  $10^{-4}$  M (—) and in cyclohexane at  $10^{-7}$  M (----), (b) 1-methyl-2-pyridone in decane (-·-·-·), and (c) 2-methoxy-pyridine in decane (·····).

The case of 2-hydroxypyridine-2-pyridone is even more illustrative. The fact that the equilibrium lies far on the side of the amide 2 was established by a variety of studies in many solvents.<sup>5</sup> In water the equilibrium constant has been estimated as  $10^3$  in favor of 2 on the basis of basicity measurements,<sup>5,11,12</sup> while in cyclohexane it had been reported some years ago to be  $>10$  in the same direction by ultraviolet spectroscopy.<sup>9a</sup> The latter experiment, which examines the equilibrium of a dilute sample in a noninteracting solvent, is the customary way of minimizing differential solvation or association of the isomers. We have had occasion to question whether this approach, in fact, is effective in accomplishing that end for the case of 1-2.

In Figure 1 are shown the ultraviolet spectra of 1-2, 2-methoxy-pyridine, and 1-methyl-2-pyridone in decane at  $10^{-4}$  M at ambient temperature. If the chromophores of the latter two compounds are taken as models for 1 and 2,<sup>5,13</sup> respectively, it is clear that 2 comprises at least 90% of the tautomeric mixture. On the other hand, if the spectrum is examined in cyclohexane at  $10^{-7}$  M, the



spectrum for 1-2, shown as the dotted line in Figure 1, is obtained.<sup>14</sup> A similar spectrum is obtained if the decane solution is heated to 120 °C. At high dilution it is clear that the hydroxypyridine 1 is detectable, and an equilibrium constant of 1.6 ( $[2]/[1]$ ) can be calculated.

The apparent change in the equilibrium constant can be attributed to the well-known association of 2<sup>15</sup> which is broken up by dilution or heating. This rationale is summarized in Scheme II and by the quantitative data in Table I.<sup>16</sup> Further support for this analysis is provided by the parallel behavior of 2-mercaptopyridine (3)-2-thiopyridone (4) and 6-chloro-2-hydroxypyridine (5)-6-chloro-2-pyridone (6). For 3-4 and 5-6 the extent of association in chloroform, directly determined by vapor phase osmometry, has been used in conjunction with ultraviolet spectral determinations of the equilibrium constants to provide the values in Table I. It should be noted that association of the hydroxy and mercapto forms 1 and 3 could occur in more concentrated solutions but would not be detected in the presence of the stronger association of 2 and 4. The data for 5-6 require that the dimer of 5 be in equilibrium with at least one other dimer, represented for economy as dimeric 6.

The results in Table I, in conjunction with the earlier assignments, suggest that the equilibrium constant for

(8) Y. N. Sheinker, E. Peresleni, I. S. Rezchinkova, and N. P. Zosimova, *Dokl. Akad. Nauk. SSSR*, 192, 1295 (1970); *Dokl. Chem. (Engl. Transl.)*, 192, 454 (1970).

(9) (a) A. Gordon and A. R. Katritzky, *Tetrahedron Lett.*, 2767 (1968); (b) A. R. Katritzky, J. D. Rowe, and S. K. Roy, *J. Chem. Soc. B*, 758 (1967).

(10) G. Simchen, *Ber.*, 103, 398 (1970).

(11) M. J. Cook, A. R. Katritzky, P. Linda, and R. D. Tack, *J. Chem. Soc., Perkin Trans. 2*, 1295 (1972); M. J. Cook, A. R. Katritzky, P. Linda, and R. D. Tack, *Chem. Commun.*, 510 (1971).

(12) A. Albert and J. N. Phillips, *J. Chem. Soc.*, 1294 (1956); S. F. Mason, *ibid.*, 674 (1958); A. Albert, *Phys. Methods Heterocycl. Chem.*, 1, 1 (1963).

(13) H. Specker and H. Gawrosch, *Ber.*, 75, 1338 (1942). The ultraviolet measurement of this equilibrium by F. C. Baker and E. C. C. Baley (*J. Chem. Soc.*, 91, 1122 (1907)) appears to be one of the earliest uses of spectroscopy for structural distinction.

(14) A spectrometer which accepts long path-length cells was assembled. For 1-2 at  $10^{-7}$  M in cyclohexane, a 3-m cell is required: P. Beak, J. B. Covington, and S. G. Smith, unpublished results.

(15) (a) L. J. Bellamy and P. E. Rogash, *Proc. R. Soc. London, Ser. A*, 257, 98 (1960); (b) G. G. Hammes and H. O. Spivey, *J. Am. Chem. Soc.*, 88, 1621 (1966); (c) M. H. Krakov, C. M. Lee, and H. G. Mautner, *ibid.*, 87, 892 (1965); (d) for a general discussion see M. D. Joesten and L. S. Schaad, "Hydrogen Bonding", Marcel Dekker, New York, N.Y., 1973, pp 279-289, 313.

(16) P. Beak, J. B. Covington, S. G. Smith, *J. Am. Chem. Soc.*, 98, 8284 (1976).

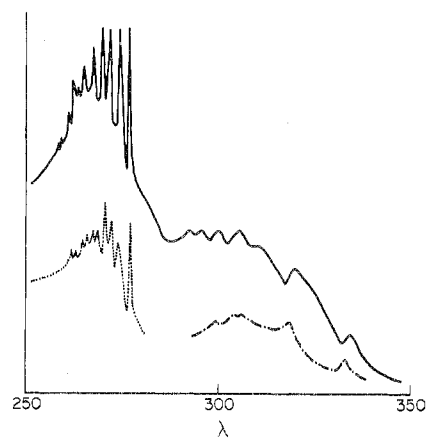
1-2 changes by a factor of ca.  $10^3$  in favor of 1 as the solvent is changed from water to cyclohexane. Moreover, the association constant for 2 increases by a factor of  $10^5$  in cyclohexane relative to dioxane.<sup>15b</sup> Clearly,  $\Delta E^\circ_{\text{solv}}$  and  $\Delta E^\circ_{\text{assoc}}$  are important, and molecular environment can have a major influence on the position of equilibrium and the extent of association for this system.

These results suggest that the recently reported equilibrium constant of 1.7 for 2/1, determined by ultraviolet spectroscopy at  $10^{-4}$  to  $5 \times 10^{-5}$  M in cyclohexane, is not correct.<sup>17</sup> In our hands, multiwavelength analysis of  $10^{-5}$  M solutions reveal that the equilibrium constant is  $>10$  in favor of 2 as the dimer.<sup>9a,18a</sup> Apparently the single wavelength determination of 1.7, which is based on molar extinction coefficients of 100 and 6300 for the model compounds in alcohol, is inadequate.<sup>17,18b</sup>

In another approach, calorimetric measurements of the basicities and heats of solution of 2-methoxypyridine and 1-methyl-2-pyridone have been used to estimate the enthalpy difference between 1 and 2 in cyclohexane as +1.1 kcal/mol.<sup>19</sup> While the success of that approach does depend on cancelation of solvations, i.e., the solvation of the cations must be compensated by the difference in solvation of the models and the protomers, it has the interesting advantage of avoiding direct measurement on the protomers, themselves, and thus obviating problems of association.<sup>20</sup>

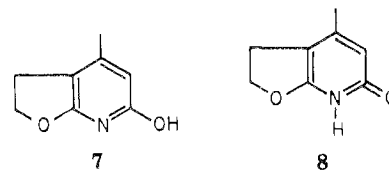
It is noteworthy that most tautomeric equilibria are measured in polar solvents or at concentrations greater than  $10^{-3}$  M in nonpolar solvents. Our results may be taken to suggest that interpretation of such solution protomeric equilibrium constants in terms of the relative stabilities of the isolated monomers is at risk unless the possibly dominating effects of solvation and association have been considered. For example, rationalization of the relative stability of 1-2 in aqueous solution in terms of the greater acidity of 1 could be misleading unless it is recognized that the difference in acidities of 1 and 2 is a reflection of differential solvation and is not a difference in intrinsic acidities of the isomers. In order to obtain a clearer picture of the importance of phase on the position of equilibrium, it is useful to consider some gas-phase results.

**Gas-Phase Studies.** The first direct detection of 2-hydroxypyridine was made by infrared observation of an OH absorption for a vaporized sample of 1-2 in 1965. The relative intensities of the OH and NH stretching bands were taken to suggest that the ratio



**Figure 2.** Vapor phase ultraviolet spectra of 2-hydroxypyridine-2-pyridone (—), 2-methoxypyridine (.....), and 1-methyl-2-pyridone (-·-·-·).

of 1:2 is ca. 2, and detection of both isomers of some substituted 2-hydroxypyridine-2-pyridone systems was reported.<sup>21</sup> Analogous infrared studies have also been reported for similar isomers trapped from the gas phase in an argon matrix.<sup>22</sup> On the basis of time- and temperature-dependent changes in the ratio of the OH and NH absorption bands assigned to 7-8, it was



concluded that equilibrium was not achieved below 347 °C in the vapor.<sup>11,23</sup> Presumably, if equilibrium is not established in the vapor, the observed ratio merely reflects the relative rates of vaporization of the isomers.

More recently, ionization potential measurements and fragmentation studies from the mass spectrum of the vapor of 1-2 have been interpreted in terms of 1 as the dominant form in the vapor.<sup>24</sup> This useful approach does not, however, resolve the question of equilibrium or allow detection of minor isomers.

The gas-phase ultraviolet spectra shown in Figure 2 allow a ratio of 1:2 of 2.5:1 to be assigned to the tautomeric isomers in the vapor.<sup>25</sup> Although the absorbance assigned to each isomer changes by approximately two and one-half on heating or cooling over a 20 °C range, the ratio of the absorbances does not change and is stable for at least 8 h. Such results are not consistent with the selective vaporization of one isomer and indicate the tautomers are in equilibrium under these conditions.<sup>26</sup> Ultraviolet examination of the vapor of 7-8 shows only 7 with less than 10% 8 present, either initially at 175 °C or on further heating at higher temperatures. In fact, under the latter

(17) J. Frank and A. R. Katritzky, *J. Chem. Soc., Perkin Trans. 2*, 1428 (1976). We are grateful to Professor A. R. Katritzky for a preprint of this article including the ultraviolet spectrum for 1-2 in cyclohexane. Professor Katritzky provided this information prior to learning of our work and our view that association dominates the situation was discussed with him in April 1976.

(18) (a) P. Beak and J. B. Covington, unpublished results, 1975. Discussion of multiwavelength analyses is given by M. J. S. Dewar and D. S. Urch, *J. Chem. Soc.*, 345 (1957). (b) The curve kindly provided by Professor Katritzky<sup>17</sup> resembles the solid line in Figure 1 and does not show a significant peak in the 270-280 nm  $\lambda_{\text{max}}$  region where 1 should absorb strongly; an equilibrium constant of 1.7 would require a curve similar to the dotted line in Figure 1.

(19) M. J. Cook, A. R. Katritzky, L. G. Hepler, and T. Matsui, *Tetrahedron Lett.*, 2685 (1976).

(20) The enthalpy of association would probably be large. The  $\Delta G^\circ_{\text{assoc}}$  of dimerization of  $-9.2 \pm 0.6$  kcal/mol calculated from Table I may be used with a hypothetical entropy of association of 36 eu (attributable to loss of translational energy in dimerization)<sup>7b</sup> to give a  $\Delta H^\circ_{\text{assoc}}$  of ca. -20 kcal/mol for 1-2 in cyclohexane.

(21) E. S. Levin and G. N. Rodionova, *Dokl. Chem. (Engl. Transl.)*, 164, 910 (1965); 172, 75 (1967).

(22) S. S. T. King, W. L. Dilling, N. B. Tefertiller, *Tetrahedron*, 28, 5859 (1972).

(23) E. S. Levin and G. N. Rodionova, *Dokl. Chem. (Engl. Transl.)*, 189, 900 (1969).

(24) T. Gronneberg and K. Undheim, *Tetrahedron Lett.*, 3193 (1972); A. Maquestiau, Y. vanHaverbeke, C. de Meyer, A. R. Katritzky, M. J. Cook, and A. D. Page, *Can. J. Chem.*, 53, 490 (1975).

(25) P. Beak and F. S. Fry, *J. Am. Chem. Soc.*, 95, 1700 (1973).

(26) P. Beak, F. S. Fry, J. Lee, and F. Steele, *J. Am. Chem. Soc.*, 98, 171 (1976).

Table II  
Protomeric Equilibrium Constants in the  
Vapor and in Water (NH/YH)

| Protomers | $K_V^a$ | $K_{aq}^b$                  |
|-----------|---------|-----------------------------|
|           | <1/10   | 66 000/1                    |
|           | <1/10   | 2000/1                      |
|           | <1/10   | 47 000/1                    |
|           | <1/10   | 15 <sup>a</sup> (ethanol)/1 |
|           | 5/100   | 61 <sup>c</sup> /10         |

<sup>a</sup> From ultraviolet spectroscopy, ref 26. <sup>b</sup> From  $pK_a$  data at ambient temperature in aqueous solution: A. Albert, *Phys. Methods Heterocycl. Chem.*, 1, Chapter 1 (1963); ref 5, 11, and 12. <sup>c</sup> From ultraviolet spectroscopy: ref 8, 9.

conditions extensive decomposition occurs, a result which could have given a misleading indication of a lack of equilibration in that system.<sup>23</sup> Infrared studies of the vapor of 1-2 show that the NH and OH stretching bonds are sharp absorptions indicative of monomeric species.<sup>21,26</sup>

From the temperature dependence of the equilibrium constant over the range of 120 to 250 °C, the thermodynamic values for the energy difference between 1 and 2 may be calculated as:  $\Delta G^\circ_{v,132^\circ\text{C}}$  0.8 kcal/mol;  $\Delta H^\circ_{v,}$   $-0.3 \pm 0.3$  kcal/mol;  $\Delta S^\circ_{v,}$   $2.0 \pm 1.5$  eu. The small entropy difference establishes that the kinetic energy difference is not large, and the conclusion may be drawn that for 1-2  $\Delta E_{\text{chem bind}} + \Delta E_{\text{opt}}$  is  $0.3 \pm 0.6$  kcal/mol. Application of the group-frequency approach, previously used to estimate the difference in zero-point energies for the amide and imidate functions,<sup>27</sup> gives a value of less than 0.1 kcal/mol for 1-2. While this is surely too low, it does indicate that the difference in  $\Delta E_{\text{chem bind}}$  between 1 and 2 is in the range of  $0.3 \pm 2.5$  kcal/mol.<sup>28</sup>

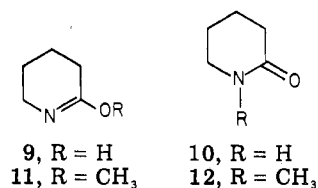
The apparent reversal in the direction of equilibrium for 1-2 on transfer from solution to the vapor is indicative of a general effect. The first four entries in Table II show that the position of equilibrium for 2-mercaptopyridine-2-thiopyridone, 4-hydroxypyridine-4-pyridone, 4-mercaptopyridine-4-thiopyridone, and 2-hydroxypyrimidine-2-pyrimidone in aqueous solution is not even a useful qualitative guide to the relative stability of the tautomers.<sup>29</sup> While this result

(27) P. Beak, J. Bonham, and J. T. Lee, *J. Am. Chem. Soc.*, 90, 1569 (1968).

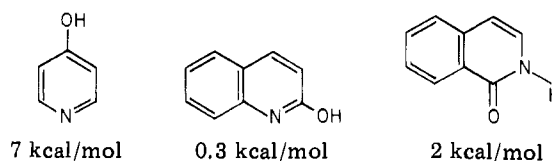
(28) While inclusion of estimates of differences in kinetic and zero-point energies increases the uncertainty in assigning differences in chemical binding energies, it is essential to establish that these factors are not large. As more cases are analyzed, it may prove to be true that these effects can be ignored in most cases. The latter situation apparently obtains for isomeric hydrocarbons: J. D. Cox and G. Pilcher, "Thermochemistry of Organic and Organometallic Compounds", Academic Press, New York, N.Y., 1970, pp 527-529.

confirms the notion that  $\Delta E_{\text{soln}}$  is generally important for such systems, the relatively small change in equilibrium constant for the transfer of the equilibrium of 6-chloro-2-hydroxypyridine-6-chloro-2-pyridone from water to the gas phase (Table II) or from associated to unassociated species (Table I) shows that control by the molecular environment is not universal. Each case must be judged individually, but gas-phase data provides the point from which understanding can begin.

In order to detect changes in tautomeric equilibria by the spectral approach, either both isomers must be detectable or the equilibrium constant must turn over with a change in medium. This limitation precludes investigation of a number of interesting cases. For example, from the infrared study of analogous compounds<sup>21,23</sup> the energy difference between 9 and 10



can be suspected to favor 10, but the actual energy difference is not known. However, comparison of the measured gas-phase enthalpy differences between 2-methoxypyridine-1-methyl-2-pyridone<sup>30a</sup> and 1-2 reveals a value of 7.4 kcal/mol, attributable to the differences in energies of the localized  $\sigma$  bonds; NH, OH vs. NCH<sub>3</sub>, OCH<sub>3</sub>. That value can then be subtracted from the known gas-phase enthalpy difference of 14.1 kcal/mol between 11 and 12<sup>30a,31</sup> to provide an estimated enthalpy difference of ca. 7 kcal/mol between 9 and 10 in favor of 10. Similarly, previous calorimetric determinations of enthalpy differences between methyltropic isomers<sup>27,30b</sup> may be used to provide the values by which the more stable tautomer is favored:



These values again differ drastically from those estimated for aqueous solution.<sup>5,32</sup>

Another solution to the problem of estimating the position of highly biased tautomeric equilibria in the gas phase has been provided recently by ion cyclotron

(29) By analogy to 1-2 it is presumed that for comparison purposes the equilibrium constants in the vapor can be extended to room temperatures without great change. The 4-mercaptopyridine and 4-hydroxypyridine isomers are also favored by a small symmetry-related entropy factor of 1.4 eu.

(30) (a) P. Beak, D. S. Mueller, and J. Lee, *J. Am. Chem. Soc.*, 96, 3867 (1974); (b) P. Beak, T. S. Woods, and D. S. Mueller, *Tetrahedron*, 28, 5507 (1972).

(31) This large energy difference between the ground state of an amide and its corresponding imidate provides a rationale for the synthetically useful conversions involving amides and imidates.<sup>30a</sup> For examples, see R. G. Glushkov and V. B. Granik, *Adv. Heterocycl. Chem.*, 12, 185 (1970); B. M. Trost and R. A. Kunz, *J. Am. Chem. Soc.*, 97, 7152 (1975); L. E. Overman, *ibid.*, 98, 2901 (1976).

(32) A misprint with respect to 4-hydroxypyridine in ref 26 is hereby corrected. The same type of approximation, that the localized  $\sigma$  bond energies do not change drastically, may be applied to other calorimetric data<sup>30</sup> to suggest, e.g., 4-hydroxy-2-pyridones will be more stable than 2-hydroxy-4-pyridones by ca. 10 kcal/mol.

Table III  
Comparison of  $\Delta E_e$  and  $\Delta E_{\text{solv}}$  for Transfer of 1-2, 3-4,  
and 5-6 from the Vapor to a Solvent

| Solvents    | 1-2            |                          | 3-4            |                          | 5-6            |                          |
|-------------|----------------|--------------------------|----------------|--------------------------|----------------|--------------------------|
|             | $\Delta E_e^a$ | $\Delta E_{\text{solv}}$ | $\Delta E_e^a$ | $\Delta E_{\text{solv}}$ | $\Delta E_e^a$ | $\Delta E_{\text{solv}}$ |
| Water       | 3.0            | 4 <sup>a</sup>           | 4.2            | >8 <sup>a</sup>          | 1.3            | 2 <sup>a</sup>           |
| Cyclohexane | 1.2            | 0.6 <sup>b</sup>         | 1.7            | >1.4 <sup>b</sup>        | 0.6            | ~0.1 <sup>b</sup>        |

<sup>a</sup> Reference 26. <sup>b</sup> Reference 16.

resonance spectrometry. Thus, the basicity of the vaporized methyl isomers can be used to provide estimated energy differences of the corresponding tautomers in the gas phase.<sup>5,12</sup> In the first report of this approach, Taft and Katritzky have confirmed the method for 1-2 and have estimated the energy difference between 9 and 10 to be 7.3 kcal/mol, in agreement with the above estimate.<sup>33</sup> It has been established that the method is also applicable to the 6-chloro cases and that such data, in conjunction with solution studies, allows the construction of thermodynamic cycles which are useful in understanding the basicity method.<sup>34</sup>

**Medium Effects.** The study of solvent effects is a matter of considerable fundamental interest. Comparisons of ionic reactions in the gas phase and in solution provide a well-known precedent for the domination of molecular energies by solvation.<sup>35</sup> The energy of solvation in Scheme I is the sum of the differences in the energy of cavitation ( $\Delta E_{\text{cav}}$ ), the energy of van der Waals interactions ( $\Delta E_{\text{vdw}}$ ), the energy of hydrogen bonding ( $\Delta E_{\text{Hb}}$ ), and the energy associated with the interaction of the electric fields of the isomeric solutes and the solvent ( $\Delta E_e$ ).<sup>36</sup> For the prototypical case of 1-2 the difference in the energies for the first

$$\Delta E_{\text{solv}} = \Delta E_{\text{cav}} + \Delta E_{\text{vdw}} + \Delta E_{\text{Hb}} + \Delta E_e$$

two terms appears to be negligible. The cavity size and the atoms involved in the dispersion interactions would be expected to be approximately the same for each of the isomers. The difference in the hydrogen bonding term for 1-2 is more difficult to assess. Whereas the difference in the energy of hydrogen bonding of phenol and aniline to pyridine in hydrocarbons is reported to be 2 kcal/mol, the difference for methanol and dimethylamine in carbon tetrachloride is less than 0.2 kcal/mol.<sup>15d</sup>

For want of a better alternative, we have chosen to temporarily neglect the possible difference in hydrogen bonding for 1-2 and to focus on the classical electric field term. By use of the Onsager equation this term may be calculated for transfer of a dipole of known magnitude from the vapor to a medium of known dielectric constant.<sup>37,38</sup> The Onsager equation provides

(33) M. J. Cook, A. R. Katritzky, M. Taagepera, T. D. Singh, and R. W. Taft, *J. Am. Chem. Soc.*, **98**, 6048 (1976), and references cited therein. We are grateful to Professors A. R. Katritzky and R. W. Taft for a preprint of this article.

(34) D. Aue, P. Beak, M. Bowers, and W. Davidson, unpublished results, 1976.

(35) See E. M. Arnett, *Acc. Chem. Res.*, **6**, 404 (1973); D. H. Aue, H. B. Webb, and M. T. Bowers, *J. Am. Chem. Soc.*, **98**, 311, 318 (1976), for leading references.

(36) See (a) R. L. Reeves, M. S. Maggio, and L. F. Costa, *J. Am. Chem. Soc.*, **96**, 5917 (1974), and (b) R. Fuchs, T. M. Young, and R. F. Rodewald, *ibid.*, **96**, 4705 (1974), for leading references.

(37) L. Onsager, *J. Am. Chem. Soc.*, **58**, 1686 (1936).

a quantitative statement of the observation that a more polar solvent appears to selectively stabilize the more polar tautomer.<sup>5,8-10</sup> In Table III calculated values for  $\Delta E_e$  are compared with  $\Delta E_{\text{solv}}$  for three systems. The results for 1-2 and 5-6 are in remarkable, and probably fortuitous, agreement. The overall prediction is in accord with the experimental order of the solvation effect, i.e., 3-4 is the most affected, and 5-6 the least affected by transfer from the vapor to solution, although the agreement for the case of 3-4 is not good. More sophisticated calculations of  $\Delta E_e$  or inclusion of hydrogen-bonding effects might give better results. Extensions of this analysis should be circumspect, since differences in hydrogen bonding must cancel if accurate estimates of the solvent effect on the tautomeric equilibria are to result from use of the simple form of the Onsager equation. This approach is likely to prove useful in cases where large differences exist in dipole moments of the tautomers. Alternatives which stress the effect of solvent cavitation<sup>36a</sup> or the use of empirical parameters<sup>9a,17</sup> have also been successful in correlating changes in tautomeric equilibrium constants. More information and testing is clearly needed. The area is rich in possibilities for theoretical and experimental work.

While conclusions about relative chemical binding energies should not be drawn from individual solution tautomeric equilibria, comparison of similar systems in the same solvent provides an appropriate compensation.<sup>27,39,40</sup> Thus, the method originally used to estimate the aromatic character of 1-methyl-2-pyridone by comparison to a nonaromatic and aromatic isomeric alkyltropic system<sup>27,40</sup> in the vapor has been extended to a variety of heteroaromatic protomeric systems in solution.<sup>11,39-42</sup>

The implications of possible large changes in stability and association of protomeric tautomers in connection with changes in molecular environment are particularly interesting for bioorganic chemistry. For example, the increase in the association energy of approximately 6

(38) (a) J. Powling and H. J. Bernstein (*J. Am. Chem. Soc.*, **73**, 4354 (1951)) first applied the Onsager equation to tautomeric equilibria some years ago; (b) S. F. Mason (*J. Chem. Soc.*, 5010 (1957)) noted changes of tautomeric equilibria in heteroaromatic systems correlated qualitatively with changes in dielectric constant; (c) R. J. Abraham and co-workers (*J. Phys. Chem.*, **73**, 1192 (1969)) have modified the Onsager equation to include the effects of the quadrupolar field and temperature dependence; (d) it should be noted that cases in which the dipole model apparently is inadequate exist: cf. F. J. Hwang, L. C. DeBolt, and H. Morawetz, *J. Am. Chem. Soc.*, **98**, 5890 (1976); (e) large effects can be predicted and present but not observed, unless the energy difference of the tautomers is such that the change in  $\Delta E_{\text{solv}}$  brings another isomer into a detectable range.

(39) P. Beak and T. S. Woods, *Tetrahedron Lett.*, 775 (1972).

(40) A series of private communications with Professor A. R. Katritzky has established that a misunderstanding had existed between the East Anglia and Urbana groups. Our comments in 1968 regarding the possibly dominating effect of phase and solvent on protomeric equilibria applied explicitly to an individual equilibrium and noted such effects could be reduced by comparing a series of equilibria.<sup>27</sup> The latter qualification was misinterpreted by the East Anglia group in their subsequent work and comments which presumed our caution applied to series as well.<sup>11</sup> We, in turn, mistook their comments to apply to individual equilibria.<sup>26</sup> This clarification should resolve the apparent differences of opinion which have existed between the groups. It should perhaps be stressed that for the difference in solution and the vapor in the present work our focus is on studies and understanding of individual protomeric equilibria. Comparisons of series, e.g., substituent effects in a single structural type, will surely prove more consistent with previous experience because of cancellation of solvent effects.<sup>39</sup>

(41) A. K. Burnham, J. Lee, T. G. Schmalz, P. Beak, and W. H. Flygare, *J. Am. Chem. Soc.*, **99**, 1836 (1977).

(42) M. J. Cook, A. R. Katritzky, and P. Linda, *Adv. Heterocycl. Chem.*, **17**, 255 (1974).

Table IV  
Relative Chemical Binding Energies for 1-2 (kcal/mol)

| Calculation      |                  |                 | Experiment |
|------------------|------------------|-----------------|------------|
| SCF-MO           | MINDO/2          | CNDO/2          |            |
| -12 <sup>a</sup> | -14 <sup>b</sup> | 11 <sup>c</sup> | 0.3 ± 2.5  |
|                  |                  | 17 <sup>d</sup> |            |

<sup>a</sup> N. Bodor, M. J. S. Dewar, and A. J. Harget, *J. Am. Chem. Soc.*, **92**, 2929 (1970). <sup>b</sup> H. G. Benson and J. N. Morrell, *J. Chem. Soc., Faraday Trans. 2*, **129** (1972). <sup>c</sup> M. Berndt, J. S. Kwiatkowski, J. Budzinski, and B. Szczodrawska, *Chem. Phys. Lett.*, **19**, 246 (1973). <sup>d</sup> Reference 47.

kcal/mol on transfer of the dimer of **2** from dioxane to cyclohexane is of sufficient magnitude to suggest that in some cases a substantial portion of energy of enzyme-substrate binding could be provided by an appropriate molecular environment at the binding site.<sup>43</sup> In the area of enzyme model studies, the effectiveness of 2-pyridone as a tautomeric catalyst may reflect a small energy difference between **1** and **2** at the catalytic site.<sup>44</sup> The results also suggest that extrapolation of tautomeric equilibrium constants from one environment to another is risky. Thus, studies of tautomerism of the purines and pyrimidines in aqueous solution, while very interesting in their own right,<sup>45</sup> may not bear on the structure and association of these bases in the nucleic acids either in ground states or during reactions. On the other hand, the fact that association and tautomerization energies can be controlled by the local environment may support the idea that apparent base mispairings, which are of considerable interest in nucleic acid chemistry and biochemistry,<sup>46</sup> result from the presence and association of "rare" tautomeric forms to a different degree than thought possible on the basis of aqueous solution studies.

**Quantum Mechanical Calculations.** Quantum mechanical calculations of total energies have been carried out for a wide variety of tautomeric heteroaromatic systems. In general, the predictions of these calculations have not been tested because the relative chemical binding energies of the isomers have not been previously available. The prototypical case 1-2 has been the object of at least twelve calculations, the four most recent of which are presented in Table IV. Comparison of these predictions with the experimental value shows all methods are in error by at least 8 kcal/mol. Clearly such results cannot be regarded as chemically useful.<sup>26,47,48</sup> Perhaps the present determinations of relative chemical binding energies can provide a point of reference for further efforts.

**Alkylations of Protomeric Systems.** It is now generally recognized that, while the physical properties

(43) W. P. Jenks, "Catalysis in Chemistry and Enzymology", McGraw-Hill, New York, N.Y., 1962; T. C. Bruice, "The Enzymes", P. D. Boyer, Ed., Academic Press, New York, N.Y., 1970, Chapter 4.

(44) P. Rony and R. O. Neff, *J. Am. Chem. Soc.*, **95**, 2896 (1973), and references cited therein.

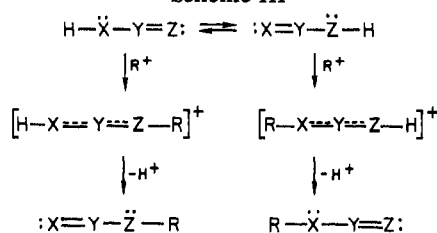
(45) For examples see M. Dreyfus, O. Bensaude, G. Dodin, and J. E. Dubois, *J. Am. Chem. Soc.*, **98**, 6338 (1976) and J. Sepiol, Z. Kazmierczuk, and D. Shugar, *Z. Naturforsch.*, **31**, 361 (1976), for interesting cases and analyses.

(46) M. D. Topal and J. R. Fresco, *Nature (London)*, **263**, 285, 289 (1976); D. Shugar, C. P. Huber, and G. I. Birnbaum, *Biochim. Biophys. Acta*, **447**, 274 (1976).

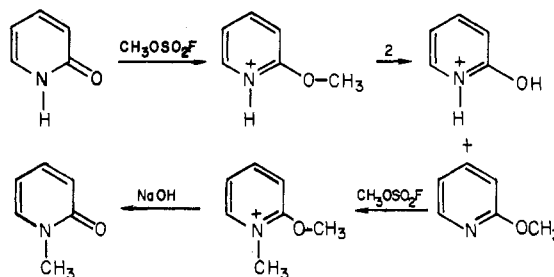
(47) For a similar conclusion from a different perspective, see M. L. Tosato, M. Cignitti, and L. Paoloni, *Gazz. Chim. Ital.*, **105**, 385 (1975).

(48) The calculations which have been done for the other systems in Table II appear to be similarly unreliable. See ref 26 for additional citations.

Scheme III



Scheme IV



of protomeric systems are determined by the structures of the species present, the chemistry of these systems is not necessarily related to the position of tautomeric equilibrium. Thus, proton transfers between heteroatoms are usually fast,<sup>49</sup> the Curtin-Hammett principle applies,<sup>50</sup> and the relative amounts of different products formed from the rapidly equilibrating tautomers will be determined solely by the relative transition-state energies leading to those products.<sup>51</sup> In effect, the value of the tautomeric equilibrium constant may be irrelevant to understanding the chemistry. Nonetheless, if the relative ground-state energies of the protomers serve as a qualitative guide to the relative transition-state energies, it could prove possible to understand and predict the reactive site of a protomeric tautomer on the basis of that equilibrium constant. The case is illustrated for alkylation in Scheme III. If the factors which determine the ground-state energy difference between the tautomers also control the relative transition-state energies for the first step, and no additional complicating reactions occur, the product will have the methyl group attached to the heteroatom which does not bear the proton in the major tautomer.<sup>52</sup>

Such a result, which is most likely for cases involving a reactive alkylating agent and an early transition state, has been reported for the reaction of methyl fluoro-sulfonate with tautomers involving four different arrangements of heteroatoms.<sup>53</sup> Thus, for example, the conversion of **13-14**, a process which can be achieved in less than 25% yield by other procedures, proceeds in 90% yield on reaction of **13** with methyl fluoro-sulfonate followed by aqueous base. Cases involving an amide, a thioamide, an iminopyridine, and a thio-

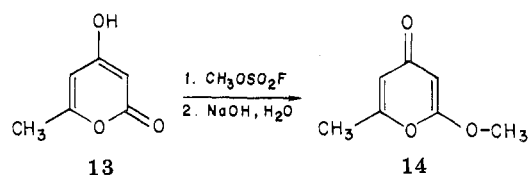
(49) M. Eigen, *Angew. Chem., Int. Ed. Engl.*, **3**, 1 (1964).

(50) D. Y. Curtin, *Rec. Chem. Prog.*, **15**, 111 (1954); E. Eliel, "Stereochemistry of Carbon Compounds", McGraw-Hill, New York, N.Y., 1962, pp 237-239; L. P. Hammett, "Physical Organic Chemistry", McGraw-Hill, New York, N.Y., 1970, pp 119-120.

(51) Failure to recognize this principle has led to errors in structural assignments to tautomers. For discussion see A. R. Katritzky and J. M. Lagowski, *Adv. Heterocycl. Chem.*, **1**, 320 (1963); for other discussions of alkylations of protomeric systems, see A. Grimison, J. H. Ridd, and B. V. Smith, *J. Chem. Soc.*, 1357 (1960); L. Skulski, *Rocz. Chem.*, **46**, 2139 (1972).

(52) It is not implied that reaction is fast with respect to proton transfer or that reaction occurs from only one isomer to each transition state.<sup>7c</sup>

(53) P. Beak and J. Lee, *J. Org. Chem.*, **40**, 147 (1975).



pyridone give higher yields of the predicted product.

On the other hand, the dominant factors for this reaction's success need further study. Precipitates are produced in a number of these cases, and reaction of 2-pyridone gives 1-methyl-2-pyridone in less than 50% yield. In the latter case it has been found that, although initial alkylation occurs as expected at oxygen, that step is followed by a second proton transfer which produces the salt of 2-pyridone as a precipitate and releases 2-methoxypyridine. The pyridine is subject to further alkylation and hydrolysis to provide the observed product as outlined in Scheme IV. Our evidence for that sequence is the detection of 2-methoxypyridine at short reaction times, the identification of the precipitate formed in the reaction, and the demonstration that the dimethylated salt gives 1-methyl-2-pyridone on exposure to workup conditions.<sup>54</sup> Thus, although the site

(54) P. Beak and J. Lee, unpublished results, 1976. Additional complications may arise from association of the tautomers.

of the initial reaction is as predicted, it is obscured by subsequent reactions, and desirable synthetic control is lost. This result raises questions about whether alkylations of other tautomeric systems suffer from similar complications.

**Overview.** While the above discussion focuses on the protomers 1 and 2, similar data from related cases as well as precedent suggest a general conclusion: both the energy difference between protomeric isomers and the strength of association of these isomers can undergo changes of several kilocalories per mole as a function of the medium. Such environmental dependence must be considered in interpretations and applications of tautomeric equilibrium constants. New experimental and theoretical investigations of medium effects and of differences in chemical binding energies are needed to provide a basis for understanding bonding, solvation, and association of heterocyclic protomeric systems. A clear and challenging goal is the construction of predictively useful models.

*I am especially grateful to my colleagues, named in ref 16, 26, 27, and 30, who have been willing to undertake the challenge of working in this area. Their exceptional abilities, insights, and persistence are very much appreciated. We are all grateful to the National Institutes of Health and the National Science Foundation for support of this work.*