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Quantitative Model of Solvent Effects on Hydroxypyridine–Pyridone and Mercaptopyridine–Thiopyridone Equilibria: Correlation with Reaction-Field and Hydrogen-Bonding Effects

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A model for the effect of reaction field and hydrogen bonding on the relative energies of protomers is applied to the equilibria between 6-chloro-2-hydroxypyridine and 6-chloro-2-pyridone, 2-mercaptopyridine and 2-thiopyridone, 6-chloro-2-mercaptopyridine and 6-chloro-2-thiopyridone, and 4-mercaptopyridine and 4-thiopyridone in a wide range of solvents. Quantitative correlation is obtained by a multivariable analysis. In addition to satisfactory statistical tests of the correlation, estimates of the differences in free energies between the isomers in the vapor phase and of the dipole moment component of the reaction-field term are obtained which compare well with the available independent values. These criteria are shown to signal an unacceptable correlation for the case of 2-chloro-4-hydroxypyridine and 2-chloro-4-pyridone. The advantage of this model, which provides an understanding of the effect of molecular environment on protomeric equilibria in terms of reasonable physical interactions, over empirical approaches is noted.

A dominating effect of molecular environment on relative energies is observed for heteroaromatic amide–imidic acid and thioamide–thioimidic acid isomer pairs. Changes in direction of protomeric equilibrium constants by orders of magnitude can be seen by comparison of vapor- and liquid-phase values.[1,2] We have been concerned with understanding these effects and now are able to offer a model which provides a satisfactory quantitative correlation of the change in relative energies of hydroxypyridine–pyridone and mercaptopyridine–thiopyridone isomer pairs as a function of phase and solvent. As heretofore, we believe the results for these equilibria to be prototypical for a number of related systems.[1,3]

While reasonable qualitative explanations have been given for the effect of solvent on the equilibria between 2- and 4-hydroxypyridines–pyridones which bear electronegative substituents at C-6, and for related imidic acids–amides,[3-6] there have been few attempts at quantitative correlations. In an empirical approach, first reported over 10 years ago, Gordon and Katritzky proposed a correlation of tautomeric equilibrium constants for five hydroxypyridines–pyridones with Z values; that suggestion has been recently extended to six additional systems.[7-10] Theoretical analyses of the effect of water on the 2-hydroxypyridine–2-pyridone and 4-hydroxypyridine–4-pyridone equilibria carried out by the supermolecular approach by Kwiatowski and Szczodrowska and by CNDO/2 procedures by Cignitti and Paoloni have been shown to correlate with experimental results.[11,12] The most specific model in this area comes from the elegant temperature-jump experiments of Bensaude, Chevrier, and Dubois, who interpret their data to show that 2-pyridones specifically bind two water molecules while the corresponding 2-hydroxypyridines bind one water, and these hydrates are then further solvated by bulk water.[13]

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

(2) P. Beak, *Acc. Chem. Res.*, **10**, 186 (1977).

(3) A preliminary report has appeared: P. Beak and J. B. Covington, *J. Am. Chem. Soc.*, **100**, 3961 (1978).

(4) J. Elguero, C. Marzin, A. R. Katritzky, and P. Linda, "The Tautomerism of Heterocycles", A. R. Katritzky and A. J. Boulton, Eds., Academic Press, New York, 1976, Supplement 1. A. Albert, "Heterocyclic Chemistry", Athlone Press, London, England, 1972. H. Tiekelman, *Chem. Heterocycl. Compd.*, **14**, 731 (1974).

(5) For 6-chloro systems see: (a) A. Cipiciani, P. Linda, and G. Savelli, *Gazz. Chim. Ital.*, 431 (1975); (b) Y. N. Sheinker, E. Peresleni, I. S. Rezchikova, and N. P. Zosimova, *Dokl. Chem.* (*Engl. Transl.*), **192**, 1295 (1970); (c) G. Simchen, *Chem. Ber.*, **103**, 398 (1970); (d) A. R. Katritzky, T. D. Rowe, and S. K. Roy, *J. Chem. Soc. B*, 758 (1967), and references cited therein.

(6) For examples see: J. Sepiol, Z. Kazimierczuk, and D. Shugar, *Z. Naturforsch. C*, **31**, 361 (1976); W. Walter and H. W. Meyer, *Justus Liebigs Ann. Chem.*, 19, 36, 54 (1975); A. W. K. Chan, W. D. Crow, and I. Gosley, *Tetrahedron*, **26**, 2497 (1970).

(7) A. Gordon and A. R. Katritzky, *Tetrahedron Lett.*, 2767 (1968).

(8) J. Frank and A. R. Katritzky, *J. Chem. Soc., Perkin Trans. 2*, 1428 (1976). Our concern about some of the equilibrium constants calculated in this work is expressed in ref 2 and 9.

(9) P. Beak, J. B. Covington, and J. M. Zeigler, *J. Org. Chem.*, **43**, 177 (1978); P. Beak, J. B. Covington, S. G. Smith, J. M. White, and J. M. Zeigler, *ibid.*, following paper in this issue.

(10) A correlation of Schiff-base prototropic equilibria with Z values has been reported by J. Leor and M. Cortigo, *J. Chem. Soc., Perkin Trans. 2*, 1111 (1977).

(11) J. S. Kwiatowski and B. Szczodrowska, *Chem. Phys.*, **27**, 389 (1978).

(12) M. Cignitti and L. Paoloni, *Gazz. Chim. Ital.*, 108, 491 (1978).

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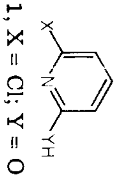
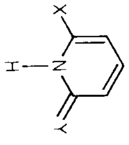
We have noted previously the value of a reaction-field rationalization for the effect of solvent on hydroxypyridine–pyridone equilibria.[1,2] In this model the energy difference between the protomers is taken to reflect the different interactions of the dipoles of the isomers with the reaction field provided by the dielectric of the medium. The present paper details a quantitative model we have proposed more recently in which differential hydrogen bonding is included as the second major effect which the solvent can have on these protomeric equilibria.[3] The approach we have taken is to first test for correlation with the reaction-field effect in selected solvents and then to extend the correlation to hydrogen-bonding solvents. From this approach we obtain an equation which is the basis for a multivariable linear-regression analysis that provides quantitative correlation of the change in the relative energies of the protomers as a function of solvent. The correlation provides estimates of the vapor-phase free-energy difference between the protomers, the coefficient of the reaction-field term, and a measure of the sensitivity of the equilibrium to hydrogen bond donation and acceptance. Tests of the method are provided by comparison of the first two terms with independently obtained values and by measures of the statistical significance of the correlation.

Results

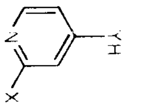
Protomeric equilibrium constants (K_T) for the isomer pairs 6-chloro-2-hydroxypyridine (**1**) and 6-chloro-2-pyridone (**2**), 2-mercaptopyridine (**3**) and 2-thiopyridone (**4**), 6-chloro-2-mercaptopyridine (**5**) and 6-chloro-2-thiopyridone (**6**), 2-chloro-4-hydroxypyridine (**7**) and 2-chloro-4-pyridone (**8**), and 4-mercaptopyridine (**9**) and 4-thiopyridone (**10**) were obtained by ultraviolet spectroscopy in the solvents indicated and used to obtain the free-energy differences shown in Table I.[14] Vapor-pressure osmometry and high dilutions were used to assure that measurements were made on monomeric species.[9] It is estimated that the maximum error in $\Delta G_s°$ is ±20%. Although the chloro-substituted systems **1**–**2** and **7**–**8** have been previously studied and discussed,[5] we have repeated and extended previous determinations to assure internal consistency. In an effort to evaluate the effect of chloro substitution on the mercaptopyridine–thiopyridone system, we have prepared **5**–**6** by reduction of 2-chloropyridyl



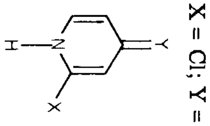
1, X = Cl; Y = O
3, X = H; Y = S
5, X = Cl; Y = S



2, X = Cl; Y = O
4, X = H; Y = S
6, X = Cl; Y = S



7, X = Cl; Y = O
9, X = H; Y = S



8, X = Cl; Y = O
10, X = H; Y = S

Table I. Free-Energy Differences between Protomeric Isomers Determined by Ultraviolet Spectroscopy and Correlated by the Reaction-Field Hydrogen-Bonding Model (kcal/mol)

	$1 \rightleftarrows 2$		$3 \rightleftarrows 4$		$5 \rightleftarrows 6$		$7 \rightleftarrows 8$	$9 \rightleftarrows 10$	
solvent	$\Delta G_s°_{\text{exptl}}$	$\Delta G_s°_{\text{correl}}$	$\Delta G_s°_{\text{exptl}}$[e]	$\Delta G_s°_{\text{correl}}$	$\Delta G_s°_{\text{exptl}}$[e]	$\Delta G_s°_{\text{correl}}$	$\Delta G_s°_{\text{exptl}}$	$\Delta G_s°_{\text{exptl}}$	$\Delta G_s°_{\text{correl}}$
vapor	2.1[a]	2.2	>2.0[c]	3.0			>1.7		
cyclohexane	1.6	1.5	1.4	1.1	⩾2.3	2.4		2.1	2.0
carbon tetrachloride	1.6	1.5	1.0	0.9	⩾2.3	2.3			
dioxane	2.2	2.2	0.7	0.7	⩾2.3	2.4		1.1	1.0
benzene	1.5	1.4	0.7	0.7				1.6	1.8
chloroform	0.47	1.0	−0.5	−0.3	1.9	1.5		0.8	0.8
diethyl ether	⩾2.3	2.2	−0.3	−0.5	⩾2.3	1.7	>1.7		
ethyl acetate	2.1	1.9	−1.0	−0.9	1.7	1.5		−0.4	−0.6
tetrahydrofuran	2.3	2.0	−1.2	−1.1				−0.6	−0.4
methylene chloride	0.9	0.9	−0.7	−0.9	0.8	1.1		0.4	0.4
1,2-dichloroethane	0.9	0.8	−1.0	−1.0	0.8	1.1		0.4	0.3
tert-butyl alcohol	0.8	1.8			0.4	0.9	>1.7	<−2.7	(−4.4)[g]
n-butyl alcohol	0.8	0.9			0.3	0.3	0.7	<−2.7	(−5.9)[g]
isopropyl alcohol	0.95	1.1	−1.9	−1.9	0.3	0.4	0.9	<−2.7	(−6.0)[g]
n-propyl alcohol	0.8	0.7			0.3	0.2	0.1	<−2.7	(−6.6)[g]
ethyl alcohol	0.8	0.4			0.15	0	>1.7	<−2.7	(−6.9)[g]
hexamethylphosphoric triamide	⩾2.3	2.7							
methyl alcohol	0.6	0.1			0	−0.2	1.0		
N,*N*-dimethylacetamide	2.3	2.2			1.5	1.1			
dimethyl sulfoxide	⩾2.3	2.2	<−2.7	−2.2					
water	−1.7[b]	−1.3	−6.6[d]	−5.7			−0.5[f]	−6.4	(−6.3)[g]

[a] At 120 °C; from ref 1. [b] From ref 5d. [c] At 70 °C; from ref 1. [d] From ref 4. [e] The values of $\Delta G_s°_{\text{exptl}}$ for 3–4 were redetermined and differ slightly from those in ref 3. [f] From pK_a data; see ref 4. [g] Equation 12.

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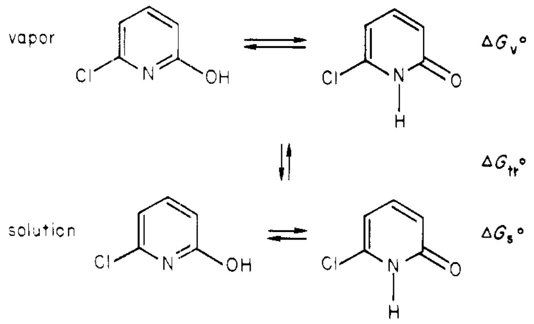
(13) O. Bensaude, M. Chevrier, and J. E. Dubois, *J. Am. Chem. Soc.*, **101**, 2423 (1979), and references cited therein. For an investigation of a pyrimidone system see M. Dreyfuss, O. Bensaude, G. Dodin, and J. E. Dubois, *J. Am. Chem. Soc.*, **98**, 6338 (1976).

(14) Details are available: J. B. Covington, Ph.D. Thesis, University of Illinois, 1978, available from University Microfilms, Ann Arbor, MI.

Scheme I



6-disulfide which was obtained from the reaction of 2,6-dichloropyridone *N*-oxide with thiourea.

Discussion

Previous studies of hydroxypyridine–pyridone and mercaptopyridine–thiopyridone equilibria established that differences in the solvation energies of the isomers can determine the relative stabilities of the promoters in solution.[1,3-8] For the most general case, the principal effects of solvation are modeled by the five energy terms designated in Scheme I to be involved in the transfer ($\Delta G_{tr}°$) of the equilibrium between 6-chloro-2-hydroxypyridine (**1**) and 6-chloro-2-pyridone (**2**) from the vapor to solution as shown in eq 1.[2,5,15,16]

$$\Delta G_s° - \Delta G_v° = \Delta G_{tr}° = \Delta G_{vdW}° + \Delta G_{cav}° + \Delta G_{str}° + \Delta G_{el}° + \Delta G_{Hb}° \quad (1)$$

$$\Delta G_s° - \Delta G_v° \simeq \Delta G_{el}° + \Delta G_{Hb}° \quad (2)$$

We have previously argued that differences in the van der Waals ($\Delta G_{vdW}°$) and cavitation ($\Delta G_{cav}°$) terms in eq 1 should be negligible for equilibria between structures as similar as the hydroxypyridine–pyridone isomers.[2] It also seems reasonable that if the difference in energy associated with restructuring the solvent ($\Delta G_{str}°$) is considered separately from the $\Delta G_{cav}°$ term it would be similar for both isomers and also could be ignored in a first approximation.[17,18] The two nonnegligible terms are the interaction of the different dipoles of the isomers with the reaction field due to the dielectric of the solvent ($\Delta G_{el}°$) and the differential hydrogen bonding of each of the isomers with the solvent ($\Delta G_{Hb}°$). Thus we suggest that eq 2 is a useful approximation of the effect of the molecular environment on protomeric equilibrium between isomers. For the ensuing discussion the case of **1**–**2** will be treated in detail. The conclusions which can be drawn from that case will be seen to apply also to other hydroxypyridine–pyridone and mercaptopyridine–thiopyridone systems.[19,20]

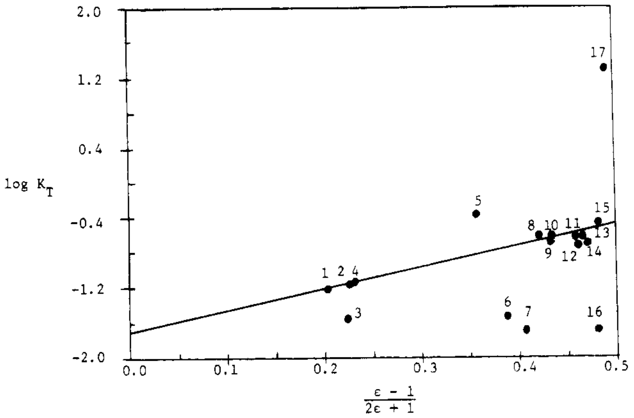


Figure 1. log K_T vs. $(\epsilon - 1)/(2\epsilon + 1)$ for **1**–**2** in cyclohexane (1), carbon tetrachloride (2), dioxane (3), benzene (4), chloroform (5), ethyl acetate (6), tetrahydrofuran (7), methylene chloride (8), 1,2-dichloroethane (9), *tert*-butyl alcohol (10), *n*-butyl alcohol (11), isopropyl alcohol (12), *n*-propyl alcohol (13), ethyl alcohol (14), methyl alcohol (15), *N,N*-dimethylacetamide (16), and water (17). The correlation line is for non-hydrogen-bonding solvents, 1, 2, 4, 8, and 9.

Dipole Reaction Field, $\Delta G_{el}°$ for 1–2. The protomeric isomers of each pair, **1**–**2**, **3**–**4**, **5**–**6**, **7**–**8**, and **9**–**10**, have different dipole moments and would be differentially stabilized by the reaction field established by electric displacement in the dielectric constant of the medium by the dipole. The earliest and most durable model for the energy of interaction of a dipole with the dielectric of the solvent is the Onsager–Kirkwood model proposed over 40 years ago.[21] Powling and Bernstein later modified the Onsager–Kirkwood equations to provide eq 3 (where μ_x =

$$\Delta E = \left(\frac{\mu_1^2}{a_1^3} - \frac{\mu_2^2}{a_2^3}\right)\frac{\epsilon - 1}{2\epsilon + 1} \quad (3)$$

dipole moment of **x**, a_x^3 = the molecular volume of the solute **x**, and ϵ = the dielectric constant of the solvent) which was found to correlate the effect of solvent on the position of the protomeric equilibrium of several keto–enol systems, and we have adopted their approach in the present study.[22] Abraham et al. have further refined the model to include solute polarizability and a quadrupole term.[23] The equation has been applied to a variety of chemical phenomena with fair to good success.[1,22-24]

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(15) (a) O. Sinanoglu, "Molecular Associations in Biology", E. B. Pullman, Ed., Academic Press, New York, 1967, p 427; (b) E. M. Arnett, *Acc. Chem. Res.*, **6**, 404 (1973); (c) D. H. Aue, H. M. Webb, and M. T. Bowers, *J. Am. Chem. Soc.*, **98**, 318 (1976); (d) R. B. Birge, M. J. Sullivan, and B. E. Kohler, *ibid.*, **98**, 358 (1976); (e) R. W. Taft, J. F. Wolf, J. C. Beauchamp, G. Scorrano, and E. M. Arnett, *ibid.*, **100**, 1240 (1978); (f) E. M. Arnett, B. Chawla, L. Bell, M. Taagepera, W. J. Hehre, and R. W. Taft, *ibid.*, **99**, 5729 (1977).

(16) This case has been chosen because both **1** and **2** can be directly observed in most solvents. While this system thus provides a satisfactory number of data points, it necessarily means that the energy differences between the isomers will not be large, and the correlation proposed for the model will be based on relatively small energy differences. On the other hand, this data is more accurate than that obtained by the indirect approaches used for cases in which there are large energy differences between the isomers. It can be argued that the small range of the present work provides a more difficult test of the model than would a system with larger energy differences.

(17) The advantage of comparing isomers in assessing differences in internal energies is well recognized. The neglect of the van der Waals, cavitation, and solvent-structure terms in the comparison of the differential solvation of these isomers should not be taken to suggest that these effects are unimportant in the total solvation effect.

(18) R. L. Reeves, M. S. Maggio, and L. R. Costa [*J. Am. Chem. Soc.*, **96**, 5917 (1974)] have found that the changes in the protomeric equilibrium for the azo dye 4-phenylazo-1-naphthol-2,4′-disulfonate correlates with solvent solubility and/or surface tension parameters. They suggest that solvent cavitation controls the energy difference. We do not find a linear correlation for K_T of **1**–**2** with either parameter.[14]

(19) We believe the correlation of log K_T for **1**–**2** with *Z* values[7,8] to be interesting but essentially empirical, such that desirable insight into the physical processes controlling the energy differences between the protomers is not obtained.

(20) Multiparameter approaches for the correlation of tautomeric structure with solvent have been suggested. For examples, see: S. Kishimoto, S. Kitahara, O. Manabe, and H. Hiyama, *J. Org. Chem.*, **43**, 3882 (1978); F. W. Fowler, A. R. Katritzky, and R. J. D. Rutherford, *J. Chem. Soc. B*, 460 (1971). See also: E. S. Amis and J. F. Hinton, "Solvent Effect on Chemical Phenomena", Academic Press, New York, 1973; J. E. Leffler and E. Grunwald, "Rates and Equilibria of Organic Reactions", Wiley, New York, 1963.

(21) L. Onsager, *J. Am. Chem. Soc.*, **58**, 1486 (1936); J. G. Kirkwood, *J. Chem. Phys.*, **2**, 351 (1936); **7**, 911 (1939).

(22) J. Powling and H. J. Bernstein, *J. Am. Chem. Soc.*, **73**, 4353 (1951). In the present case we have returned to the earlier and later[23] use of the molecular volume of the solute instead of that of the solvent advocated by Powling and Bernstein.

(23) K. Laidler and H. Eyring, *Ann. N.Y. Acad. Sci.*, **39**, 303 (1941); R. J. Abraham, *J. Phys. Chem.*, **73**, 1192 (1969), and references cited therein.

Qualitatively, the model explains the frequent observation that a more polar isomer is preferentially stabilized in more polar solvents.[1,2,4-6,13]

In an assessment of the simplest model for the reaction field, we have plotted log K_T(NH/OH) vs. $(\epsilon - 1)/(2\epsilon + 1)$ for the isomer pairs under consideration. The analysis for **1**–**2** is shown in Figure 1. The total plot of Figure 1 does not reveal any correlation. However, if attention is restricted to the essentially non-hydrogen-bonding solvents cyclohexane, carbon tetrachloride, benzene, methylene dichloride, and 1,2-dichloroethane,[25] a least-squares line with a slope of (2.5 ± 0.2) × 10^{-1}, an intercept of −1.71, and a correlation coefficient of 0.9944 which fits eq 4 is obtained. This result is expressed in free-energy terms in eq 5, where $\Delta G_{el}^0 = -3.4(\epsilon - 1)/(2\epsilon + 1)$ and $\Delta G_v^0 = -2.2$ kcal/mol.

$$\log K_T = -2.5\left(\frac{\epsilon - 1}{2\epsilon + 1}\right) - 1.7 \qquad (4)$$

$$\Delta G_s^\circ = -3.4\left(\frac{\epsilon - 1}{2\epsilon + 1}\right) - 2.2 \text{ kcal/mol} + \Delta G_{Hb}^\circ \qquad (5)$$

The reliability of this result can be evaluated in two ways. First, eq 5 provides a prediction of the gas-phase free-energy difference between **1** and **2** as 2.2 kcal/mol, a result which compares favorably with the observed value of 2.1 kcal/mol. Second, the estimated dipole moments and molecular volumes of **1** and **2** can be used to calculate the coefficient of the ΔG_{el}° term in eq 5 as −3.0 kal/mol.[26,27] This value corresponds to the slope of −3.4 for the regression line in eq 5.

In the present work the procedure used to obtain eq 4 and all other correlation lines is a multiple-variable linear-regression analysis.[28] As a result, some values are different from those given in corresponding equations in our preliminary communication.[3]

If the above comparison of constants between eq 4 and the independently obtained values is taken to support the reaction-field model for the non-hydrogen-bonding solvents, the line shown in Figure 1 comes surprisingly close to correlating the alcohols and then divides the remaining solvents into two classes. The solvents below the line are electron-pair donors while the two solvents above the line can be electron-pair acceptors in a hydrogen bond.

Hydrogen Bonding, ΔG_{Hb}° for 1–2. Nonempirical evaluation of the effect of hydrogen bonding on the protomeric equilibria for **1**–**2**, **3**–**4**, **5**–**6**, **7**–**8**, and **9**–**10** appears to be beyond the reach of present theory. Each protomer can donate and accept electron pairs in hydrogen bonds, and each hydrogen bond can have an energy of several kilocalories per mole.[29] The effect of acceptance and donation may well be different for each protomer of a pair, and the net effect which obtains for one system may not extrapolate to a different structural type.

Accordingly, we have used the α and β values recently proposed by Kamlet and Taft for solvent hydrogen bonding to analyze the data.[30] While the *a* and *b* values for donation of hydrogen and electron pairs as defined by those authors are empirical, this approach retains the desirable feature of having a direct relationship to a physically defined interaction so that insight into the solvation processes may be retained. Precedent for this approach may be found in the work of Highet and Chou, who found a correlation of $\alpha-\beta$ with log K_T for a phenol–dienone protomerism.[31]

Qualitatively, the pertinent effect most clearly suggested by Figure 1 and Table I is that hydrogen bond acceptance by the solvents dioxane, tetrahydrofuran, ethyl acetate, dimethylacetamide, hexamethylphosphoric triamide, and ether favor 6-chloro-2-hydroxypyridine (**1**) more than would be expected for the reaction-field effect alone. Apparently the free energy of **1** is lowered more by accepting an electron pair at the hydroxyl hydrogen than the free energy of **2** is lowered by accepting an electron pair at the amide hydrogen. If this interpretation is correct, the deviations for the solvents from the reaction-field regression line should be proportional to Taft's β values. A plot of β vs. the deviation from the regression line has a correlation coefficient of 0.91 for the four testable solvents, dimethylacetamide, tetrahydrofuran, ethyl acetate, and dioxane, and the intercept of 0.31 ± 0.29 has a standard deviation comparable to its deviation from the 0.0 point which theory predicts should be on the line. While the correlation is less than might be desired, it appears sufficiently useful to allow further interpretation.[32]

Analysis of the effect of alcoholic solvents reveals a fortuitous cancellation of compensating effects. As noted heretofore, electron-pair donation from the solvent favors **1**, while proton donation from the alcoholic solvents favors **2**. In the case of water, the latter effect must dominate. These effects can be expressed quantitatively by following Taft's approach in terms of coefficients of different signs for the α and β terms in eq 6. The coefficients then reflect

$$\Delta G_{Hb}^\circ = (2.1 \pm 0.3)\beta + (-1.9 \pm 0.3)\alpha \qquad (6)$$

the sensitivity of a given equilibrium to hydrogen bond donation and acceptance.[30] These coefficients are the empirical parameters of this model.

$\Delta G_s^\circ - \Delta G_v^\circ$ for 1–2. The fundamental assumption of this approach is that a linear free-energy relationship exists between the free-energy difference between the isomers and the interaction of the isomers with the reaction field and the hydrogen-bonding capabilities of the molecular environment. Substitutions of eq 5 and 6 into eq 2 provides eq 7 (where $\Delta G_v{}^\circ{}_{1-2} = 2.2$ kcal/mol), which is

$$\Delta G_s{}^\circ{}_{1-2} - \Delta G_v{}^\circ{}_{1-2} = (-3.4 \pm 0.3)\left(\frac{\epsilon - 1}{2\epsilon + 1}\right) + (2.1 \pm 0.3)\beta - (1.9 \pm 0.3)\alpha \qquad (7)$$

a quantitative correlation for the model proposed in

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[24] For some examples, see: J. Powling and H. J. Bernstein, *J. Am. Chem. Soc.*, **73**, 1815 (1951); R. J. Abraham and M. A. Cooper, *Chem. Commun.*, 588 (1966); R. J. Abraham and M. D. Cooper, *J. Chem. Soc. B*, 202 (1967); R. J. Abraham, H. D. Banks, E. L. Eliel, O. Hofer, and M. K. Kaldustion, *J. Am. Chem. Soc.*, **94**, 1913 (1972); H. Kwart and T. L. Lilley, *J. Org. Chem.*, **43**, 2374 (1978); D. M. Hayes, G. L. Kenyon, and D. A. Kollman, *J. Am. Chem. Soc.*, **100**, 4331 (1978); J. L. M. Abboud and R. W. Taft, private communication, Feb 1979.

[25] Chloroform is a moderate hydrogen bond donor. For example the energy of hydrogen bonding of chloroform to HMPA has been estimated as 1.5 kcal/mol while that for methylene dichloride is ca. 0.2 kcal/mol.[23]

[26] The values of μ_1 = 0.55 D and μ_2 = 3.2 D are obtained by vector addition of the carbon–chlorine bond moment to the dipole moments previously used for 2-hydroxypyridine and 2-pyridone.[1] The molecular volumes were estimated as indicated.[1]

[27] See J. L. Abboud, M. J. Kamlet, and R. W. Taft, *J. Am. Chem. Soc.*, **99**, 8325 (1977), and references cited therein for discussion of a π scale. Good correlation of the π scale and log K_T for 1–2 in cyclohexane and the alcoholic solvents is observed.

[28] Errors cited are standard deviations. L. Poole and M. Borchers, "Some Common Basic Programs", 2nd ed., A. Osborne Associates, Berkeley, CA, pp 147–50.

[29] M. D. Joesten and L. S. Schaad, "Hydrogen Bonding", Marcel Dekker, New York, 1973; P. Schuster, G. Zundel, and C. Sandorfry, "The Hydrogen Bond", North-Holland Publishing Co., Vol. I, New York, 1976.

[30] M. J. Kamlet and R. W. Taft, *J. Am. Chem. Soc.*, **98**, 377, 2886 (1976). See also M. J. Kamlet, J. C. Abboud, and R. W. Taft, *ibid.*, **99**, 6027 (1977).

[31] R. J. Highet and F. E. Chou, *J. Am. Chem. Soc.*, **99**, 3538 (1977).

[32] The equilibrium in hexamethylphosphoramide and diethyl ether lies so far on the side of 1 that equilibrium constants could not be determined by ultraviolet spectroscopy and are not included in the plot.

Scheme I. Good agreement between the observed and correlated energies, of course, is predetermined because the experimental data is part of the input for eq 7. The significant results are that the proposed model of two dominating interactions leads to the correlation and that two of the four variables obtained by the correlation correspond to independently determined values.

If the model is accepted, the protocol for further application and testing is straightforward. Accordingly, we have allowed the coefficients of the three terms on the right in eq 7 to be explanatory variables and the ΔG_s° term to be a dependent variable in the multiple linear-regression analysis.[28] This provides eq 8 in which ΔG_v° is a constant

$$\Delta G_s^\circ{}_{1-2} - \Delta G_v^\circ{}_{1-2} = -3.2\left(\frac{\epsilon - 1}{2\epsilon + 1}\right) - 2.1\alpha + 2.0\beta \qquad (8)$$

($\Delta G_v^\circ{}_{1-2} = 2.2$ kcal/mol). The corrected value of $\Delta G_v^\circ{}_{1-2}$ of 2.2 kcal/mol compares favorably with the experimental value of 2.1 kcal/mol. The coefficient of the reaction-field term of −3.2 is close to the independently obtained value of −3.0, and the coefficients for the hydrogen-bonding terms of −2.1 and +2.0 are within experimental error of the same value in eq 7. Comparison of the $\Delta G_s^\circ{}_{\mathrm{correl}}$ by eq 8 and $\Delta G_s^\circ{}_{\mathrm{exptl}}$ in Table I show the established agreement. For eq 8 the coefficient of determination, R^2, of 0.862 provides an F factor of 27.06, which gives a 1 in 1.43 × 10^5 possibility that the correlation of eq 8 is not significant.[33] The standard error of estimate for eq 7 of ±0.4 kcal/mol is 10% of the total range of ΔG_s°, and this value is exceeded in 3 of the 17 solvents for which a comparison can be made.[16,34] We also wish to emphasize that multiple linear-regression analyses are generally available, and application to protomeric equilibrium data in the form of eq 8 is straightforward. The model appears to be both satisfactory and convenient.

$\Delta G_s^\circ - \Delta G_v^\circ$ for 3–4. The protomeric equilibrium constants for 2-mercaptopyridine (**3**) and 2-thiopyridone (**4**) can be directly determined in a wide range of solvents. Analysis of the data for 11 solvents by the multiple linear-regression approach provides eq 9, where $\Delta G_v^\circ{}_{3-4} = 3.0$ kcal/mol.

$$G_s^\circ{}_{3-4} - G_v^\circ{}_{3-4} = -9.4\left(\frac{\epsilon - 1}{2\epsilon + 1}\right) - 0.7\beta \qquad (9)$$

The value of $\Delta G_v^\circ{}_{3-4}$ of 3.0 kcal/mol obtained is consistent with an independent estimate of >2.0 kcal/mol from vapor-phase ultraviolet measurements and a value of 2.4 kcal/mol from mass spectrometry.[1,35] The coefficient of the dielectric term of −9.4 is comparable to a value of −8.6 obtained by calculation of the first term of eq 3.[36] The R^2 value for eq 9 is 0.972, the F factor is 138.9, and the possibility that the correlation obtains from chance is 1 in 1.0 × 10^6. As shown in Table I, all points are within the standard error of estimate of 0.2 kcal/mol, which is 6% of the total range of ΔG_s°, except for dimethyl sulfoxide which is a limit value and is apparently off by at least 15%.

An interesting point revealed in eq 9 is that apparent small effect of the hydrogen-bonding terms. This does not necessarily suggest hydrogen bonding is unimportant in the solvation of the two protomeric isomers, particularly since only one alcohol is included in the data, but it does suggest that hydrogen bonding does not selectively contribute to the stabilization of one form.

$\Delta G_s^\circ - \Delta G_v^\circ$ for 5–6. The relative free energies of 6-chloro-2-mercaptopyridine (**5**) and 6-chloro-2-thiopyridone (**6**) were determined in three non-hydrogen-bonding, three hydrogen-bonding acceptor, and six hydrogen bond donor–hydrogen bond acceptor solvents as shown in Table I. Multiple linear-regression analysis provides eq 10, where $\Delta G_v^\circ{}_{5-6} = 3.5$ kcal/mol.

$$\Delta G_s^\circ{}_{5-6} - G_v^\circ{}_{5-6} = -5.7\left(\frac{\epsilon - 1}{2\epsilon + 1}\right) - 1.4\alpha + 0.4\beta \qquad (10)$$

There is no available experimental value of $\Delta G_v^\circ{}_{5-6}$ for comparison although the results for cyclohexane can be taken to suggest that the value will be >2.3 kcal/mol. The coefficient of the dielectric term of −5.7 can be compared to a value of −6.6 obtained from eq 3.[38] The correlation gives an R^2 value of 0.801, an F factor of 9.39, and a possibility of 1 chance in 1.43 × 10^2 that the agreement is not significant. The standard error of estimate is 0.4 kcal/mol, which is, however, 20% of the observed range. Acceptance of the correlation in this case is questionable, although the trends seem correct.

$\Delta G_s^\circ - \Delta G_v^\circ$ for 7–8. In an effort to extend the model to a 4-hydroxypyridine–4-pyridone system, Gordon and Katritzky[7] redetermined the effect of solvent on the protomeric equilibrium between 2-chloro-4-hydroxypyridine (**7**) and 2-chloro-4-pyridone (**8**). However, the chromophores of both isomers could be observed only in alcoholic solvents and water. Attempts to correlate this data showed clearly by the significance test that there are too few points to obtain a reliable result. In fact, even if the coefficient of the dipole moment term is estimated from the dipole moments of the individual isomers, an expression is obtained which has 1 chance in 8 of being fortuitous. Moreover, the $\Delta G_v^\circ{}_{7-8}$ obtained in that case suggests **8** should be the more stable isomer in the vapor phase in contrast with our observation. It is reassuring that the tests of significance we have used reveal this case to be unsatisfactory, a result we attribute to limited data.

$\Delta G_s^\circ - \Delta G_v^\circ$ for 9–10. Direct measures of the equilibrium between 4-mercaptopyridine (**9**) and 4-thiopyridone (**10**) can be made in five non-hydrogen-bonding and three hydrogen bond acceptor solvents as shown in Table I. In all alcoholic solvents only **10** can be observed. Analysis of the data provides eq 11, with $\Delta G_v^\circ{}_{9-10} = 3.4$ kcal/mol.

$$\Delta G_s^\circ{}_{9-10} - \Delta G_v^\circ{}_{9-10} = -7.2\left(\frac{\epsilon - 1}{2\epsilon + 1}\right) - 2.0\beta \qquad (11)$$

The value of 3.4 kcal/mol for the **9**–**10** system is consistent with other measures which establish **9** to be the only detectable protomer.[1,39] The required dipole moments do

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[33] J. E. Freund, "Mathematical Statistics", 2nd ed., Prentice-Hall, Englewood Cliffs, NJ, 1971, p 219; J. Shorter, "Correlation Analysis in Organic Chemistry: an Introduction to Linear Free Energy Relationships", Clarendon Press, Oxford, 1973, pp 103–9. R. A. Avner, "Basic Statistical Package. PLATO", University of Illinois, Urbana, Illinois, 1978.

[34] The points for chloroform and *tert*-butyl alcohol which deviate geometrically have the least certain α values.[31] Because of the uncertainty about the chloroform value, it was not included in the correlation of eq 6.

[35] C. B. Theissling, N. M. M. Nibbering, M. J. Cook, S. El-Abbady, and A. R. Katritzky, *Tetrahedron Lett.*, 1777 (1977).

[36] The dipole moments of **5** and **6** were modeled by those of 2-(thiomethyl)pyridine (1.68 D) and 1-methyl-2-thiopyridine (5.22 D).[37] The molecular volumes used were 29.84 cm^3/mol for **5** and 25.44 cm^3/mol for **6**.

[37] H. Lumbroso and D. M. Bertin, *Bull. Soc. Chim. Fr.*, 1728 (1970).

[38] The dipole moments of 1.63 and 4.64 D, respectively, for **5** and **6** were approximated by vector addition of a dipole moment of 1.58 D for a C–Cl bond to the dipole moments of **3** and **4**. The molecular volumes used were 29.84 and 25.44 cm^3/mol for **5** and **6**, respectively.[1]

[39] A. Maquestiau, Y. Van Haverbeke, C. De Meyer, A. R. Katritzky, and J. Frank, *Bull. Soc. Chim. Belg.*, 84, 465 (1975); M. J. Cook, S. El-Abbady, A. R. Katritzky, C. Guimon, and G. Pfister-Guillouzo, *J. Chem. Soc., Perkin Trans. 2*, 1652 (1977).

not appear to be available for testing of the coefficient of the dielectric term. The R^2 value for the correlation is 0.989, the F value is 240, and there is 1 chance in 10^5 that the correlation is not significant.

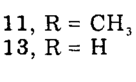
The absence of a term for hydrogen bond donors is due to the fact the alcoholic solvents are not included in the data base. The effect of the alcohols on the equilibrium does suggest that hydrogen bonding from the solvent does have a major effect on the equilibrium. In an effort to evaluate this effect we have reanalyzed the data for **9**–**10** in Table I by inclusion of the indirectly determined point for water. In that case, eq 12 is obtained, where $\Delta G_v°_{9-10}$

$$\Delta G_s°_{9-10} - \Delta G_v°_{9-10} = -7.3\left(\frac{\epsilon - 1}{2\epsilon + 1}\right) - 5.8\alpha - 2.3\beta \qquad (12)$$

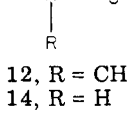
= 3.5 kcal/mol. The R^2 value is 0.997, the F value is 611, and the probability of chance correlation is 1 in 10^6. The standard error of estimate is 0.16 while the coefficients in eq 12 are comparable to those of eq 11. The large negative α coefficient in eq 12 does predict that **10** would be greatly stabilized by hydrogen bonding involving an electron pair of the substrate.

$\Delta G_v°$. The free-energy difference between isolated isomers in the gas phase, $\Delta G_v°$, is a measure of relative chemical binding energies which is useful as a test of theory, as well as a reference point for the effect of the molecular environment on protomeric equilibria.[1,2] The correlations of eq 8–11 appear to provide useful estimates of $\Delta G_{vap}°$.

As an example of the value of such information, we will show how the approach we have used earlier to provide a general estimate of the free-energy difference by which an amide is more stable than an imidic acid can be used with the present data to provide an estimate of the free energy between the thioamide and thioimidic acid groups.[40] The vapor free-energy difference between 2-mercaptopyridine (**3**) and 2-thiopyridone (**4**) of 3.0 kcal/mol in favor of **3** is obtained from eq 8. The free-energy difference of 7.6 kcal/mol between 2-(methylthio)pyridine and 1-methyl-2-thiopyridone determined calorimetrically favors the former.[41a] Comparison shows that the net changes in localized bond energies associated with the methylthio to mercapto and methylamino to amino bond transformations in such systems is 4.6 kcal/mol. Addition of that value to the 2.1 kcal/mol by which 2-(methylthio)-2-piperidene (**11**) is less stable than 1-methyl-2-thiopiperidone (**12**) leads to the estimate that 2-mercapto-1-piperidene (**13**) will be less stable than 2-thiopiperidone (**14**) by 6.7 kcal/mol.



11, R = CH_3
13, R = H



12, R = CH_3
14, R = H

In view of the demonstration that substituents and unstrained rings do not greatly affect the free-energy differences between amide–imidate groups, the value for **13**–**14** should be general.[41b] Accordingly, the thioamide function should generally be found to be more stable than the thioimidic acid by 7 ± 4 kcal/mol in the vapor phase.[42] Although the error may seem large, it should be noted that this appears to be the first experimentally based quantitative estimate of the relative chemical binding energies of these functional groups.[43]

$\Delta G_s°$. The prospect of a linear free-energy relationship which describes solvent effects on protomeric equilibria in terms of specific interactions is interesting. The approach appears to offer new insights, particularly for hydrogen-bonding effects.

Qualitatively, for example, the opposing contributions of hydrogen-bonding electron-pair donation and acceptance on the stability of the imidic acid–amide pairs explains the otherwise anomalous effect of alcohols on the equilibrium of **1**–**2**. The fact that electron-pair donation from the solvent favors **1** relative to **2** while the same effect favors **10** relative to **9** is interesting. Also, the small effect of hydrogen bonding on the thioimidic acid–thioamide equilibria of **3**–**4** and **5**–**6** stands in contrast to the large effect solvent hydrogen bonding has on the similar, but vinylogous, functions in **9**–**10**. Clearly the juxtaposition of the groups involved in hydrogen bond acceptance and donation in **3**–**4** and **5**–**6** is very different from that for **9**–**10**, but in the absence of the present approach dissection of the effect would not be possible.

Quantitative use of the model to predict solvation energies for systems where data are unavailable should be done only cautiously. An example is the use of eq 12 to provide solvation energies for alcoholic solvents. Comparison with indirectly estimated values may be useful, but the errors in such cases need to be carefully estimated.[44] Ultimately the assumed independence of hydrogen-bonding and reaction-field effects may prove to be oversimplified.

Extensions. Cases in which both isomers can be directly detected in a sufficient variety of solvents to provide a large number of data points are the most reliable and therefore most useful in establishing the correlation. However, there are only a limited number of such systems, and, perforce, these are the ones in which the free-energy differences between the isomers are least sensitive to changes in molecular environment.[16] Cases in which only one isomer can be detected or reliably estimated clearly provide little useful information about the effect of molecular environment on protomer stability since the differences which exist in the free energies of the isomers are immeasurable. This dilemma, in which the most reliable cases are least sensitive and the most sensitive cases are least reliable, seems inherent with present methodology.

The perturbing influences of self-association and impurities in the solvents on the apparent position of protomeric equilibria must be taken into account in interpretations of quantitative studies.[9,45] Again a dilemma exists. Self-association is reduced by using exceedingly dilute solutions, but in that case trace impurities in the solvent can become stoichiometrically significant. The fact

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[40] These estimates are for isolated amide–imidic acid and thioamide–thioimidic acid groups. Incorporation into aromatic rings as in the present cases clearly has a major affect of the relative energies. For discussion, see ref 2 and A. K. Burnham, J. Lee, T. G. Schmulz, P. Beak, and W. H. Flygare, *J. Am. Chem. Soc.*, **99**, 1836 (1977).

[41] (a) P. Beak and J. T. Lee, *J. Org. Chem.*, **34**, 2125 (1969); (b) P. Beak, J. Lee, and J. M. Zeigler, *ibid.*, **43**, 1536 (1978).

[42] The additive experimental errors amount to 6.6 kcal/mol; we believe there is substantial cancellation of errors which is not reflected in that estimate, however, and would ascribe an error of ±4 kcal/mol to the estimate.

[43] It has been estimated that the thioamide is favored in solution by ca. 10 kcal/mol by a pK_a method: M. J. Cook, A. R. Katritzky, P. Linda, and R. D. Task, *J. Chem. Soc., Perkin Trans. 2*, 1080 (1973). For a discussion of the qualitative stability of thioamides, see: W. Walter and F. Voss, "Chemistry of the Amides", S. Patai, Ed., Interscience, New York, 1970, p 383; W. Walter, *Z. Chem.*, **10**, 371 (1970).

[44] For leading references and a recent discussion of this approach, see D. H. Aue, L. D. Betowski, W. R. Davidson, M. T. Bowers, P. Beak, and J. Lee, *J. Am. Chem. Soc.*, **101**, 1361 (1979).

[45] O. Bensaude, M. Chevrier, and J. E. Dubois, *Tetrahedron Lett.*, 2221 (1978); O. Bensaude, M. Chevrier, and J. E. Dubois, *J. Am. Chem. Soc.*, **100**, 7055 (1978).

that low levels of possible impurities such as water or sodium ion can influence protomeric equilibria has recently been clearly demonstrated.[45,46]

Understanding of the effect of molecular environment on protomeric equilibria may be pertinent to important questions in molecular biology. In view of the environmental dependence of protomeric equilibria, the frequency of spontaneous mutation is not necessarily expected to correlate with the relative energies of the less stable protomers of nucleic acid bases as measured in aqueous solutions. Unusual models of equilibration in base pairing are not required to explain a lack of correlation.[47,48] If our results can be taken as a guide, it follows that the frequencies of the "rare" forms and the strength of their association within the nucleic acid or at the site of replication may differ by orders of magnitude from those in aqueous solution.[49] Studies of the environmental dependence of the associations and relative energies of the pyrimidine base pairs may define a range of reasonable values which will clarify the possibilities.[13,50]

Summary

The proposed model for the differential solvation of protomers in terms of reaction-field and hydrogen-bonding effects appears to provide a quantitative correlation for the change in relative energies of hydroxypyridine–pyridone and mercaptopyridine–thiopyridone isomer pairs which is satisfactory. This approach, which provides correlation in terms of reasonable physical interactions, seems preferable to empirical approaches. The protocol for application of the model is straightforward, and extension to related systems seems desirable.

Experimental Section

Ultraviolet spectra were recorded on a Cary 14 spectrophotometer, and the ratios of protomers were determined by the method of Dewar and Urch with the appropriate methylated isomers as models and with appropriate wavelength shifts where better correlation was obtained.[14,51] In cases where solvent interference allowed observation of only one protomer, equilibrium constants were obtained from material-balance calculations.

Preparations of the compounds investigated have been cited previously.[9]

A solution of 2,6-dichloropyridine *N*-oxide[52] (0.618 mol) and 1 equiv of thiourea in ethanol was heated at reflux for 2 h. After the solvent was removed in vacuo the resulting brown solid was washed with 10% sodium hydroxide, air-dried, and sublimed at 70 °C (0.1 torr) to afford 1.04 g (40% yield) of 2-chloropyridinyl 6-disulfide: mp 97–98 °C; ^{1}H NMR (CDCl$_3$) δ 7.5 (m, 4, ring H's), 7.1 (m, 2, ring H's); mass spectrum, *m/e* (relative intensity) 288 (M$^+$, 100); osmometric mol wt 288. Anal. Calcd for $C_{10}H_6N_2Cl_2S_2$: C, 41.54; H, 2.08; N, 9.69; Cl, 24.54; S, 22.15. Found: C, 41.50; H, 2.17; N, 9.48; Cl, 24.38; S, 21.93.

A sample of 2-chloropyridinyl 6-disulfide (3.5 mol) and 2 equiv of zinc dust were heated in 50 mL of acetic acid at 65 °C for 2 h. Addition of water and extraction with methylene chloride was followed by washing with 10% sodium bicarbonate solution, which was in turn washed with methylene chloride. The combined methylene chloride extracts were dried ($MgSO_4$) and evaporated in vacuo to afford a yellow solid. Sublimation at 40 °C (0.2 torr) gave a yellow solid: 93% yield; mp 60–61 °C; ^{1}H NMR (CDCl$_3$) δ 7.35 (m, 1, ring H), 7.1 (m, 1, ring H), 6.9 (m, 1, ring H), 6.4 (s, 1, SH); mass spectrum, *m/e* (relative intensity) 145 (M$^+$, 100); IR (Nujol) 2650, 1520, 1415, 1150, 790 cm^{-1}. Anal. Calcd for C_5H_3ClNS: C, 41.25; H, 2.75; N, 9.63; Cl, 24.37; S, 22.10. Found: C, 41.42; H, 2.64; N, 9.40; Cl, 24.67; S, 21.85.

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Registry No. **1**, 73018-09-4; **2**, 16879-02-0; **3**, 73018-10-7; **4**, 2637-34-5; **5**, 73018-11-8; **6**, 67131-59-3; **7**, 17368-12-6; **8**, 17228-67-0; **9**, 4556-23-4; **10**, 19829-29-9; 2,6-dichloropyridine *N*-oxide, 2587-00-0; 2-chloropyridinyl 6-disulfide, 72917-33-0.

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(46) Determination of the influence of trace impurities is clearly limited by available methods. For example, the equilibrium constants which we have reported for **15**–**16** at 10^{-6} M in cyclohexane could be in error if 10^{-6} water were present. Detection of this level of water is difficult, and the correspondence of the observed equilibrium constant for **15**–**16** with the vapor-phase value suggests there is not a serious problem in this case.

(47) J. D. Watson and F. H. Crick, *Nature (London)*, 171, 964 (1953). J. D. Watson and F. H. Crick, *Cold Spring Harbor Symp. Quant. Biol.*, **18**, 123 (1953). For discussion and leading references, see: D. M. Brown, *Pure Appl. Chem.*, 18, 187 (1969); J. W. Drake, *Nature (London)*, **221**, 1132 (1969); D. Shugar, C. P. Huber, and G. I. Birnbaum, *Biochim. Biophys. Acta*, **447**, 274 (1976). B. Pullman and A. Pullman, *Adv. Heterocycl. Chem.*, **13**, 77 (1971). C. B. Reese and A. Saffhill, *J. Chem. Soc., Perkin Trans. 2*, 2397 (1971). Y. P. Wong, K. L. Wong, and D. Kearns, *Biochem. Biophys. Res. Commun.*, **49**, 1580 (1972). M. Daniels, *Proc. Natl. Acad. Sci. U.S.A.*, **69**, 2488 (1972). D. Lictenberg, F. Bergmann, M. Rahat, and Z. Neiman, *J. Chem. Soc., Perkin Trans. 1*, 2950 (1972). F. Jordan and H. D. Sostman, *J. Am. Chem. Soc.*, **94**, 7898 (1972). K. C. Ingraham and M. Ashraf El-Bagoumi, *ibid.*, **96**, 1674 (1974).

(48) M. D. Topal and J. R. Fresco, *Nature (London)*, **263**, 285 (1976).

(49) Indeed, one of the simplest controls an organism could exercise over mutation would be appropriately fashioning the molecular environment at the base-pairing site. Changes in orders of magnitude do not require, of course, a change in the major protomer in a given case.

(50) For a recent example, see J. J. Nowak, K. Szezepaniak, A. Barski, and D. Shugar, *Z. Naturforsch., C*, **33**, 876 (1978).

(51) M. J. S. Dewar and D. S. Urch, *J. Chem. Soc.*, 345 (1957).

(52) R. J. Rousseau and R. K. Robbins, *J. Heterocycl. Chem.*, **2**, 196 (1965).