Equilibration Studies. Protomeric Equilibria of 2- and 4-Hydroxypyridines, 2- and 4-Hydroxypyrimidines, 2- and 4-Mercaptopyridines, and Structurally Related Compounds in the Gas Phase

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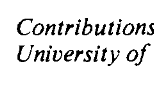
Abstract: Ultraviolet spectroscopy reveals that 2-hydroxypyridine (**3**), 6-chloro-2-hydroxypyridine (**11**), 4-hydroxypyridine (**15**), 2-hydroxypyrimidine (**19**), 4-pyrimidone (**25**), 4-methyl-6-hydroxy-2,3-dihydro-7-azabenzofuran (**29**), 2-mercaptopyridine (**31**), 4-mercaptopyridine (**35**), 5-acridone (**40**), and 9-anthrone (**44**) are the major protomeric isomers in the vapor. Infrared spectroscopy confirms the assignments for **3**, **15**, **19**, and **25**, and the infrared results show that the isomers are monomeric in the vapor. The fact that the protomers are in equilibrium in the vapor is established by the constancy of the ratio of the absorptions of 2-hydroxypyridine (**3**) and 2-pyridone (**4**) as the intensities of the absorptions increase and decrease with temperature changes. Equilibrium constants or a limit on an equilibrium constant, are calculated for the ten systems studied. The results are discussed in terms of the relative chemical binding energies of the protomeric isomers, and it is shown that three presently used quantum mechanical predictions of relative stability of **3**–**4** are in error by at least 10 kcal/mol. The large differences between the stabilities of the tautomeric forms in the vapor and in solution again reveal the dominant influence that environment can have on relative molecular stabilities. It is further shown that analysis of this difference for **3**–**4** in terms of the Onsager dipole interaction model is surprisingly effective in providing understanding of the environmental effect. The implications of this work for future determinations of tautomeric equilibria, for calculations of stability, and for applications of tautomeric constants to biological problems are noted.

The position of equilibrium for protomeric systems in solution has often been used to deduce general structure-stability relationships.[1] For example, equilibria between a wide variety of iminols **1** and the corresponding amides **2** have been shown to favor the amide,[2,3] and those results have been extended beyond the initial studies to such diverse areas as quantum mechanical calculations and theories of genetic mutation.



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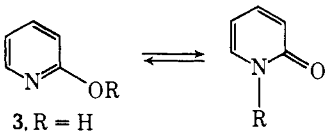
The important role that molecular environment can play in such equilibria may be illustrated by the case of the 2-hydroxypyridine (**3**)-2-pyridone (**4**). Determination that the equilibrium for **3**–**4** in solution lies far on the side of **4** is one of the classic studies of tautomerism. As early as 1907 ultraviolet spectral data were interpreted in favor of the amide form,[4] but it was not until 1942 that comparison of the spectra of the protomeric system with those of 2-methoxypyridine (**5**) and 1-methyl-2-pyridone (**6**) firmly established the validity of that conclusion.[5] Qualitative support for the predominance of **4** in liquid media is also provided by infrared[3b,6] and nuclear magnetic resonance[6d,7] spectral data and dipole moment studies,[6d] although **4** is highly dimerized in nonpolar solvents.[6d,8] Basicity measurements of **3**–**4**, with **5** and **6** as model compounds, have provided a quantitative estimate of the equilibrium in aqueous solution at 25° as ca. 10^3 in favor of **4**.[9,10] Structure determination by x-ray crystallography also supports **4** as the favored structure in the solid.[11] However, studies of the vapor of **3**–**4** by infrared[12] and mass spectrometry[13] and infrared investigation of material trapped from the vapor in an argon matrix[14] indicate that comparable amounts of the tautomers are present. The contrast between the relative amounts of **3** and **4** in the vapor and in solution have been attributed to a lack of equilibrium in the vapor.[10,12c]



3, R = H
5, R = CH_3
4, R = H
6, R = CH_3

We now present more specific support for our previous contention that an equilibrium of 2.5:1 is established for **3**–**4** in the vapor phase[15] and report extensions of these studies to ultraviolet and infrared determinations of gas phase equilibria of iminol-amide and thioiminol-thioamide functions in other six-membered heteroaromatics. These results provide fundamental information about the differences in chemical binding energies of the systems studied and demonstrate a large medium effect on these protomeric equilibria. We also show that the latter effect can be rationalized for some 2-substituted pyridines by the Onsager dipole-medium interaction model.

Results

Ultraviolet Spectra in the Gas Phase. The gas phase ultraviolet spectra of 2-hydroxypyridine-2-pyridone (**3**–**4**) and of the model compounds 2-methoxypyridine (**5**) and 1-methyl-2-pyridone (**6**) are presented in Table I.[16]

Acceptance of **5** and **6** as models and comparison of the spectra in Table I show that ultraviolet absorptions attributable to both **3** and **4** are observed in the vapor at 130 and 250°. The absorption bands in the spectrum of **3**–**4** in the gas phase at 135 ± 3° are stable for 8 hr and a 95% recovery of material with solution ir, NMR, and uv spectra identical with those of **4** was achieved after the sample had been heated in the gas cell for 6 hr at 120–150°. Material used to obtain spectra at 250° was recovered in 90% yield and shown to have the solution uv spectrum of **4**. Spectra below 240° were obtained in a conventional spectrometer with a double windowed cell. Trial experiments showed that double windows were necessary to prevent condensation on the windows. If condensation occurs, a spectrum is obtained

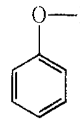
Table I. Ultraviolet Spectra in the Vapor Phase and in Solution

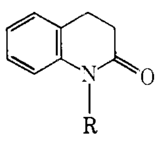
Compd(s)	Phase	T, °C	λ_{max}, nm	ϵ
3–4	Vapor	130	297, 271	a
	Vapor	250	299, 271	b
4	Water (pH 6)^c	Ambient	293	5900
	Ethanol	Ambient	305	6000
	Cyclohexane	Ambient	300	
	Melt	>108	310	
5	Vapor	Ambient	271	
	Vapor	250	270	
	Water (pH 7)^c	Ambient	269	3230
	Ethanol	Ambient	271	4450
6	Vapor	55	305	
	Vapor	250	307	
	Water (pH 5)^c	Ambient	297	5700
	Ethanol	Ambient	302	5550

^{a} The absorbance ratio at λ_{max} $A(3)/A(4)$ = 2.17. ^{b} The absorbance ratio at λ_{max} $A(3)/A(4)$ = 1.96. ^{c} A. I. Scott, "Interpretation of Ultraviolet Spectra of Natural Products", Pergamon Press, New York, N.Y., 1964, pp 178–184.

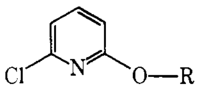
which has a λ_{max} at 300 nm and corresponds to that obtained from a thin film of melted **4**. Spectra taken above 240° were obtained on a uv spectrometer modified for high temperature work.

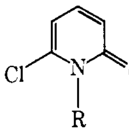
The use of methylated compounds as model chromophores for protomeric isomers is well established.[5,17] Empirical justification for the present case is based on the correspondence of the ultraviolet spectrum of anisole (**7**) [λ_{max} 271, 277 nm (ϵ 2000, cyclohexane)] with that of phenol (**8**) [λ_{max} 272, 277 nm (ϵ 2000, cyclohexane)][18] and on the correspondence of the spectrum of 3,4-dihydrocarbostyril (**9**) [λ_{max} 252 nm (ϵ 10000 dioxane)] with that of 1-methyl-3,4-dihydrocarbostyril (**10**) [λ_{max} 253 nm (ϵ 14000 dioxane)].[19] Also included in Table I are solution spectra which show that, although shifts of λ_{max} do occur with changes in medium, for these cases the shifts are not large enough to affect the assignments. In fact, the spectra of **5** and **6** in Table I in the vapor phase are virtually identical with those in ethanol, with the exception of fine structure observed in the gas phase spectrum of **5**. For the present work (vide infra), this correspondence is taken to justify the comparison of ethanol spectra of the models with vapor phase spectra of the protomers.

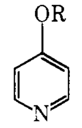

7, R = H
8, R = CH$_3$

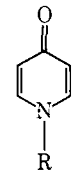

9, R = H
10, R = CH$_3$

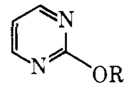
The ultraviolet spectra of a number of monocyclic, six-membered, nitrogen-containing heteroaromatics have been obtained and are presented in Table II along with the spectra of the corresponding methylated isomers. The spectra in ethanol and the tautomeric assignments made therefrom are generally consistent with previous assignments for solutions.[3] Of more interest are the vapor phase spectra. The spectra of **11–12**, **13**, and **14** in Table II show 6-chloro-2-hydroxypyridine (**12**) to be the major form in the vapor. The same protomer is favored in ethanol but, in highly aqueous ethanolic solutions, 6-chloro-2-pyridone is preferred.[20] The spectra in the table show that 4-hydroxypyridine (**15**) and 2-hydroxypyrimidine (**19**) predominate in the vapor phase, whereas 4-pyridone[9,17b,21] and 2-pyrimidone[9a,9b,22] are the only detectable forms in ethanolic solution. In the case of 4-pyrimidone, however, the amide form **25** predominates in both solution,[9a,9b,22] and the gas phase, although absorption due to at least one other protomer, either **23** or **24**, is also observed in the vapor phase. Those spectra are shown in Figure 1, where the spectrum of **27** is reported at 150° because at higher temperatures rearrangement to **28** occurs.

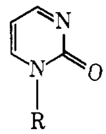

11, R = H
13, R = CH$_3$

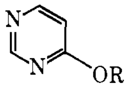

12, R = H
14, R = CH$_3$

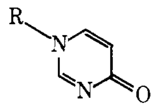

15, R = H
17, R = CH$_3$

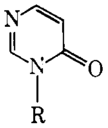

16, R = H
18, R = CH$_3$

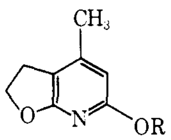

19, R = H
21, R = CH$_3$

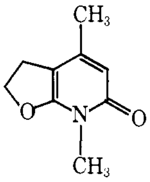

20, R = H
22, R = CH$_3$

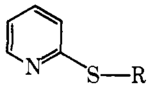

23, R = H
26, R = CH$_3$

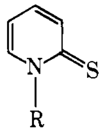

24, R = H
27, R = CH$_3$

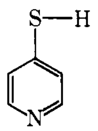

25, R = H
28, R = CH$_3$

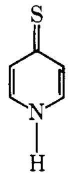

29, R = H
51, R = CH$_3$

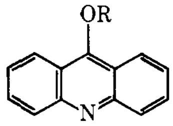

30, R = H
52, R = CH$_3$

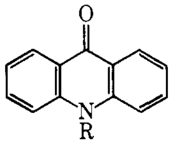

31, R = H
33, R = CH$_3$

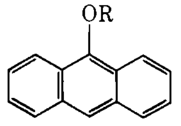

32, R = H
34, R = CH$_3$

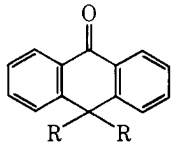

35, R = H
37, R = CH$_3$


36, R = H
38, R = CH$_3$


39, R = H
41, R = CH$_3$


40, R = H
42, R = CH$_3$


43, R = H
45, R = CH$_3$


44, R = H
46, R = CH$_3$

The vapor phase spectra of 4-methyl-6-hydroxy-2,3-dihydro-7-azabenzofuran recorded in Table II shows both tautomers can be observed and that the hydroxy form predominates. The tautomer **29** is also the major form (60%) in ethanol, whereas the amide **30** predominates in highly aqueous ethanol.[17a,23] The report of Levin and Rodionova,[12c] that a change in the ratio of the protomers **29–30** is observed on heating in the vapor phase, prompted us to study the vapor spectra as a function of temperature.[12c] We found that at 180° the absorbances of **29** and **30** both decreased. Examination of the material in the cell after cooling indicated that thermal decomposition had occurred and heating to higher temperatures gave only more decomposition. The earlier work[12c] was carried out at 345–360°, a temperature at which decomposition of this compound could be extensive.

The spectra of the 2- and 4-thio-substituted pyridine rings suggest that the 2-mercapto and 4-mercapto forms **31**

Table II. Ultraviolet Spectra in the Vapor Phase and in Solution

Compd(s)	Phase	T, °C	λ_{max}, nm	ϵ
11–12	Vapor	100 ± 3	285, 300	
	Ethanol[a]	Ambient	277, 305	5130, 1240
12	Aqueous	Ambient	304	7000
13	Aqueous[a]	Ambient	308	7400
14	Aqueous[a]	Ambient	276	5400
15	Vapor	250	240	
16	Ethanol	Ambient	257	14700
17	Vapor	160	240	
	Ethanol	Ambient	218, 235 (sh)	10200, 2200
18	Vapor	175	258	
	Ethanol	Ambient	265	30000
19	Vapor	220	258[b]	
20	Ethanol	Ambient	298	4710
21	Ethanol	Ambient	264	4780
22	Ethanol	Ambient	302	5400
23–25	Vapor	220	255, 275	*c*
25	Ethanol	Ambient	218, 270	12000, 3850
26	Vapor	170	248	
	Ethanol	Ambient	248	3150
27	Vapor	150	254	
	Ethanol	Ambient	242	16000
28	Vapor	190	275	
	Ethanol	Ambient	218, 275	7590, 3710
29–30	Vapor	175	287, 325	*d*
	Ethanol[e]	Ambient	295, 326	
51	Ethanol[e]	Ambient	290	7250
52	Ethanol[e]	Ambient	326	9550
31	Vapor	175	233, 284, 380	*f*
32	Ethanol	Ambient	287, 362	10200, 4860
33	Vapor	35	248, 290	*g*
	Ethanol	Ambient	248, 291	10400, 4080
34	Vapor	110	245, 293, 368	*h*
	Ethanol	Ambient	287, 357	12900, 6370
35	Vapor	150	235, 257 (sh)	*i*
36	Ethanol	Ambient	230, 342	5920, 14300
37	Vapro	35	248, 262 (sh)	*j*
	Ethanol	Ambient	263	11800
38	Vapor	190	235, 350	*k*
	Ethanol	Ambient	231, 348	6520, 25000
40	Vapor	270	371, 363 (sh), 353	*l*
			295 (sh), 268, 238	
	Ethanol	Ambient	398, 368, 363 (sh)	8870, 8410, 4670
			344 (sh), 307, 294	1860, 1400, 2330
			268 (sh), 265 (sh), 255	117100, 36000, 53700
41	Vapor	200	368 (sh), 353, 338	*m*
			242, 238	
	Ethanol	Ambient	385 (sh), 370 (sh), 354	3500, 5700, 8770
			348 (sh), 337, 323 (sh)	7190, 5260, 2630
			253	156000
42	Vapor	230	377, 368, 353	*n*
			295, 277, 239	
	Ethanol	Ambient	400, 383, 365 (sh)	8180, 7720, 3630
			305, 293, 223 (sh)	1360, 2630, 15900
			263 (sh), 256	30900, 48600
44	Vapor	220	298, 286, 250	*o*
	Ethanol	Ambient	305, 290 (sh), 268 (sh)	2920, 3850, 13500
			260, 248 (sh)	26000, 13500
45	Vapor	100	376, 372, 357	*p*
			353, 340, 325	
			310, 250	
	Ethanol	Ambient	388, 368, 249	6400, 7300, 4600
			333, 318, 256	2100, 820, 188000
			248	95000
46	Vapor	150	302, 296, 290	*q*
			257	
	Ethanol	Ambient	268, 290 (sh), 300 (sh)	15600, 6000, 4220

[a] References 20 and 21g. [b] Shoulders at 252, 263 nm. [c] Ratio of absorbances is 9:10. [d] Ratio of absorbances is 1:10. [e] References 17a and 12c. [f] Ratio of absorbances is 10:4:0.5. [g] Ratio of absorbances is 10:3. [h] Ratio of absorbances at 293 and 268 nm is 10:2. The absorbance at 245 nm is three sharp absorbances. [i] Ratio of absorbances is 10:4. [j] Ratio of absorbances is 10:4. [k] Ratio of absorbances is 10:6. [l] Ratio of absorbances is 1.6:1.3:1.4:0.8:4.3:10. [m] Ratio of absorbances is 0.2:0.5:0.4:10:8.5. [n] Ratio of absorbances is 2.5:1.5:1.5:0.8:3.6:10. [o] Ratio of absorbances is 1.4:1.4:10. [p] Ratio of absorbances is 1.5:1.3:1.6:10. [q] Ratio of absorbances is 9 .8:6.2:10:7.8:6.8:3.6:1.6.

and **35** are dominant in the vapor. Again, these results are in contrast to the solution studies.[3b,21f,24]

The results of the vapor phase ultraviolet studies of 5-acridone and 9-anthrone and their derivatives compiled in the table are consistent with the predominance of the carbonyl tautomers **40** and **44** for both compounds and, in these cases, the carbonyl forms are predominant in solution[25] as well.

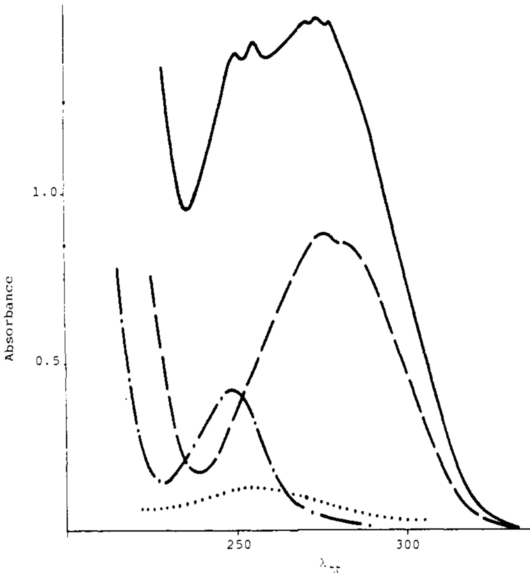


Figure 1. Gas phase ultraviolet spectra: (**23–25**) 4-Hydroxypyrimidine–4-pyrimidone (—, 255°); (**28**) 3-methyl-4-pyrimidone (- - -, 218°); (**27**) 1-methyl-4-pyrimidone (· · ·, 150°); (**26**) 4-methoxypyrimidone (- · -, 170°).

Infrared Spectra in the Gas Phase. The first indication that the composition of **3–4** in the vapor is different from that in solution was provided by the infrared investigations of Levin and Rodionova. Subsequent work by them has shown that a number of hydroxypyridine–pyridone systems have different compositions in the vapor from that in solution. For example, the Russian workers have reported 6-chloro-2-hydroxypyridine and 4-methyl-6-hydroxy-2,3-dihydro-7-azabenzofuran to be the dominant protomers in the vapor.[12] The vapor phase infrared spectra summarized in Table III were obtained in the present study and support the tautomer assignments made to **3–4** on the basis of the ultraviolet studies (vide supra). The assignments of OH and NH stretching frequencies are in agreement with previous work.[12,26] Both bands in the case of **3–4** are sharp doublets, an effect which could be attributed to unresolved rotational states or Fermi resonance.[12,27] In the case of the 4-pyrimidone, the ir spectrum allows a choice for the minor tautomer to be made in favor of the hydroxy compound **23**.

Equilibrium in the Gas Phase. It has been suggested on the basis of the change observed in the intensities of the NH and OH absorptions for **29–30** at 345–360° that the composition of such protomeric systems in the gas phase could be controlled by the relative rates of vaporization of the protomers and not by their relative stabilities.[10,12c] However, the enol of acetone has been shown to equilibrate with its keto tautomer in the gas phase by wall collisions at substantially lower temperatures under conditions[6,28a] otherwise comparable to the present work. Moreover, the similarity of the ratio of absorbances for **3–4** at 130 and 250° of 2.17 and 1.96 (Table I) might be regarded as surprising if dependence on the relative rates of vaporization were significant.

In order to establish whether the relative rates of vaporization determine the relative amounts of **3** and **4** in the vapor, the changes in absorption for these isomers were studied as a function of temperature from 120 to 139° (Table IV). Although the absorbances attributed to each protomer change by a factor of ca. 2.5 over this range the averaged ratios of the absorbances vary by a factor of less than 0.12. The values in Table IV are averages of four to ten measurements and were made on both cooling and heating cycles. Clearly there are no apparent rate differences for the vaporization of the two protomers under these conditions. On the other hand, if the protomers in fact had the same rates of vaporization, the composition of the vapor should reflect the composition of the melt and it has been shown by ultraviolet spectroscopy (vide supra) that the only detectable isomer in the melt is **4**, the minor isomer in the vapor. The rates of vaporization of the protomers must then be different, and consistency of the ratio of the isomers in the vapor is observed because the isomers are in equilibrium. Although vapor-liquid equilibrium can be slow,[28c] equilibration in the melt would be fast, and precedent also exists for equilibration by wall collisions.[28] Either mechanism could be operative for equilibration of the vapor phase systems in the present study.

Table III. Infrared Spectra of the Vapor

Compd(s)	T, °C	OH_{Str}, cm^{-1}	NH_{Str}, cm^{-1}
3–4	225	3600	3450
15	270	3650	
19	280	3550	
23–25	280	3590	3440

Table IV. Variable Temperature Gas Phase Ultraviolet Spectra of 2-Hydroxypyridine (3)–2-Pyridone (4)

T, °C	$A(3)^a$	$A(4)^a$	$A(3)/A(4)^a$
120 ± 3	0.65 ± 0.02	0.31 ± 0.01	2.08 ± 0.04
132 ± 3	1.27 ± 0.21	0.59 ± 0.12	2.17 ± 0.12
139 ± 3	1.67 ± 0.14	0.76 ± 0.14	2.19 ± 0.12

[a] The error limit is the range observed on successive measurements in both heating and cooling cycles.

Table V. Vapor and Solution Equilibrium Constants. $K_T = [NH]/[OH]$

Compd(s)	T, °C	$K_{T(vapor)}$	$K_{T(soln)}{}^a$
3–4	130	0.4 ± 0.25 (uv) 0.5 ± 0.3 (ir)	910[b]
11–12	120	0.05, 0.03[c]	1.6[d]
15–16	250	<0.1	1900
19–20	220	<0.1	>15[e]
23–25	220	1.8 ± 1.0	>4[e]
29–30	175	<0.1	0.3[f]
31–32	170	<0.1	70000[c,h]
35–36	150	<0.1	47000[c,g]
39–40	270	>10	>5[h]
43–44	220	>10	Variable[i]

[a] From pK_a data at ambient temperatures in aqueous solution at 25–30° unless otherwise stated. [b] Reference 9. [c] References 12c and 14. [d] Reference 20, in ethanol the K_T as determined by ultraviolet spectroscopy is 0.16. [e] Spectra measured in ethanol. [f] Reference 59 and redetermination of the spectra in ethanol. [g] Reference 24a. [h] No OH tautomer is detectable: R. M. Acheson, M. L. Burstall, C. W. Jefford, and B. F. Sansom, *J. Chem. Soc.*, 3742 (1954). [i] K_T varies from ca. 10^3 in isooctanol and benzene to 1 in pyridine (ref 25).

Lack of Association in the Vapor. The infrared absorptions assigned to the NH and OH stretching vibrations of **3–4**, **15**, **19**, and **23–25** are doublets with widths at half height of ca. 40 cm^{-1}. Association by hydrogen bonding[6d,8] would be expected to give absorptions with half-widths of at least 400 cm^{-1} which would be centered ca. 600 cm^{-1} lower in frequency.[29] We estimate that a maximum of 10% association could be present in these experiments and the composition of the vapor is considered to reflect the relative stability of monomers.

Equilibrium Constants in the Vapor. The vapor phase equilibrium constants determined for the protomeric systems investigated in this work are shown in Table V. For cases in which only one isomer is observed the differences in absorption are such that values of greater than 10 (or less than 0.1) can be assigned. Equilibrium constants for systems in which both protomers can be observed are based on the assumption that the diagnostic absorption bands of the isomers in the vapor at the temperature required for measurement will have the same band shape and the same relative extinction coefficients as those of the methylated models in solution. For cases in which differences in λ_{max} are evident between the model and the corresponding protomer, a shift of λ_{max} is included in the calculation. Although these approximations may introduce some error, the equilibrium constants should be correct to at least a factor of 2. Moreover, some confidence in the quantitative results of the uv analysis is provided by the fact that analysis of the vapor phase infrared spectra of **3–4** gives essentially the same equilibrium constant if the approximation that OH and NH stretching vibrations have equal molar absorption coefficients is made.[12,14]

Discussion

The equilibria represented by the equilibrium constants in column three of Table V are for isolated molecules in their ground electronic and vibrational states. Analysis of the relative energies of these protomers is of interest for evaluation of chemical binding energies and discussion of phase effects on such equilibria.

Chemical Binding Energies. Evaluation of kinetic and zero point energy contributions to the vapor phase equilibria presented in Table V would allow the determination of quantitative differences in chemical binding energies for those cases in which both protomers can be detected. By the same type of entropic analysis which was previously used to suggest that the kinetic energy difference is less than 0.5 kcal/mol between 2-methoxypyridine (**5**) and 1-methyl-2-pyridone (**6**) at 130°,[30] it can be suggested that the kinetic energy contribution to the energy difference between 2-hydroxypyridine (**3**) and 2-pyridone (**4**) is small.[31] A more convincing estimate of the entropy difference between **3** and **4** comes from the study of K_T as a function of temperature. The values of K_T of 2.40, 2.53, 2.56, 2.25, and 2.14 at 120, 132, 139, 250, and 350° give a plot of ln K vs. $1/T$ which provides a $\Delta H_{isom}°$ of -0.3 ± 0.3 kcal/mol and $\Delta S_{isom}°$ of +3 Gibbs. Accordingly $\Delta G_{isom}°$ at 132° is 0.8 kcal/mol and the entropy contribution at this temperature is ca. 1 kcal/mol. If the difference in zero point energies of ±1.5 kcal/mol estimated for **5** and **6**[30] is accepted for **3** and **4**, the difference in chemical binding energy of **3–4** is $+0.3 \pm 2.5$ kcal/mol. The equilibrium for **3–4** shown in Table V provides then a reasonable approximation of the differences in chemical binding energy between the protomers. Presumably the equilibria for other systems in Table V also reflect this fundamental energy difference.

It is apparent that unless kinetic and zero point energy effects unexpectedly reverse the trend, 4-hydroxypyridine[32] (**15**), 2-hydroxypyrimidine (**19**), 2-mercaptopyridine (**31**), 4-mercaptopyridine[32] (**35**), 5-acridone[32] (**40**), and 9-anthridone[32] (**44**) should be considered to have the lower chemical binding energy of the possible protomers in each case. For the cases of **3–4** and **23–25**, the relative chemical binding energies are sufficiently close that reliable conclusions about the protomer of lowest chemical binding energy cannot be drawn.

The relative chemical binding energies of many protomeric isomers of heteroaromatic systems have been calculated by quantum mechanical methods, but such calculations have not been subject to test because experimental information about relative chemical binding energies have not been available. With the present determination of this energy for 2-hydroxypyridine (**3**)-2-pyridone (**4**), the predictions of three popular methods can be evaluated by the comparison of theory and experiment shown in Table VI.

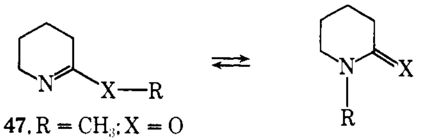
Table VI. Relative Chemical Bonding Energies of 2-Hydroxypyridine–2-Pyridone as Determined by Experiment and by Calculation (kcal/mol)

Compd(s)	SCF–MO	MINDO 2	CNDO 2	Experiment
3–4	−11.9[a]	−14.2[b]	11.3[c]	0.3 ± 2.5

[a] Reference 35a. [b] Reference 36a. [c] Reference 35b.

All of the calculations predict a difference in stabilities of the isomers of at least 11 kcal/mol, but the SCF-MO and MINDO/2 methods predict **4** to be the more stable, while the CNDO/2 procedure predicts **3** to be heavily favored. None of the predictions is in accord with the experimental facts. Clearly the predictions of relative stabilities made by these quantum mechanical approaches cannot yet be considered reliable for complex heteroaromatic systems.[33-37] The data in Table V and extrapolations therefrom (vide infra) should provide stimulation and calibration for further theoretical efforts.

Comparison of the vapor phase enthalpy difference for **3–4** of -0.3 ± 0.4 kcal/mol with that of -7.7 ± 2.3 kcal/mol for **5–6** 30 suggests a value of ca. 7.4 kcal/mol due to the difference in local bond energies (NH, OH vs. NCH_3, OCH_3). If this value is applied to the previously reported gas phase enthalpy differences of 14.1 ± 2.0 kcal/mol for 2-methoxy-3,4,5,6-tetrahydropyridine (**47**) and 1-methyl-2-(1-*H*)-3,4,5,6-tetrahydropyridone (**48**), a gas phase enthalpy difference of ca. 7 kcal/mol is predicted between valerolactim (**49**) and valerolactam (**50**) in favor of (**50**).[38] If the same local bond difference approximation is applied to the 0.1 ± 1.8 kcal/mol energy difference between 4-methoxypyridine (**17**) and 1-methyl-4-pyridone (**18**), an estimated enthalpy difference of 7 kcal/mol in favor of **16** is obtained for the pair **15–16**. Clearly, similar estimates could be made for enthalpies of other closely related systems.[39] It does not appear that these predicted enthalpy differences can be tested at present, but the values should be useful until measurements are available.



47, R = CH_3; X = O
49, R = H; X = O

48, R = CH_3; X = O
50, R = H; X = O

In principle the differences in chemical binding energies for **3–4** and **23–25** could be combined with local σ-bond energy values to give an estimate of the differences in π-bond energy for the protomers. However, this has not been done because there does not appear to be a reliable value for the enthalpy contribution of C-2 in **49**.[40]

The Dominant Effect of Solvent and Phase. The positions of vapor phase protomeric equilibrium for the hydroxy- and mercaptopyridines and pyrimidines **3**, **15**, **19**, **25**, **29**, **31**, and **35** differ from the positions of equilibrium for the same systems in aqueous or ethanolic solution by as much as 10^5. The contrast between the vapor and solution equilibria for those cases and for related systems can be seen by comparison of $K_{T_{vapor}}$ and $K_{T_{soln}}$ in columns three and four of Table V. Even for the last two entries in the table, which show that 5-acridone (**40**) and 9-anthrone (**44**) are favored in both the vapor and solution, substantial differences could exist between the gas phase and solution, but those differences would not be detected by ultraviolet spectroscopy as long as the protomer which is dominant in solution is also favored in the vapor by a factor of 10 or more. The possibility that the differences in equilibria in the gas phase and aqueous solution are primarily due to differences in temperature can be discounted by the small entropy difference between **3** and **4** such that the gas phase free energy values at 130° could be extrapolated to 25° with relatively small change. The results compiled in Table V make it abundantly clear that molecular environment can have a dominant effect on the position of protomeric equilibria in such heteroaromatic systems.[30] Claims to the contrary[10] or the use of solution data to support the results of theoretical calculations[35a] cannot be sustained.

The dependence of the position of equilibrium on phase and solvent finds analogy in recent studies which have revealed astonishing differences between ionic reactions in the gas phase and in solution,[41] and in previous reports that the medium has a significant effect on the position of some,[3,17a,42,43] but not all,[44] tautomeric equilibria. The present results support the earlier caution[30] against the use of individual protomeric equilibria to estimate chemical binding energies and suggest that the same concerns about the effects of solvent which are now coming into focus for a number of ionic reactions apply also to formally neutral species.[41,43,45] A thermodynamic cycle for dissecting these effects has been suggested[46] in terms of the formal conversions of each of the tautomers to the gas phase by the processes of desolvation and vaporization. In general an enthalpy difference will exist between solution and gas phase equilibria unless any differences in the heats of solution of the isomers are closely compensated for by an opposite difference in the heats of vaporization. That such compensation is unlikely for the equilibria in Table V follows by analogy to our earlier analyses for the case of **3–4**.[46,47]

A semiquantitative evaluation of the differences in enthalpies for transfer of the protomers from aqueous solution to the vapor may be obtained if estimates of protomeric equilibrium constants in solution, which have been made by the pK_a method[9,10] (Table V), are provisionally accepted and entropy differences are ignored.[48] With this approach and the data for 2-hydroxypyridine–2-pyridone in Table V, an enthalpy effect of ca. 4 kcal/mol can be calculated for the transfer of this protomeric equilibrium from aqueous solution to the vapor at 25°. From the data of Table V, enthalpies of transfer for related systems can be calculated as 2 kcal/mol for 6-chloro-2-hydroxypyridine–6-chloro-2-pyridone and >8 kcal/mol for 2-mercaptopyridine–2-thiopyridone. If such enthalpies could be generally determined, it might be possible to estimate vapor phase equilibria, and thereby relative chemical binding energies, from the many previous studies of tautomerizations in solution.

Although large differences for protomeric equilibria in the vapor and in aqueous solution should not be regarded as surprising, the position of equilibrium in a nonpolar solvent might be expected to be close to that in the gas phase. However, there does appear to be a difference between the equilibrium for **3–4** in cyclohexane and in the vapor. As shown in Table I, the ultraviolet spectrum of the tautomers in cyclohexane shows only **4** in contrast to the predominance of **3** in the vapor phase, and this appears to be true even at 10^{-4} *M*. On the other hand, it cannot be concluded from these data that the energy difference between the tautomers in the vapor and in cyclohexane are necessarily very different. As much as 10% of **3** could be present, undetected in the cyclohexane solution. Moreover, the apparent dominance of **4** could be due to association,[6d,8] and there could be a substantial temperature effect on that equilibrium constant. Further studies are underway to clarify this issue.

Table VII. Energy of Transfer of the Protomeric Equilibria of Some 2-Substituted Pyridines from the Vapor to Solution as Calculated by the Modified Onsager Equation[a] (kcal/mol)

Solvent	3–4[b]	3–4[c]	11–12[c]	31–32[c]
Water	5.0	3.0	1.3	4.2
Ethanol	4.7	2.8	1.3	4.0
Benzene	1.7	1.4	0.6	2.0
Carbon tetrachloride	1.7	1.4	0.6	1.9
Cyclohexane	1.5	1.2	0.6	1.7

[a] Reference 51. [b] Polarizability term included. [c] Polarizability term excluded.

The phase dependent equilibria summarized in Table V are consistent with previous studies of solvent effects on tautomeric equilibria which suggest that, as solvent polarity increases, the more polar isomer is stabilized relative to the less polar isomer.[42–44] The fundamental model for the polarity part of such a solvation effect is the energy of a dipole interacting with a dielectric medium as formulated by Onsager in 1936.[49] In fact, Powling and Bernstein in 1951 found that the Onsager equation could account quantitatively for the effect of solvents on the relative energies of the tautomers of some 1,3-dicarbonyl compounds, although separate correlation lines were obtained for protic and nonprotic solvents.[50] More recently, Abraham and co-workers have modified the Onsager equation to include the effect of solute volume and polarizability.[51]

Although direct application of the Onsager model to the protomeric equilibria of the present study is clearly naive since the equations do not include the effect of solvent cavitation nor account for specific solute–solvent interactions such as hydrogen bonding,[52] we have, nonetheless, explored the application of the modified Onsager equation to the 2-substituted pyridine systems **3–4**, **11–12**, and **31–32** as a first approximation. The methylated isomers **5** and **6** were used to provide the necessary physical constants (Appendix).[53] The results are summarized in Table VII for some solvents commonly used in tautomeric investigations. The first entry in the second and third columns in the table shows that the calculated energies of transfer from water to the gas phase for the equilibrium **3–4** are 5.0 and 3.0 kcal/mol, including and excluding the polarizability term respectively. Those values are remarkably, and perhaps fortuitiously, close to the value of 4 kcal/mol noted above. The trend of decreasing relative stabilization of the more polar isomer **4** as the polarity of the solvent decreases, apparent in both columns, is in agreement with the qualitative trend usually noted. It must be noted, however, that this prediction is for the monomeric isomers and may not actually apply to the real case since **4** is known to be highly dimerized in nonpolar media.[6d,8] It is also interesting to note that even cyclohexane is predicted to have an appreciable effect on the position of equilibria relative to that in the gas phase. Comparison of columns two and three reveals that inclusion of the polarizability term increases the energy differences by a factor of 1.7 in water and by a factor of 1.2 in cyclohexane. The first entry in column four of 1.3 kcal/mol is in reasonable agreement with the effect of 2 kcal/mol noted previously. The first entry in column five of 4.2 kcal/mol is in disagreement with the value of >8 kcal/mol calculated from Table V although, if inclusion of the polarization term were to have an effect of a factor of 1.7, closer agreement would be found. However, in view of the assumptions, quantitative agreement between theory and experiment should probably not be expected. Of more significance is the fact that this application of the modified Onsager equations is in agreement with the trend of solvent effects noted experimentally; the equilibrium of chloropyridines is least sensitive and that of the thiopyridines most sensitive, to the polarity of the medium.

Conclusions and Implications

The above determinations of chemical binding energy differences for the isomeric systems **3–4, 11–12,** and **23–25** provide the point from which understanding of stabilities and solvation effects should begin. Our studies show that the quantum mechanical theories which have been applied to the determination of the relative stabilities of such isomers do not give useful results.

The fact that equilibria for the hydroxypyridines, mercaptopyridines, and hydroxypyrimidines are very different in the vapor and in polar solvents demonstrates that the environment can have a dominant effect on the stabilities of these and probably other formally neutral systems. Analysis of these differences by the Onsager equation offers a fundamental, if patently incomplete, explanation for the effect of environment on these equilibria, and further testing and modification of this approach appears warranted.

Clearly the position of tautomeric equilibria at least in polar media should not be interpreted in terms of the fundamental stabilities of the systems involved. Future determinations of tautomeric equilibria in solution must take into account the effect of molecular environment if approximations of energy differences between the unperturbed isomers are of interest.

Presumptive extrapolation of protomeric equilibria, whether obtained by theory or experiment, to molecular environments different from those for which the measurement or prediction is made is clearly unwise. For example, the tautomeric equilibria which have been suggested to affect RNA transcription and DNA replication[54] can be reliably evaluated only under the conditions of the biological processes.[55] In particular studies of protomeric equilibria of the purine and pyrimidine bases while of fundamental interest in their own right may not be relevant to the positions of such equilibria for these bases in biological systems. In another area, the action of 2-pyridone as a model for a tautomeric catalyst[56] may reflect in part a small energy difference between **3** and **4** at the catalysis site.

Experimental Section[57]

Purification of Materials. The purifications of 2-pyridone, 2-methoxypyridine, and 1-methyl-2-pyridone follow earlier procedures.[58] Solid 2-pyridone (J. T. Baker Chemical Co.) was purified by repeated sublimation to give white, crystalline, analytically pure material, mp 106–107°. Upon storage over anhydrous calcium sulfate in a dry argon atmosphere, this material remained white for about 1 month. Freshly purified material was always used for the experiments reported herein. 2-Methoxypyridine (Aldrich Chemical Co.) was purified to analytical quality by distillation, bp 41–43° (14–15 Torr). 1-Methyl-2-pyridone was purified to analytical quality by distillation: bp 74–76° (0.4–0.5 Torr); mp ~25°. Ir, NMR, uv, and mass spectral properties of these materials are consistent with those expected for the assigned structures.

Other compounds purified by similar methods and characterized by similar criteria are: 6-chloro-2-pyridone and 4-pyridone (Aldrich Chemical Co.), 4-methyl-6-hydroxy-2,3-dihydro-7-azabenzofuran,[59] 4-methoxypyridine,[30] 1-methyl-4-pyridone,[30] 2-hydroxypyrimidine (Aldrich Chemical Co. as the HCl salt), 2-methoxypyrimidine,[22] 1-methyl-2-pyrimidone,[22] 4-hydroxypyrimidine,[60] 4-methoxypyrimidine,[22c] 1-methyl-4-pyrimidone,[22e] 3-methyl-4-pyrimidone,[58] 2-thiopyridone,[61] 2-methylthiopyridine,[62] 1-methyl-2-thiopyridone,[61,62] 4-thiopyridone,[63] 4-methylthiopyridine,[63] 1-methyl-4-thiopyridone,[24c] 5-acridone,[25a] 1-methyl-5-acridone,[25a] 9-anthrone,[25d] 9-methoxyanthracene,[25a] and 5,5-dimethylanthrone.[25d]

Ultraviolet Spectra. Some ultraviolet studies of 2-pyridone, 2-methoxypyridine, and 1-methyl-2-pyridone were carried out in sealed 10-mm quartz cells at 250 and 340° in the tube furnace sample chamber of a Carey 17-H spectrometer.[64] Most gas phase spectra were obtained in a conventional spectrometer with a sample cell consisting of double quartz Optasil windows on a 25 mm quartz pipe fitted with a 4-mm vacuum stopcock and wrapped with a heater. The inner windows are separated by 10 cm and the outer windows are separated from the inner ones by 20 mm, with the intervening volume evacuated. The cell body is wrapped with 16-ga chromel wire (0.248 Ω/ft) secured at the ends of the cell body by binding lugs and covered with refractory cement and fiberglass insulation. The voltage applied to the cell is regulated from one or two 6.3-V filament transformers by a 0–140-V Variac autotransformer. Temperature is measured at thermocouple wells in the cell walls.

In the measurement of uv spectra, the slit width of the Cary 14 was always set at an arbitrary 30 and the baseline recorded vs. air from 400 to 200 nm with both an empty cell and a loaded cell at ambient temperature, except in cases where the sample had sufficient vapor pressure to give a spectrum at ambient temperature.

Spectra were recorded in the heated cell, which had been loaded at room temperature and evacuated and filled with argon for 3–5 cycles to remove residual oxygen. In the case of volatile compounds, excess sample was pumped off if initial runs indicated an absorbance greater than 2.

Variable temperature studies of 2-hydroxypyridine–2-pyridone were carried out with 5 mg of 2-pyridone in the cell and spectra were recorded at ca. 120, 130, and 140°, in both ascending and descending temperature cycles. In all cases, the absorbance and the ratio of the absorbances were the same at the same temperature. In another measurement, the spectrum of 2-hydroxypyridine–2-pyridone was observed to be stable for 8 hr at 130°. In a separate run, material was isolated from the spectral cell after 6 hr at 120–150° and shown to be at least 95% 2-pyridone by ir, uv, and NMR criteria, although the presence of a small amount of water could be detected in the NMR spectrum.

A uv spectrum was recorded of thin film of 2-pyridone–2-hydroxypyridine melted between two 1 × ⅛ in. Optasil-1 quartz windows. The windows were heated around the edge with a chromel ribbon under a potential difference of 3 V and complete melting was confirmed by observation of the sample through a microscope with transmitted cross-polarized red light. The ultraviolet spectrum exhibited a very broad absorption centered at about λ_{max} 310 nm.

The ultraviolet spectrum of 4-methyl-6-hydroxy-2,3-dihydro-7-azabenzofuran in the gas phase at 175° exhibited absorptions at λ_{max} 287 nm ($A = 0.6$) and λ_{max} 325 nm ($A < 0.1$). The ratio of the intensities of the two absorptions seemed to remain approximately the same over a period of 2 hr at 175°, but the overall intensity decreased continually. The cooled material which was recovered had partially decomposed to an orange-brown oil.

A sample of 100 mg of analytically pure 4-methyl-6-hydroxy-2,3-dihydro-7-azabenzofuran was melted for 5 min at a temperature of 260°. The cooled residue dissolved slowly in Me_2SO-d_6, and the NMR spectrum showed none of the resonances expected for the original material. The spectra of other compounds recorded in this study were taken in the same apparatus but with adjustment of temperature as necessary to produce the required absorptions.

Infrared Spectra. A cell for gas phase infrared studies identical to that used for the ultraviolet spectra was constructed except that 4 Suprasil W-2 quartz disks (Amersil, Inc.) were used for windows. This cell was useful for observation of absorptions from 4000 to 2500 cm^{-1}. Absorptions were recorded at high temperature, usually with a vertical scale expansion, and were calibrated by the 3027.1-cm^{-1} absorption of polystyrene.

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Appendix

The equation[51c] applied to **3–4** is:

$$\Delta(\Delta E) = (E_3{}^{V} - E_4{}^{V}) - (E_3{}^{S} - E_4{}^{S})$$

$$= \frac{\mu_3{}^2}{\alpha_3{}^3}\left[\frac{X}{1 - l_3 x}\right] - \frac{\mu_4{}^2}{\alpha_4{}^3}\left[\frac{X}{1 - l_4 s}\right] \qquad (1)$$

μ = dipole moment of the isomer

$X = (\epsilon + 1)/2\epsilon + 1)$; ϵ = dielectric constant of the solvent $l = [2(N_D^2 - 1)]/(N_D^2 + 2)$; N_D = refractive index of the solute. For the calculations involving **11–12** and **31–32**, the polarization term (l) was omitted. The physical constants required by the equations were molecular volumes of **11**, **12**, **31**, and **32** which were estimated to be 10, 25, 20, and 25% larger than those of **3** and **4**. It should be noted that the calculations are not particularly sensitive to these approximations. The dipole moments of **31** and **32** were estimated by vector addition of the carbon–chlorine bond ($\mu = 1.58$)[64] to the moments assigned to **3** and **4**.[65]

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Ionization of Oxyphosphoranes. Phosphonium Ions and Hexacoordinated Phosphorus Anions

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Abstract: Conductivity measurements of purified phenoxyphosphoranes in dry acetonitrile allow the determination of the equilibrium constants the reactions 1 ($R_nP(OC_6H_5)_{5-n} \rightleftharpoons R_nP(OC_6H_5)_{4-n}{}^+ + C_6H_5O^-$ (K_1)) and 2 ($R_nP(OC_6H_5)_{6-n}{}^- \rightleftharpoons R_nP(OC_6H_5)_{5-n} + C_6H_5O^-$ (K_2)) with n = 1, 2, and 3. The formation of $P(OC_6H_5)_6{}^-$, an analogous anion, has been confirmed by ^{31}P NMR spectroscopy. The data have been combined with those for the rate of ionization of various phenoxyphosphoranes to show that the association of phenoxide ion and phosphonium ions in acetonitrile proceeds with the speed of collision.

The mechanism for the hydrolysis of phosphate esters requires the formation of pentacovalent intermediates which then decompose to products; in some instances, the hydrolysis is necessarily accompanied by a ligand reorganization (pseudorotation) of the trigonal bipyramidal intermediate.[1,2] One of the steps in the acid-catalyzed process is presumably the addition of water to a protonated ester:

$$(RO)_3POH^+ + H_2O \rightleftharpoons (RO)_3P(OH)_2 + H^+ \qquad (3)$$

The addition of a nucleophile to a phosphonium salt parallels the addition of water to a protonated phosphate ester, so that the rate and equilibrium of reactions such as (3) are needed for the full quantitative understanding of phosphate hydrolysis. Abundant qualitative evidence for the ionization of phosphoranes had previously been obtained[3] by NMR spectroscopy. The rates of dissociation of some phenoxyphosphoranes to phosphonium salts and phenoxide ion in acetonitrile as solvent have been measured by NMR spectroscopy.[4]

In order to obtain the corresponding rates of recombination of phenoxide ions with phosphonium ions, the equilibrium constants for the dissociations are needed. These have now been obtained by conductivity measurements in the same solvent. These measurements show, however, that the ionization is not a simple one, but is accompanied by the formation of hexacoordinated phosphorus anions. The ionization constants for the formation of these anions can also be obtained from the conductivity measurements and have been confirmed by ^{31}P NMR spectroscopy. This paper reports the determinations of some of these ionization constants and the calculations that can be based on the new data.

Experimental Section

General. The phosphonium salts and phosphoranes here described are sensitive to moisture and were routinely weighed and handled inside a Labconco drybox, filled with nitrogen. The effects of static electricity were minimized by a weak source of alpha particles (Staticmaster Ionizing unit, VWR Scientific No. 58580-041); transfers of solids were nearly impossible without it. The phosphoranes were recrystallized under nitrogen in a double Schlenk recrystallization tube (Ace Glass 7772-11); lesser precautions proved inadequate. The recrystallized compounds were stored under nitrogen at −20°.

Elementary microanalyses were performed by the Galbraith Laboratories, Inc., Knoxville, Tenn. Satisfactory analysis of triflate salts for sulfur could not be obtained by oxidation followed by precipitation of barium sulfate but were performed on a Leco Corp. sulfur analyzer. Melting points were obtained in sealed capillaries and are corrected. Variable-temperature proton NMR spectra were recorded on a Varian A-60 spectrometer equipped with a Varian V-6031B variable-temperature probe. The temperature was calibrated[5] by the spectrum of methanol or glycol. ^{31}P NMR spectra were obtained by Mr. W. E. Hull on a Varian XL-100 spectrometer at 40.5 MHz in Fourier transform mode. Chemical shifts for ^{31}P are recorded relative to that of 85% phosphoric acid, and those for protons relative to tetramethylsilane.

Materials. Sodium phenoxide[6] was dried in vacuo for at least a