

Fundamental Solution Properties of 4-Hydroxy-1,3,3a,7-tetraazaindenes

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Abstract

The UV spectra and the pK_a and pK_{sp} of 14 different variations of 4-hydroxy-1,3,3a,7-tetraazaindene (TAI) measured in water at 25°C are discussed in this report. The acidity of the tautomeric proton correlated with the electronic inductive effect of the substituent as measured by Hammett's σ_p constants; pK_a values ranged from 3.4 to 6.5. The solubility products of the 1:1 TAI:Ag salts were measured at equilibrium using a solid-state silver sulfide electrode. pK_{sp} values ranged from 9.6 to 12.9 and increased with substituent bulk at the 2-position and with electron-withdrawing substituents at the 5-position. Oxidation of a thioalkyl substituent at either the 2- or 5-position decreased the pK_{sp} value. A carboxylic acid group at the 2-position yielded a soluble silver complex with $\log \beta_1$ of 7.9; however, carboxylic acid substitution at the 5-position yielded a sparingly soluble salt with pK_{sp} of 10.4. pK_a and pK_{sp} values were observed to be correlated only for substituents in definite homologous series; however, there is no general correlation within the 14 examples.

Introduction

Since Birr's discovery of the photographic significance of 4-hydroxy-6-methyl-1,3,3a,7-tetraazaindene,¹ extensive discussions have focused on the properties of this class of fused heterocycles. Much of the reported work relate to Birr's original compound²⁻⁵ and on other structural modifications of the azaindene nucleus.⁶⁻¹⁰ Recently, Tani explored the linear relationship between pK_a and pK_{sp} of a group of substituted 4-hydroxy-tetraazaindenes.¹¹

Our ongoing investigations of substitutional variations of 4-hydroxy-1,3,3a,7-tetraazaindene (TAI) have generated results that are generally consistent and sometimes conflicting to those already published. Our investigations suggest that pK_a and pK_{sp} may be related only in selected cases and not as a general rule. This is illustrated with a sampling of some fundamental solution properties for a selected variety of these substituted TAIs. These include acid dissociation constants, equilibrium and non-equilibrium silver(I)-salt solubility product constants, and ultraviolet absorption spectra.

Experimental

The substituted TAIs discussed in this report are shown in Table 1. These materials were synthesized or purified by G.

J. Burgmaier of the Kodak Research Laboratories. Aqueous TAI solutions were prepared in either 0.05 M sodium borate decahydrate (pH 9) or a borate/phosphate buffer¹² (pH 6).

UV spectra were recorded at 25°C with a Varian Cary 219 UV-vis spectrophotometer. The digitally stored absorbance vs wavelength data were automatically adjusted for any absorbance contributed by the reference solution.

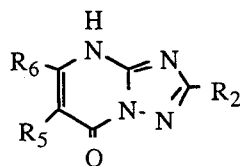
Hydrogen ion potentials were monitored with a Russell SW711/DWG1435 glass pH electrode referenced to a Corning 476030 Ag/AgCl electrode. The reference electrode was separated from the test solution by a double-junction salt bridge. The glass pH electrode was calibrated at 25°C against commercially available pH 4, 7, and 10 standard buffer solutions to obtain the corresponding H^+ potentials. Nineteen calibrations yielded well-behaved Nernstian values with these corresponding linear regression statistics (at 95% confidence): slope = -58.5 ± 0.3 mV, intercept = 393 ± 2 mV, RMS error = 2.4, $R^2 = 0.9997$.

Silver ion potentials were monitored with an Orion 9416 silver sulfide solid-state electrode referenced to the same salt-bridge/electrode configuration described above. Prior to each calibration at 25°C, the silver sulfide electrode was polished and subsequently immersed in aqueous 0.1 M silver nitrate and rinsed in purified water. The electrode was calibrated against 3 standard solutions prepared in aqueous 0.05 M sodium borate decahydrate: 0.1 M KI saturated with AgI (pAg 14.96), 0.01 M KBr saturated with AgBr (pAg 10.19), and 0.1 mM KBr saturated with AgBr (pAg 8.19). Forty-three calibrations were modeled by the expression $vAg = s(pAg) + vAg_0$, where s and vAg_0 represent the Nernstian slope and intercept, respectively. These calibrations yielded the following linear regression statistics with 95% confidence: slope = -59.4 ± 0.2 mV, intercept = 606 ± 2 mV, RMS error = 2.4, $R^2 = 0.9998$.

Titration were performed with a Radiometer/Copenhagen autotitrator. A minimum of two replicate titrations for each TAI allowed an estimate of uncertainty. Both the vH vs volume KOH and the vAg vs volume $AgNO_3$ data were analyzed using a non-linear least-squares curve-fitting program adapted from Meites.¹³

Equilibrium potentials for Ag^+ -TAI mixtures were obtained by monitoring the vAg of fixed, known ratios of TAI to silver ion. The mixture was held with stirring at 40°C in a closed, light-tight glass vessel until the vAg changed by less than 0.005 mV/min. The temperature was rapidly changed to 25°C, and the stabilized vAg was recorded and used for determination of the equilibrium solubility product constant.

TABLE 1. Substituted 4-Hydroxy-1,3,3a,7-tetraazaindenes



Cpd	Designation	R ₂	R ₅	R ₆
1	6-Me TAI	H	H	CH ₃
2	5-Br TAI	H	Br	CH ₃
3	5-I TAI	H	I	CH ₃
4	5-CN TAI	H	CN	CH ₃
5	2-Me TAI	CH ₃	H	CH ₃
6	2-COOH TAI	COOH	H	CH ₃
7	2-SMe TAI	SCH ₃	H	CH ₃
8	2-SOMe TAI	SOCH ₃	H	CH ₃
9	2-SO ₂ Me TAI	SO ₂ CH ₃	H	CH ₃
10	2-MeSMe TAI	CH ₂ SCH ₃	H	H
11	2-MeSO ₂ Me TAI	CH ₂ SO ₂ CH ₃	H	H
12	6-MeSMe TAI	H	H	CH ₂ SCH ₃
13	6-MeSO ₂ Me TAI	H	H	CH ₂ SO ₂ CH ₃
14	5-COOH TAI	H	COOH	H

Results and Discussion

4-Hydroxy-1,3,3a,7-tetraazaindenes are essentially acidic amides whose tautomeric forms are treated as nitrogen or oxygen acids.^{6,14} IR spectra^{15,16} and x-ray diffraction data³ of the Ag⁺-salt of 6-Me TAI indicate that silver ions bind predominantly with the 7-position nitrogen. Hence, the OH and the 7-NH tautomers appear to be the most important tautomeric forms.⁴ The 7-NH tautomer is used as the representative structure in this discussion.

pK_a Values of Substituted TAIs

UV Spectroscopy: The tautomeric forms participate in the absorption of ultraviolet radiation.⁷ The presence and nature of the R₂, R₅, and R₆ substituents affect the electronic transitions⁶ as well as the acidity of the tautomeric proton.

A main absorption band between 270 and 300 nm exists for the TAIs in their fully deprotonated state, as shown in Table 2. Substitution with a methylthio group at the 2-position produces a high extinction band around 230 nm, indicative of the lone-pair electron's participation in ring conjugation. This band disappears with oxidation to the sulfoxide or sulfone (2-SOMe TAI and 2-SO₂Me TAI) and is absent when the methylthio group is insulated from the heterocycle by at least one methylene group (2-MeSMe TAI).

Substitution of 6-Me TAI's 5-position hydrogen by Br, I, CN, or carboxylate results in a bathochromic shift for the two main absorption bands. This effect is consistent with hydrogen bonding between the 4-hydroxy and the adjacent substituent.⁷

Spectroscopic determination of pK_a,¹⁷ exemplified by the variation in absorption with pH shown in Fig. 1, allowed independent confirmation of acidity constants found by potentiometric titration. The pK_a values determined by the two techniques agreed nicely and were consistent with those found spectroscopically by Tani.¹⁶

TABLE 2. Absorption Spectra of 4-Hydroxy-1,3,3a,7-tetraazaindenes^a

Designation	λ _a	λ _b	λ _c
6-Me TAI		256 (6.6)	280 (12.4)
		256 (6.4) ^b	278 (10.8) ^b
5-Br TAI		260 (6.7)	292 (11.6)
5-I TAI		260 (8.1)	295 (10.9)
5-CN TAI		262 (9.1)	288 (12.4)
2-Me TAI		254 (6.2)	280 (11.9)
2-COOH TAI			286 (10.9)
2-SMe TAI	229 (28.0)		281 (11.1)
2-SOMe TAI			284 (13.0)
2-SO ₂ Me TAI			284 (13.0)
2-MeSMe TAI			281 (12.5)
2-MeSO ₂ Me TAI			280 (13.3)
6-MeSMe TAI		251 (7.0)	288 (10.0)
6-MeSO ₂ Me TAI		253 (5.4)	292 (10.8)
5-COOH TAI		263 (9.5)	291 (13.2)

(a) Wavelength is given in nanometers; the extinction, in parentheses, is $\epsilon \times 10^{-3}$ with 95% confidence limits of ± 500 . Wavelength regions: λ_a from 220 to 240 nm, λ_b from 240 to 270 nm, λ_c from 270 to 300 nm. Spectra measured in 0.05 M sodium borate decahydrate at 25°C.

(b) From ref 6, pH and solvent conditions not known.

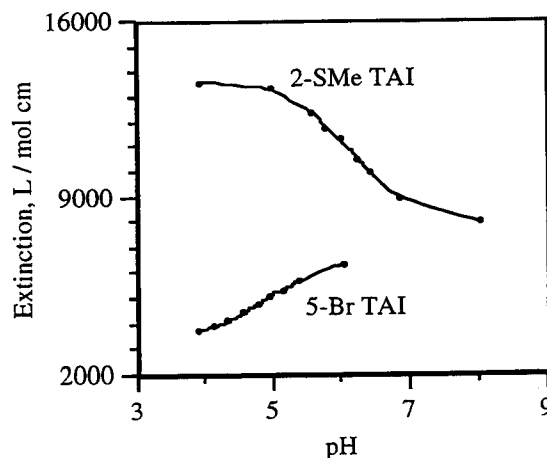


Figure 1. Sensitivity of absorption as a function of pH of 2-SMe TAI (at 267 nm) and of 5-Br TAI (at 260 nm).

Potentiometry: Ionization constants of the TAI protons determined potentiometrically are listed in Table 3, and titration curves for representative monoprotic and

diprotic TAIs are shown in Fig. 2. For TAIs with carboxyl residues (i.e., 2-COOH TAI and 5-COOH TAI), the more acidic proton was attributed to carboxylic acid dissociation. The less acidic proton was assigned to the heterocyclic tautomer. Whether at the 2-position or the 5-position, the carboxyl group had only a slight effect on the acidity of the TAI proton. Spectroscopic techniques were not amenable to pK_a determinations for these two diprotic TAIs: the absorption spectra lacked isosbestic points and the data could not be fit to defined models.¹⁷

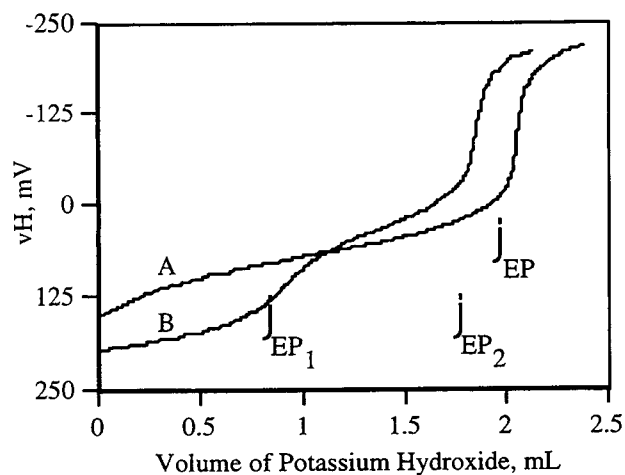


Figure 2. Alkalimetric titrations of 6-Me TAI (2.06 mM, curve A) and 5-COOH TAI (0.03 mM, curve B) with 0.1 M potassium hydroxide in 0.1 M aqueous potassium nitrate at 25°C. The equivalence points for the monoprotic acid and for the diprotic acid (EP_1 and EP_2) are indicated. The vH was followed with a glass pH electrode and a triple-junction Ag/AgCl reference electrode.

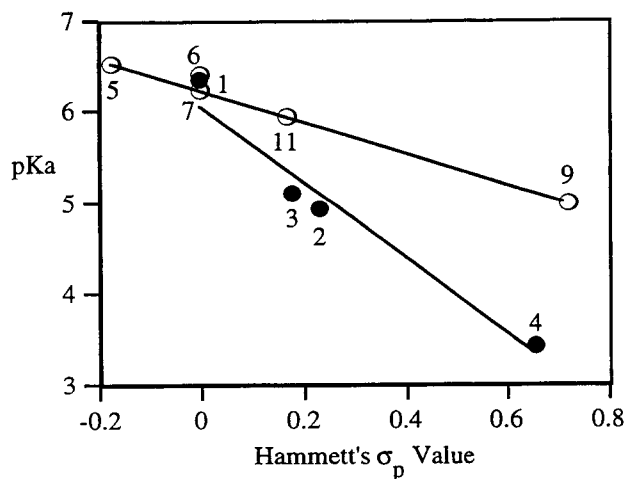


Figure 3. Correlation between Hammett's substituent constants and potentiometrically derived acidity constants for the tautomeric TAI proton. Open circles are TAIs with 2-position substituents. Closed circles are TAIs with 5-position substituents. Hammett constants taken from ref 18. Numbers refer to the TAIs identified in Table 1.

Substitution at the 5-position with Br, I, or CN resulted in up to an 800-fold increase in acidity. Substitution at the 2-position with a methylthio residue increased acidity by about 0.1 pK unit. Substitution with a methylthiomethyl residue completely eliminated the change in acidity. Apparently, the methylene group insulates the heterocycle from the inductive effects of the thioether, and this is in agreement with the UV absorption behavior. However, in the 6-position, replacement of the methyl by a methylthiomethyl group resulted in a 12-fold acidity increase.

TABLE 3. Acid Dissociation Constants for 4-Hydroxy-1,3,3a,7-tetraazaindenes at 25°C

Designation	pK_a^1
6-Me TAI	6.35, 6.4 ^a , 6.34 ^b , 6.27 ^c , 6.47 ^d
5-Br TAI	4.93
5-I TAI	5.08
5-CN TAI	3.42
2-Me TAI	6.52
2-COOH TAI	2.56, 6.40
2-SMe TAI	6.21, 6.23 ^b
2-SOMe TAI	5.36
2-SO ₂ Me TAI	4.99
2-MeSMe TAI	6.35
2-MeSO ₂ Me TAI	5.93
6-MeSMe TAI	5.48
6-MeSO ₂ Me TAI	4.28
5-COOH TAI	3.32, 6.12

1. Determined potentiometrically. The uncertainty is 0.01 at 1 standard deviation of 3 replicate titrations: (a) ref 2 at 20°C; (b) ref 9; (c) ref 16, determined spectroscopically; (d) ref 5 at 18°C.

Hammett Correlations: Figure 3 shows correlations between Hammett substituent constants¹⁸ and pK_a values for TAIs. Using a combined model describing pK_a as a function of σ_p for the 2- and 5-positions separately, the resulting regression gave a correlation coefficient greater than 0.97 and indicated that pK_a is about 3 times more sensitive to 5-substitution than to 2-substitution. Taken further, using the individual inductive and resonance contributions of σ_p (where $\sigma_p = \sigma_I + \sigma_R$) suggested that the inductive effect—regardless of substituent position—was nearly 1-1/2 times more important than the resonance effect.

pK_{sp} Values of Substituted TAIs

Determination of the silver-salt solubility product constants (pK_{sp}) for TAIs requires the deprotonation of the free acid to the nitrogen anion and subsequent binding of silver ion to yield the sparingly soluble salt. Table 4 lists the pK_{sp} values for the investigated TAIs.

TABLE 4. Solubility Products of the 1:1 Ag⁺-TAI Salts at 25°C

Designation	pK _{sp} ¹	pK _{sp} ²	log β ₁
6-Me TAI	10.1, 10.15 ^a , 10.5 ^b , 9.7 ^c , 10.7 ^d , 10.52 ^e	11.58, 11.43 ^a	
5-Br TAI	10.3	12.86	
5-I TAI	11.0	12.84	
5-CN TAI	9.5	11.48	
2-Me TAI	9.6	10.60	
2-COOH TAI			7.9
2-SMe TAI	9.9, 9.94 ^a	11.09, 10.92 ^a	
2-SOMe TAI	9.1	9.86	
2-SO ₂ Me TAI	8.6	9.64	
2-MeSMe TAI	12.5	12.94	
2-MeSO ₂ Me TAI	9.4	10.49	
6-MeSMe TAI	11.5	12.51	
6-MeSO ₂ Me TAI	9.5	10.12	
5-COOH TAI	9.8	10.43	

1. Calculated from argentometric titrations at 1/2-equivalence point; (a) ref 9 as "transient salt" in NaClO₄; (b) ref 11; (c) ref 1; (d) ref 8a at 60°C; (e) ref 5 at 18°C.

2. Determined by "relaxation" method (uncertainty 0.06, ±1 standard deviation); (a) ref 9 as "stable salt" in NaClO₄.

Pouradier and Pailliotet⁹ found that the pK_{sp} of 6-Me TAI and 2-SMe TAI was time dependent, reorganizing from a less stable "transient" salt to a more stable form. During studies on the pK_{sp} of benzotriazoles, Battaglia observed equilibrium times as long as 2 to 3 hours.¹ A typical argentometric titration curve, shown in Fig. 4, did not allow sufficient equilibration time even though the pK_{sp} calculated from such data agreed well with literature values. The relaxation method, illustrated in Fig. 5, yielded equilibrium solubility product constants.

Silver-salt solubility increased with oxidation of the alkylthioether substituent. The parent alkylthioethers (2-SMe TAI, 2-MeSMe TAI, 6-MeSMe TAI) formed silver salts that were from 28 to 280 times less soluble than their corresponding sulfoxides and sulfones. Electron-withdrawing groups at the 5-position, except for the cyano residue, decreased Ag⁺-TAI solubility by an order of magnitude.

However, as shown in Fig. 6, no clear correlation exists between pK_a and pK_{sp} for this series of TAIs, independent of whether the "transient" or equilibrium solubility product was used.

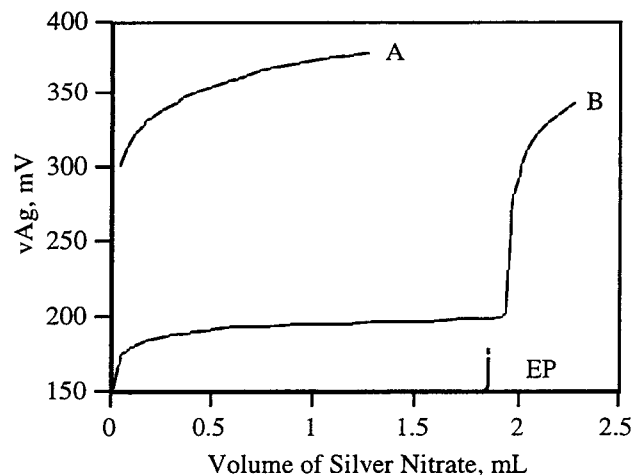


Figure 4. Titration of 0.49 mM 5-Br TAI in 0.05 M sodium borate decahydrate (pH 9) at 25°C (curve B) with 0.025 M silver nitrate. The equivalence point (EP) of the 1:1 tetraazaindene complex with silver ion is indicated. The blank titration, or dilution curve, in 0.05 M sodium borate decahydrate (curve A) is shown.

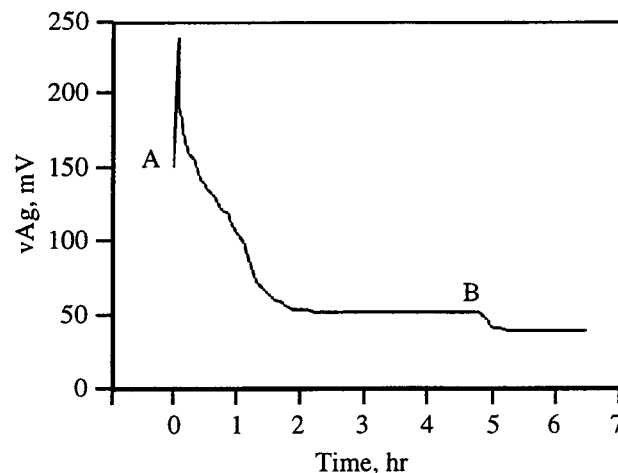


Figure 5. Time-dependent silver-ion potentials of a mixture of 1.07 mM 5-Br TAI and 0.54 mM silver nitrate in 0.05 M sodium borate decahydrate (pH 9). The temperature was held at 40°C from point A to point B, then the mixture was rapidly cooled to 25°C. The silver nitrate was injected at point A.

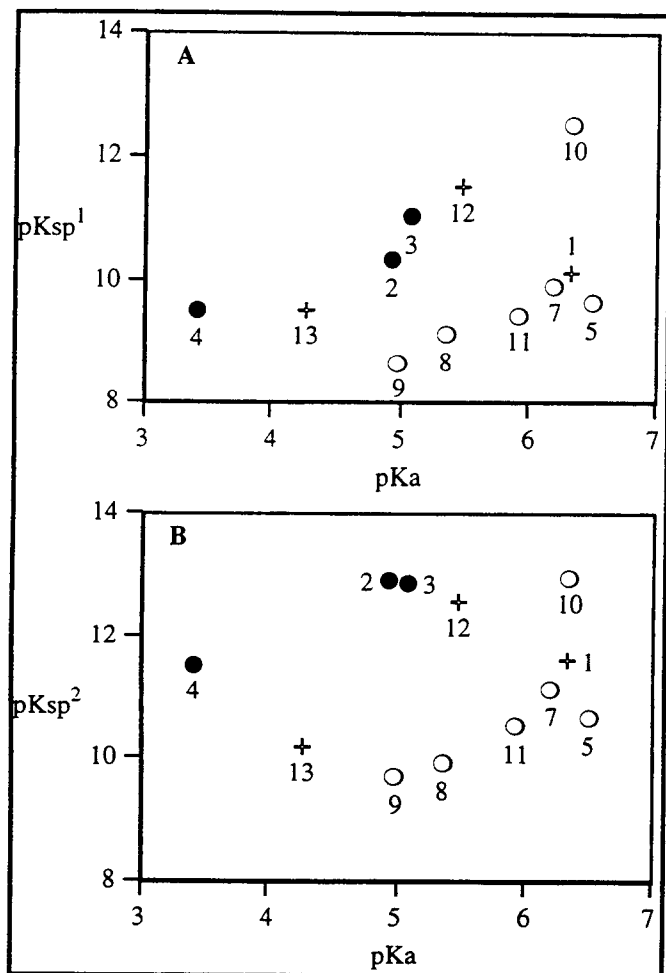


Figure 6. Relationship between pK_a and pK_{sp} for TAIs. pK_{sp}^1 refers to values determined by titration. pK_{sp}^2 refers to values determined by the relaxation method. Numbers refer to the TAIs identified in Table 1. Closed circles represent TAIs with 5-position substituents. Open circles represent TAIs with 2-position substituents. Crosses represent TAIs with 6-position substituents.

Conclusions

The absence of a correlation between pK_a and pK_{sp} could come from two sources: (1) lack of accuracy in experimental measurements and (2) inherent physical/chemical properties. Great attention was paid to acquiring solution equilibria of high accuracy and precision, and we are unable to attribute the lack of correlation to anything other than that there are several physical/chemical parameters that control the solution properties of TAIs.

If the predominant factor in the acidity of the TAI proton and the ligation of silver ion is electron density at the nitrogen atom, then a better correlation would be evident between pK_a and pK_{sp} . Other factors, such as steric hindrance, need to be explored before we can better understand the relationship between pK_a and pK_{sp} for TAIs.

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