Acidity Constants of Benzimidazolium Ketone and Pyridinium Aldehyde Hydrates

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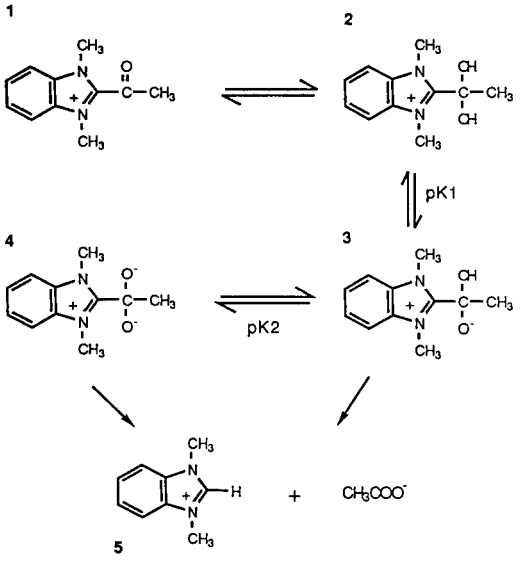
Received December 21, 1989

Acidity constants (p*K*a) of the hydroxyl groups of the quaternary heterocyclonium carbinols 2-hydroxymethyl-1-methylpyridinium and 2-(1-hydroxyethyl)-1,3-dimethylbenzimidazolium ions are 11.5 ± 0.5. Acidity constants of the corresponding *gem* diols, the hydrates of 2-formyl-1-methyl-pyridinium and 2-acetyl-1,3-dimethylbenzimidazolium ions hence are estimated to be 9 ± 0.5. Accordingly, acidity constants of the hydroxyl groups of pyridine aldehyde salt hydrates are 12-13, not 4-5 as previously reported; and conversely, acidity constants of the pyridinium groups are 4-5, not 12-13.

J. Heterocyclic Chem., **27**, 987 (1990).

Our investigations of the deacylation of the 2-acetyl-1,3-dimethylbenzimidazolium cation (**1**, Scheme 1) and related compounds have made it necessary to ascertain acidity constants for the hydroxyl groups of their hydrates (**2**, Scheme 1). As Bruice [1] and Lienhard [2] showed for analogous thiazolium compounds, and as we have shown for the benzimidazolium compound [3], these facile deacylations proceed through the hydrates and are cleanly first-order in hydroxide ion throughout the *p*H range 4 to 9. This behavior requires that p*K*1 in Scheme 1 be either above 9 or below 4, the key intermediate being the *gem* diol monoanion, **3**, in the first case and the dianion, **4**, in the second.



Scheme 1. Mechanisms for deacylation of quaternary 2-acylbenzimidazolium and 2-acylthiazolium cations

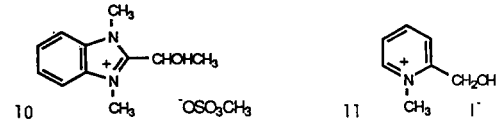
The first alternative is intuitively more attractive, and both Bruice and Lienhard utilize it. Reactions involving *gem* diol dianions are known, of course [4], but only in strongly alkaline media. For such a mechanism to operate at *p*H 4 would be unprecedented. Nevertheless, and to our considerable surprise, it comes to our attention [5] that Nakamoto and Martell, in two major papers [6], reported acidity constants in the range 4.2-5.2 for the hydroxyl groups of pyridin-2-aldehyde hydrate (**6**, Scheme 2) and a number of related pyridine aldehyde hydrates. The acidities of our heterocyclonium ketone hydrates would be expected to be similar to those of the pyridinium aldehyde hydrates, and values so low would bear crucially on deacylation mechanisms of interest to us.

It is known that the acidity constants of *gem* diols typically are about 2.5 units lower than those of the corresponding monohydric alcohols [7]. To further lower the acidity constant from 15.7, the value for methanol [8], or from 13.3, the value for formaldehyde hydrate [9], to 4.2, the pyridinium ring would have to induce a Δ*p*K of 9 units. This seems improbable. Lienhard [2] has estimated the inductive effect of a similarly situated positively charged nitrogen to be somewhat less than that of a dichloromethyl group, yet chloral hydrate has a p*K*a only 3.5 units lower than acetaldehyde hydrate [9]. Even two trifluoromethyl groups, as in hexafluoroacetone hydrate [7], only lower the p*K*a to 6.45. Yet Nakamoto and Martell's values seem not to have been challenged nor even commented on.

Results and Discussion.

Ketone **1** is hydrated some 35% (nmr) in water or in deuterium oxide. It deacylates rapidly in neutral solution [3], half-life 27 seconds at *p*H 7.7, but is stable for days at *p*H 3 or below. Since the half-life is some eight hours at *p*H 4.7, a p*K*a of 4-5, or even as high as 6, should be determinable by titration to half-neutralization in the conventional manner. In the event, addition of as little as 0.2 mole of sodium hydroxide (or even imidazole or disodium phosphate) per mole of total ketone produced rapid deacylation to an extent corresponding to the amount of base added. Clearly, the base raises the *p*H of the solution to a value well above that permitted by a p*K*a below neutrality. Direct determination thus being impossible, we have measured acidity constants for the carbinols **10** and **11**. These compounds are stable to alkali at room temperature, although they are destroyed by refluxing base [10]. The

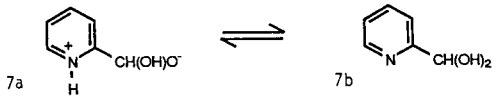
first is directly cognate to the benzimidazolium ketone hydrate **2**, the second to the pyridinium aldehyde hydrate **6**. The *p*H values reached upon simple addition of alkali to their solutions indicate p*K*a values of 11.5 ±0.5 for both compounds. Inductive effect adjustments [7] provide p*K*a estimates of 9 ±0.5 for both **2** and **6** and 13 ±0.5 for the uncharged pyridine aldehyde hydrate **7**.



10 11

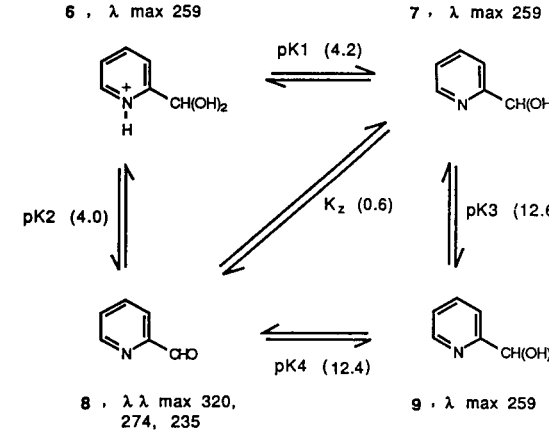
Taken together, the above results confirm that the acidity constant for the benzimidazolium *gem* diol **2** likely is about 9 and cannot possibly be anywhere near 4. Accordingly, the dianion mechanism for its deacylation is firmly excluded.

What then of the published acidity constants for the pyridine aldehyde hydrates? Nakamoto and Martell's assignments are based on changes of ultraviolet spectra with *p*H. They find the unhydrated aldehyde, **8**, to have intense $\pi \rightarrow \pi^*$ bands at 274 and 235 nm, while the several species with the sp^3 side-chain carbon, **6**, **7** and **9**, all absorb at 259 nm, neither the ionization of the dihydroxymethyl nor that of the pyridinium group affecting λ max significantly. We note that the ultraviolet measurements can afford no discrimination between the zwitterionic structure **7a** and the corresponding proton-switched molecule **7b** for the singly protolysed entity in the equilibrium.



7a 7b

For some reason the zwitterion structure **7a** was assigned to this species. It being that pyridine is a weaker base than alkoxide by some ten orders of magnitude, it seems to us rather that the non-zwitterionic structure **7b** should predominate overwhelmingly. This would mean that the authors simply misassigned p*K*1 and p*K*3. The former, 4.2, should represent protolysis of the pyridinium ion, for which it is an entirely plausible value. The latter, 12.6, would then be the p*K*a of the *gem* diol grouping of the neutral molecule. These values are as would be expected for such functional groups, and are consistent with those we report for the quaternary heterocyclonium compounds in which there is no ambiguity as to the site of protolysis. Acidity constants for hydrates of pyridine 3- and 4-aldehydes and 3-methoxypyridine 2- and 4-aldehydes are based on similar interpretations of ultraviolet spectra, and all must therefore be reassigned. The proper assignments and tabulated values [11] are presented in Scheme 2.



Compound	pK1	pK2	pK3	pK4	Kz
2-aldehyde	4.2	4.0	12.6	12.4*	0.6
3-aldehyde	4.2*	4.0*	12.9	12.7	0.8
4-aldehyde	5.2	5.0	12.0*	11.8*	0.6
3-methoxy-2-aldehyde	4.4	4.0	12.8*	12.4*	0.4
3-methoxy-4-aldehyde	4.8	4.7	11.5*	11.3*	0.8

Scheme 2. Corrected solution equilibria and acidity constants for pyridine aldehyde hydrates

Nakamoto and Martell also report spectroscopic data and deduce acidity constants for 3-hydroxypyridine 2- and 4-aldehydes and for 2- and 4-hydroxymethyl-3-hydroxypyridines. These systems and their spectra are complex. Nevertheless, it is clear that some of the constants for these pyridoxine and pyridoxal models are unexpected. While the numerical values undoubtedly are sound, it seems that the assignments of them should be viewed with caution.

EXPERIMENTAL

Elemental analyses were obtained from Galbraith Laboratories Inc., or Atlantic Microlab Inc. The ^1H nmr spectra were determined on a Varian EM360A spectrometer. Ultraviolet spectra were determined on an IBM 9420 spectrometer. The *p*H measurements line were observed on a Corning Digital 110 instrument. 2-Hydroxymethyl-1-methylpyridinium iodide was prepared as described by Golding and Katritzky [10]. 2-Acetyl-1-methylbenzimidazole was prepared as described by Cheeseman [12].

2-Acetyl-1,3-dimethylbenzimidazolium (**1**) Methosulfate and Iodide.

Quaternization of 2-acetyl-1-methylbenzimidazole with methyl iodide [13] was unreliable. Reproducible results were obtained with dimethyl sulfate. A mixture of 2-acetyl-1-methylbenzimidazole (1.74 g, 0.01 mole) and dimethyl sulfate (1.5 g, 0.012 mole) was kept in a water bath at 60°. All liquified within 30 minutes and then crystallized overnight. The crystalline solid, broken up under ethyl acetate to remove excess reagent, was practically

pure **1** methosulfate (2.8 g, 95%); ^{1}H nmr (deuteriodimethylsulfoxide): δ 2.95 (s, 3H), 3.35 (s, 3H), 4.2 (s, 6H), 7.9 (m, 4H); uv (water, *p*H 3): λλ max 298, 279, 273 (sh), 237 nm.

The methosulfate may be used directly for many purposes, but is hygroscopic and does not keep well. For further purification, characterization and storage it is conveniently converted into the sparingly soluble iodide. The **1** methosulfate (2.7 g) in *p*H 3 water (10 ml) was filtered into a solution of sodium iodide (20 g) in water (15 ml). Pale yellow needles soon separated. These were collected and leached thoroughly with absolute alcohol to afford **1** iodide (2.5 g, 80% overall), mp 196-198° (lit [13] 185-188°); ^{1}H nmr (deuteriodimethyl sulfoxide): δ 2.95 (s, 3H), 4.2 (s, 6H), 7.9 (m, 4H); uv (water, *p*H 3): λλ max 298 (ε 7.1 x 10^3), 279, 273 (sh). The low wavelength peak is obscured by iodide absorbance below 240 nm.

Anal. Calcd. for $C_{11}H_{13}IN_2O$: C, 41.79; H, 4.14; N, 8.86. Found: C, 41.77; H, 4.13; N, 8.85.

2-(1-Hydroxyethyl)-1-methylbenzimidazole.

Sodium borohydride (1 g) was stirred into a solution of 2-acetyl-1-methylbenzimidazole (1.74 g, 0.01 mole) in a mixture of methanol (15 ml) and water (5 ml). After 1 hour excess borohydride was destroyed with aqueous acetic acid. The product was extracted into dichloromethane. The solution was dried with sodium sulfate and evaporated. The crystalline residue, after leaching with water to remove trace inorganics, was analytically and spectroscopically pure, yield, 1.69 g (96%), mp 109-110°; ^{1}H nmr (deuteriochloroform): δ 1.85 (d, 3H), 3.45 (s, 3H), 5.15 (q, 1H), 7.15 (m, 4H), 7.45 (m, 1H).

Anal. Calcd. for $C_{10}H_{12}N_2O$: C, 68.16; H, 6.86; N, 15.90. Found: C, 68.05; H, 6.93; N, 15.75.

2-(1-Hydroxyethyl)-1,3-dimethylbenzimidazolium (**10**) Methosulfate.

A mixture of 2-(1-hydroxyethyl)-1-methylbenzimidazole (0.53 g, 0.003 mole) and dimethyl sulfate (0.45 g, 0.0036 mole) was warmed gently until liquid and then cooled in water bath at room temperature as an exothermic reaction set in. After 1 hour the crystalline cake was broken up under ethyl acetate. Recrystallization from methanol-ethyl acetate (1:3) mixture gave pure **10** methosulfate (0.75 g, 83%), white crystals mp 161°; ^{1}H nmr (deuterium oxide): δ 1.9 (d, 3H), 3.8 (s, 3H), 4.15 (s, 6H), 5.85 (q, 1H), 7.8 (m, 4H).

Anal. Calcd. for $C_{12}H_{18}N_2O_5S$: C, 47.67; H, 6.00; N, 9.27. Found: C, 46.55; H, 5.90; N, 9.13.

Equilibrium Hydration of 2-Acetyl-1,3-dimethylbenzimidazolium (**1**) Salts.

Solutions (5-10% w/v) of **1** (methosulfate or iodide) in deuterium oxide, weakly acidic to preclude deacylation, exhibited in the ^{1}H nmr spectra a methyl singlet corresponding to the hydrate (*gem* diol) at δ 1.95 in addition to the singlet characteristic of the unhydrated ketone at δ 2.95. Solutions spiked with a little acetic acid showed an additional methyl singlet at δ 2.1. The 1.95:2.95 integral ratio, 1:2, indicated that some 35% of the ketone is hydrated. All of the nmr peaks (δ 1.95, 2.95, 4.2, and 7.9, as well as 3.8 for the methosulfate) were easily discerned also in water as long as spinning rates were adjusted to minimize overlap with spinning side bands. Rough kinetic experiments in which spectra were obtained within half a minute of dissolving the solid indicated the hydration half-life to be 20-30 seconds, independent of acidity in the *p*H range 1-6. This hydration behavior is similar to that reported by Lienhard [2] for the 2-acetyl-3-methylthiazolium cation.

Behavior of **1** Iodide Upon Incremental Addition of Alkali.

(a) Potassium hydroxide solution (140 μl, 1.0 molar, 140 μ moles) was added in portions to a well agitated solution of **1** iodide (72 mg, 220 μ moles) in water (1.0 ml). After each addition the *p*H was determined as quickly as possible and was followed to a value stable for several minutes. The ^{1}H nmr spectrum of the solution then was determined before the next addition was made. Decomposition (%) was estimated from nmr peaks corresponding to acetate ion (close to ketone hydrate at δ 1.95 but distinguishable from it) and 1,3-dimethylbenzimidazolium ion (δ 4.05, 9.15). Data obtained were:

Total Base Added (μl)	*p*H after:			% Decomposition (nmr)	
	30 sec	2 min	4 min	10 min	
20	5.05	4.82	4.71		
40	5.25	5.01	4.93	4.74	20-30
90	5.42	5.26	5.18	4.97	50-60
140	5.63	5.43		5.05	80-90

(b) To **1** iodide (70 mg, 220 μ moles) in water (1.0 ml) was added imidazole (7.5 mg, 110 μ mole). The *p*H of the solution, as quickly as it could be measured, was about 6.5, falling, rapidly at first and then more slowly, to 5.3. The nmr spectrum of the solution showed 70-80% deacylation to acetate ion (δ 1.95) and 1,3-dimethylbenzimidazolium ion (δ 4.05, 9.15).

Acidity Constants of Hydroxyethylbenzimidazolium **10** Methosulfate and Hydroxymethylpyridinium **11** Iodide.

Potassium hydroxide solution (1.0 *M*, 50 μl, 50 μ moles) was added to a solution of **10** methosulfate (60 mg, 200 μ moles) in freshly boiled, cooled deionized water (0.95 ml). The *p*H of the mixture was 11.0, which corresponds to a p*K*a of 11.48. Addition of a further portion (50 μl) of base raised the *p*H to 11.5, indicating the same acidity constant.

Similar results were obtained with **11** iodide, indicating a p*K*a of 11.5 for this salt also. The *p*H of a control, 50 μl of base in 0.95 ml of boiled deionized water, was 12.6, confirming that the observed *p*H changes are indeed significant. Since no correction is made for non-ideality, the p*K*a values are considered to be valid to within ±0.5 units, adequate for our purposes.

Acknowledgements.

Acknowledgement is made to the donors of the Petroleum Research Fund administered by the American Chemical Society for support of this research.

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[11] Consideration of the K1 K2 Kz and K3 K4 Kz equilibrium triangles reveals that Nakamoto and Martell mixed up one of the K1 K2 pairs and three of the K3 K4 pairs. For pyridin-3-aldehyde hydrate, for example, p*K*1 should be 4.2, p*K*2 4.0, and not vice versa. Also, p*K*4 for the 2-aldehyde hydrate should be 12.4, not 12.6. The changes are minor and have been made and are asterisked in Scheme 2.

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