group. Each of the three main lines showed fine structure due to long range C–H coupling, but the central multiplet had a width at half-height of 12 Hz compared to the outside multiplets of 8 Hz.
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(21) Compare J_{C_2H} for propanone (126), 3-pentanone (124), and 2,4-dimethyl-3-pentanone (128)[22] with that for propane (CH_3, 125; CH_2, 128),[9a] and that for cyclohexanone (129, this work) with cyclohexane (126).[9a]
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The Rates of Ionization of Arylamino Ketones Possessing the Potentiality for Intramolecular Imine Formation and Intramolecular Proton Abstraction

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Abstract: The rates of ionization of a series of compounds of the general structure $Ar(CH_2)_nNHCH_2CH_2CH_2COCH_3$ where Ar is phenyl or 2-pyridyl and *n* is 0, 1, or 2 have been measured by deuterium exchange methods. On the basis of the results it is concluded that (a) the formation of the cyclic pyrrolinium compounds enhances the rate of ionization by ca. 10^7 when pyridine is the proton acceptor, (b) the proximity to the pyrrolinium ring of a second positive charge (i.e., the protonated pyridine ring in the 2-pyridyl compounds) enhances the ionization rate via an inductive effect, a field effect, or both, and (c) intramolecular proton transfer occurs to a small but probably real extent in the ionization of the 2-pyridyl compounds in which *n* is 1 and 2.

The aldolization reaction of dihydroxyacetone has been shown to be susceptible to pyridine catalysis,[1] and its in vivo counterpart with dihydroxyacetone phosphate is known to involve imine intermediates.[2] As part of a program dealing with the synthesis of polyfunctional catalysts for this process, a series of arylamino ketones has been studied to assess the consequences of (a) the intramolecular imine formation, (b) the proximity of positive charge to the imine moiety, and (c) the proximity of a pyridyl moiety to the site of carbanion formation, employing the rate of deuterium exchange as the assay procedure.

Synthesis of Arylamino Ketones. By means of the reaction sequence shown in Figure 1, compounds of the general structure $Ar(CH_2)_nNHCH_2CH_2CH_2COCH_3$ were synthesized in which the aryl group is a pyridyl or a phenyl moiety and *n* has values of 0, 1, and 2. The starting material in every instance was 5-chloro-2-pentanone[3] which was converted to the ketal with methyl orthoformate, alkylated with the appropriate arylalkylamine, and hydrolyzed to the product **1–5**. Except for compound **1**, the isolated compounds exist primarily in the cyclic iminium form (**2b–5b**) rather than the amino ketone form (**2a–5a**).

The assignment of structure to compounds **2b–5b** is based on the elemental analysis of the perchlorate salts and on the ir and NMR characteristics. For additional verification, two alkyl-substituted pyrrolinium perchlorates of known structure[4,5] were prepared, and their spectral characteristics were compared with those of compounds **2b–5b**.

pK_a Values of Compounds 1–5. Using titrimetric (for **1a, 3b, 4b,** and **5b**) and spectrophotometric (for **2b**) techniques, the pK_a values of compounds **1–5** were determined (see Table I). The value for the pyridylamino ketone **1** agrees well with the reported values for 2-aminopyridine of 6.82[6] and 6.51,[7] supporting the open chain structure (**1a**). The phenyl analog (**4**) of compound **1** has a pK_a that is approximately 3 pK units greater than that of aniline (pK_a = 4.62), commensurate with the cyclic iminium structure (**4b**). The greater tendency for the phenylamino ketone **4a** to cyclize, compared with the pyridylmethyl ketone **1a**, is probably attributable to the greater basicity of the nitrogen atom in **4a**; although the macroscopic pK_a of 2-aminopyridine exceeds that of aniline by ca. 2 pK units, the amino group of 2-aminopyridine behaves as a less basic entity than the amino group of aniline. In fact, the pK_1 of 2-ammoniumpyridinium dication has been determined to be −7.6.[8]

The pK_a values for the pyrrolinium moiety of **2b, 3b,** and **5b** are 11.00, 11.87, and 11.76, respectively, in agreement with the reported values of 11.94 for 1,2-dimethyl-Δ^1-pyrrolinium perchlorate, 11.92 for 1-ethyl-2-methyl-Δ^1-pyrrolinium perchlorate, and 11.90 for 1-butyl-2-methyl-Δ^1-pyrrolinium perchlorate;[9] the group attached to the nitrogen atom of the pyrrolinium ring has relatively little effect on its pK_a. The pyrrolinium moiety, however, has a considerable influence on the pK_a value of the pyridinium moiety, reducing it to 1.41 in **2b** and 3.42 in **3b**.[10]

Of interest with respect to the rate of proton exchange

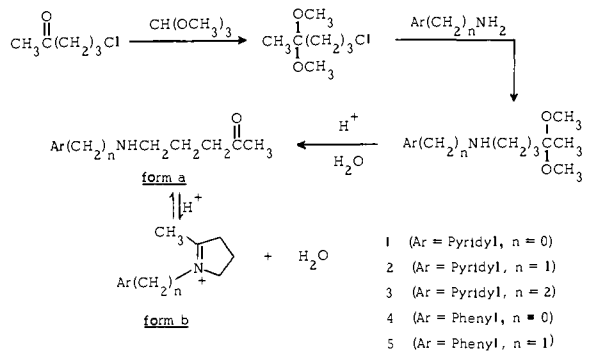
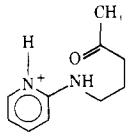
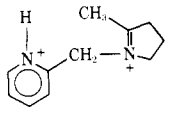
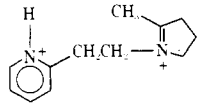
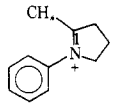
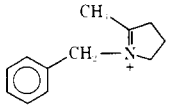


Figure 1. Synthesis of arylamino ketones.

Table I. pK_a Values of Compounds 1–5 at 26°

Compd	pK_1	pK_2
 1a	6.89 ± 0.10	
 2b	1.41 ± 0.06	11.01 ± 0.11
 3b	3.42 ± 0.05	11.87 ± 0.05
 4b	7.70 ± 0.03	
 5b	11.76 ± 0.10	

with compounds **2** and **3** are the true (microscopic) pK_a values for the pyrrolinium moiety, i.e., the value of pK_d in the equilibrium cycle shown in Figure 2. From the measured values of pK_1 and pK_2 for **2b** and **3b** ($pK_1 = pK_c$ and $pK_2 = pK_e$) and on the assumption that pK_f is ca. 6 (i.e., the value for 2-alkylpyridines[11]), values of 6.40 and 9.30 can be calculated for pK_d of **2b** and **3b**, respectively.

Rate of Proton Exchange in Compounds 1–5. By means of a method similar to that used by Hine and coworkers[12] in the study of the rate of proton exchange in isobutyraldehyde, the rate of deuterium incorporation of compounds **1–5** in D_2O–dimethyl sulfoxide-d_6 (4:1) was measured by NMR spectroscopy. Although the protons of the methyl group attached to C-2 of the pyrrolinium ring in **2b–5b** as well as the methylene protons at C-5 of the ring are activated by the adjacent iminium function, the methyl protons are found to exchange 10–100 times more rapidly than the methylene protons. The disappearance of the resonances arising from the methyl group was used as a means for assessing the rate of proton exchange, and the data in Table II for compounds **1–5** at various pH levels were obtained.

The pH of each solution was calculated from the amount of hydrogen ion or hydroxide ion that was added, the concentration of the substrate, and the pK_a of the substrate.

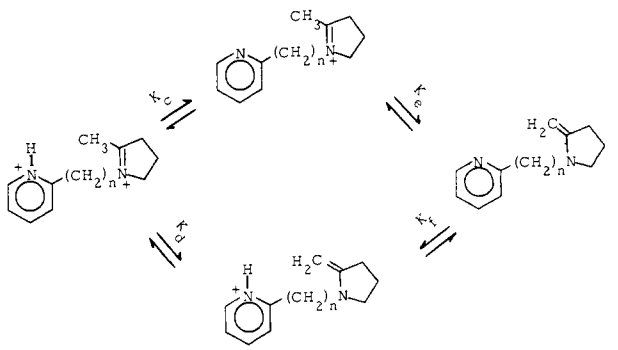


Figure 2. Acid–base equilibria of compounds **2** and **3**.

Although pK_a values in aqueous dimethyl sulfoxide are different from those in pure water, the differences are predicted to be relatively small,[13] and any corrections should be essentially the same for all of the compounds involved. Attempts to maintain a constant ionic strength in the various solutions by adding potassium chloride failed because of precipitate formation in the H_2O-DMSO solvent. Since a comparison of the water-catalyzed exchange of compound **4b** at a hydrogen ion concentration of 0.57 M and 1.4×10^{-3} M shows almost no variation in rate (although the ionic strength is considerably different in the two reaction mixtures), the inability of maintaining a constant ionic strength is thought not to cause significant errors.

Discussion

All of the kinetic data, with the exception of the reaction of **5b** in the presence of pyridine, conform to the expression

$$k[A]_t = k_A[A] + K_{AH}[AH^+] + k_{AH_2}[AH_2^{2+}] + k_{A\text{-}AH}[A][AH^+]$$

where $[A]_t$ is the total concentration of the reactant in all forms, and [A], $[AH^+]$, and $[AH_2^{2+}]$ are the concentrations of the reactant in the uncharged, monoprotonated, and diprotonated forms, respectively. By employing this expression and using the kinetic data shown in Table II, the specific rates shown in Table III are obtained. The specific rates k_A, k_{AH}, and k_{AH_2} correspond to the water-induced deprotonation of the free base species, the monoprotonated species, and the diprotonated species. The specific rate $k_{A\text{-}AH}$ corresponds to the free base-induced deprotonation of the monoprotonated species, calculated on the assumption that no other base is involved; to the extent that bases other than A do act as the proton acceptor, however, the value shown in Table III will be diminished. Hydroxide ion, for example, might act in this capacity, and attempts were made to determine the k_{OH} value for the deprotonation of compounds **4b** and **5b**. Because of the necessity of working at very low hydroxide concentrations, however, accurate assessments of this value were not possible; only for **5** was an approximate value of $9 \pm 3 \times 10^3$ M^{-1} min^{-1} obtained. Hydroxide-induced deprotonation for compound **1** was considered to contribute very little, for if it is assumed that it is comparable in rate to that of the hydroxide-induced ionization of acetone[14] (4×10^{-3} M^{-1} min^{-1}), the calculated rate at pH 7 is only 0.03% of the observed value. The mechanism pictured in Figure 3, therefore, is postulated to be the major pathway for the deprotonation of compound **1**.

Pyridine was demonstrated to be an effective catalyst, a reaction of **5b** carried out in 0.15 M pyridine solution proceeding at a considerably increased rate and providing a $k_{pyridine}$ value of 1.5 M^{-1} min^{-1}. This is approximately 10^7 times greater than the pyridine-catalyzed deprotonation of acetone[15] (8×10^{-8} M^{-1} min^{-1}) and dyhydroxyacetone[1] (10^{-7} M^{-1} min^{-1}), an enhancement factor comparable to

Table II. Rates of Proton Exchange in the Methyl Groups of Compounds 1–5

Compd	$[H^+]$	[A]	$[AH^+]$	$[AH_2^{2+}]$	k, min^{-1}
1a	0.57	Very small	0.33		Less than 10^{-7}
	1.8×10^{-7}	0.18	0.25		$3.85 \pm 0.13 \times 10^{-3}$
	1.2×10^{-7}	0.18	0.17		$3.28 \pm 0.09 \times 10^{-3}$
	1.0×10^{-7}	0.18	0.14		$3.10 \pm 0.10 \times 10^{-3}$
	5.7×10^{-8}	0.18	0.08		$2.50 \pm 0.08 \times 10^{-3}$
	3.5×10^{-7}	0.09	0.24		$2.50 \pm 0.08 \times 10^{-3}$
2b	0.58		0.015	0.185	$2.1 \pm 0.1 \times 10^{-2}$
	0.59		0.025	0.375	$2.0 \pm 0.1 \times 10^{-2}$
	8.7×10^{-2}		0.09	0.17	$1.5 \pm 0.1 \times 10^{-2}$
	1.0×10^{-2}		0.19	0.05	$0.64 \pm 0.03 \times 10^{-2}$
3b	0.34		0	0.28	$5.0 \pm 0.4 \times 10^{-4}$
	7.0×10^{-3}		0.015	0.265	$1.5 \pm 0.1 \times 10^{-3}$
	1.9×10^{-3}		0.047	0.233	$4.3 \pm 0.2 \times 10^{-3}$
	8.0×10^{-4}		0.09	0.19	$6.3 \pm 0.3 \times 10^{-3}$
	2.1×10^{-4}		0.18	0.10	$12 \pm 1 \times 10^{-3}$
4b	0.57	1×10^{-8}	0.28		$13 \pm 1 \times 10^{-4}$
	1.4×10^{-3}	4×10^{-6}	0.28		$13 \pm 1 \times 10^{-4}$
	1.0×10^{-4}	6×10^{-5}	0.28		$16 \pm 1 \times 10^{-4}$
	8.4×10^{-5}	7×10^{-5}	0.28		$17 \pm 1 \times 10^{-4}$
5b	0.33	2×10^{-12}	0.31		$8 \pm 1 \times 10^{-5}$
	1.0×10^{-7}	6×10^{-6}	0.38		$13 \pm 1 \times 10^{-4}$
	1.0×10^{-7}	3×10^{-6}	0.19		$10 \pm 1 \times 10^{-4}$
	3.3×10^{-8}	2×10^{-5}	0.31		$27 \pm 1 \times 10^{-4}$
	7.7×10^{-9}	7×10^{-5}	0.31		$85 \pm 3 \times 10^{-4}$
	3.8×10^{-7}[a]		0.34		$2.2 \pm 0.2 \times 10^{-1}$

[a] Carried out in 0.15 M pyridine solution.

Table III. Specific Rates for k_A, k_{AH}, k_{AH_2}, and k_{A-AH} for the Ionization of Compounds 1–5

Compd	k_A	k_{AH}	k_{AH_2}	k_{A-AH}
1	8.9×10^{-4}	10^{-7}		3.3×10^{-2}
2		2.3×10^{-3}	2.2×10^{-2}	
3		1.9×10^{-2}	5×10^{-4}	
4	1.6	1.3×10^{-3}		5.5
5	3.7	8×10^{-5}		120

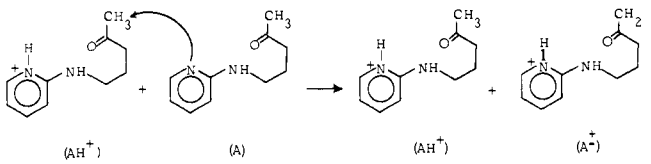


Figure 3. Postulated mechanism of α-proton abstraction in compound **1**.

those previously reported as resulting from imine formation.[15]

Of particular interest in the present investigation was the possibility of discerning intramolecular proton abstraction in the ionization process. Some evidence in support of this possibility was adduced in the following fashion. For compounds **2b, 3b,** and **5b** all of which possess the general structure

$$XCH_2N^+\!\!<$$

(where X is 2-pyridyl, 2-pyridylmethyl, and phenyl, respectively), the logs of the k_{AH} and k_{AH_2} values were plotted against the pK_a values of the corresponding $XCH_2N^+H_3$ compounds. Thus, for the k_{AH} values of **2b, 3b,** and **5b,** the pK_a values of the monoprotonated forms of 2-(aminomethyl)pyridine (8.62 at 25°), 2-(2-aminoethyl)pyridine (9.64 at 25°), and benzylamine (9.33 at 25°)[16] were used. To obtain the pK_a values of the diprotonated forms of 2-(aminomethyl)pyridine and 2-(2-aminoethyl)pyridine it was assumed that they would differ from those of the monoprotonated forms by the same increments as the di- and monoprotonated forms of ethylenediamine (3.08 pK units) and trimethylenediamine (1.74 pK units).[16] If the rates of deprotonation of **2b, 3b,** and **5b** are responsive only to the electron-withdrawing capacity of the XCH_2 moieties, all of the points should fall on a straight line. A plot of these data, shown in Figure 4, reveals, however, that only the points corresponding to the k_{AH_2} values for **2b** and **3b** and the k_{AH} value for **5b** do so, the points for k_{AH} for **2b** and **3b** both falling well above the line. On the assumption that the specific rates falling on the line represent only intermolecular proton transfer, it is postulated that those specific rates falling above the line represent a combination of intermolecular *and intramolecular* proton transfer. Although the very low basicity of the pyridine nitrogen in **2b** reduces the likelihood

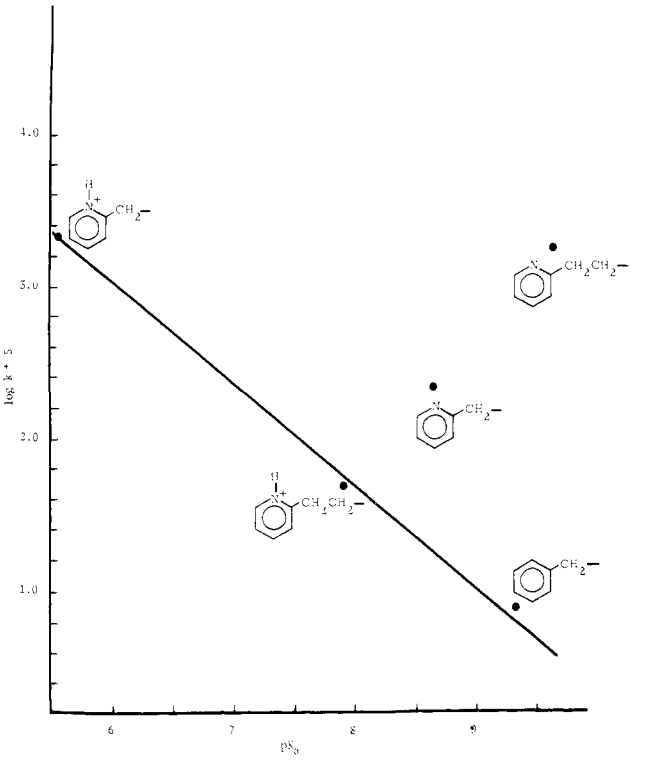


Figure 4. The rates of the water-induced deprotonation of **2b, 3b,** and **5b** plotted vs. the pK_a values of the analogous $ArCH_2NH_3^+$ ammonium ions.

of intramolecular proton transfer, it was anticipated that this phenomenon would occur in **3b** where the basicity of the pyridine is close to that of a carboxylate ion[17] and where the stereoelectronic requirements appear, on the basis of models, to be attainable.[18] The present data appear to support this expectation.

Although compound **3b** appears to derive more benefit than compound **2b** from intramolecular proton transfer (see Figure 4), the intermolecular water-induced deprotonation of the dication is considerably faster for **2b** than for **3b** (see Table II). The 43-fold difference in rate is ascribed to the proximity of the positive charge in **2b** to the site of proton abstraction, the positive charge enhancing the acidity of the methyl group via an inductive effect, a field effect, or both.

Experimental Section[21]

***N*-(2′-Pyridinium)-5-amino-2-pentanone Perchlorate (1a).** To a solution of 75.9 g (0.63 mol) of 5-chloro-2-pentanone[3] and 80.0 g (0.75 mol) of trimethyl orthoformate in 250 ml of anhydrous methanol was added one drop of 98% sulfuric acid. The mixture was refluxed for 6 hr, stirred at room temperature for 16 hr, and then worked up to give, after distillation, 93.5 g. (89%) of a colorless liquid: bp 71–75° (12 mm); ir (liquid) 1375 (CH_3), 1120, 1105, 1073, and 1005 cm^{-1} (C–O); NMR (CCl_4) δ 1.20 (s, 3, CH_3CO_2), 1.57–2.00 (m, 4, C–$CH_2CH_2CO_2$), 3.10 (s, 6, OCH_3), and 3.52 (t, 2, J = 6 Hz, C–CH_2Cl). Using a procedure patterned after one in the literature,[22] a suspension of 1.8 g (0.075 mol) of sodium hydride in 50 ml of toluene was treated with 6.0 g (0.064 mol) of 2-aminopyridine. The mixture was refluxed until hydrogen evolution ceased (ca. 3 hr), and then 10.2 g (0.61 mol) of 5-chloro-2-pentanone dimethyl ketal was added. After refluxing for 20 hr, the mixture was cooled, treated with 15 ml of water, and processed to yield a brown oil which was distilled, extracted with dilute hydrochloric acid, and distilled again to give 6.0 g (51%) of ***N*-(2′-pyridyl)-5-amino-2-pentanone dimethyl ketal** as a pale yellow oil: bp 107–108° (0.05 mm); ir 3400 (N–H), 3290 (N–H), 1605, 1560, and 1505 (pyridine), 1175, 1153, 1075, and 1050 cm^{-1} (C–O); NMR (CCl_4) δ 1.18 (s, 3, CH_3), 1.45–1.73 (m, 4, C–$CH_2CH_2CO_2$), 3.07 (s, 6, OCH_3), 3.00–3.67 (m, 2, NCH_2C), 5.35 (t, 1, J = 5 Hz, N–H), 6.26 (m, 1, C-3 H of pyridine), 6.47 (m, 1, C-5 H of pyridine), 7.27 (m, 1, C-4 H of pyridine), and 8.00 ppm (m, 1, C-5 H of pyridine).

Anal. Calcd for $C_{12}H_{10}N_2O_2$: C, 64.26; H, 8.99; N, 12.49. Found: C, 64.02; H, 8.94; N, 12.44.

A 3.5-g (0.015 mol) sample of the ketal was added to a solution of 3.5 ml of 70% perchloric acid in 10 ml of water. The solution was heated to 60° and allowed to cool to room temperature over a period of 5 hr and then maintained at 5° for 14 hr. Filtration yielded 3.4 g (81%) of **1a** perchlorate which was recrystallized two times from 20% aqueous ethanol to give 2.1 g (50%) of a colorless solid: mp 114–115.5°; ir (Nujol) 3315 (N–H), 3210 (N–H), 2020 (ClO_4^-), 1695 (C=O), 1650 and 1615 (pyridinium), and 1150–1050 cm^{-1} (ClO_4^-); NMR (DMSO-d_6) δ 1.75–2.20 (m, 2, $CH_2CH_2CH_2$), 2.20 (m, 2, CH_3), 2.72 (t, 2, J = 7 Hz, $CH_2C{=}O$), 3.22–3.65 (m, 2, NCH_2), 6.83–7.33 (m, 2, C-3 and C-5 H of pyridine), and 7.88–8.22 ppm (m, 2, C-4 and C-6 H of pyridine).

Anal. Calcd for $C_{10}H_{15}ClN_2O_5$: C, 43.09; H, 5.39; N, 10.05. Found: C, 43.11; H, 5.40; N, 10.22.

1-(2′-Pyridiniummethyl)-2-methyl-Δ^1-pyrrolinium Diperchlorate (2b). 5-Chloro-2-pentanone ethylene ketal was prepared from 5-chloro-2-pentanone and ethylene glycol and obtained as a colorless oil after distillation through a 9 in. Vigreux column: bp 84–86.5°; ir (liquid) 1375 (CH_3), 1125, 1103, 1065, and 1052 cm^{-1} (C–O); NMR (CCl_4) δ 1.23 (s, 3, CH_3CO_2), 1.60–2.10 (m, 4, C–$CH_2CH_2CO_2$), 3.52 (m, 2, J = 6.5 Hz, C–CH_2Cl), 3.85 ppm (s, 4, OCH_2CH_2O). A 5.5-g (0.033 mol) sample of the ketal was treated with 10 g (0.09 mol) of 2-aminomethylpyridine, and the mixture was heated for 45 min at 100° in an atmosphere of nitrogen. The product was isolated as described above to give, after distillation, 5.7 g (73%) of *N*-(2′-pyridylmethyl)-5-amino-2-pentanone ethylene ketal as a colorless liquid: bp 113–115° (0.06 mm); ir (liquid) 3320 (N–H), 1590, 1565, and 1465 (pyridine), 1250, 1220, 1147, and 1122 cm^{-1} (C–O); NMR (CCl_4) δ 1.22 (s, 3, CH_3), 1.42–1.75 (m, 5, C–$CH_2CH_2CO_2$), 2.58 (t, 2, J = 6 Hz, NCH_2), 3.77 (s, 2, $PyCH_2N$), 3.80 (s, 4, OCH_2CH_2O), 6.91–7.70 ppm (m, 3, C-3, C-4, and C-5 H of pyridine).

Anal. Calcd for $C_{13}H_{20}N_2O_2$: C, 66.07; H, 8.53; N, 11.85. Found: C, 65.70; H, 8.25; N, 11.59.

A 2.5-g (0.01 mol) sample of this material was added to a solution of 3.0 ml (0.02 mol) of 70% perchloric acid in 5 ml of water, and the product, isolated as described above, was recrystallized three times from 95% ethanol to give 1.9 g. (51%) of the diperchlorate of **2b** as colorless crystals: mp 208–210°; ir (Nujol) 2025 (ClO_4^-), 1665 ($C{=}N^+R_2$), 1635 (pyridinium), and 1010–1250 (ClO_4^-); NMR (DMSO-d_6) δ 1.83–2.60 (m, 2, C-4 H of pyrrolinium), 2.63 (s, 3, CH_3), 3.38 (t, 2, J = 7 Hz, C-3 H of pyrrolinium), 4.18 (t, 2, J = 7 Hz, C-5 H of pyrrolinium), 6.27 (s, 2, $PyCH_2N$), 7.83–8.17 (m, 2, C-3 and C-5 H of pyridine), 8.22–8.53 (m, 1, C-4 H of pyridine).

Anal. Calcd for $C_{11}H_{16}Cl_2N_2O_8$: C, 35.20; H, 4.27; N, 7.47. Found: C, 35.08; H, 4.23; N, 7.75.

1-[2′-(2″-Pyridiniumethyl)]-2-methyl-Δ^1-pyrrolinium Diperchlorate (3b). A 36.0-g (0.3 mol) sample of 2-(2′-aminoethyl)pyridine was treated with 17.0 g (0.1 mol) of 5-chloro-2-pentanone dimethyl ketal, and the reaction was carried out as described above to yield, after distillation, 11.5 g (42%) of ***N*-[2′-(2″-pyridylethyl)]-5-amino-2-pentanone dimethyl ketal** as a pale yellow liquid: bp 118–119° (0.05 mm); ir (liquid) 3300 (N–H), and 1580 and 1555 cm^{-1} (pyridine); NMR (CCl_4) δ 1.17 (s, 3, CH_3), 1.25 (s, 1, N–H), 1.33–1.65 (m, 4, $NCH_2CH_2CH_2CH_2$), 2.58 (t, 2, J = 6 Hz, NCH_2CH_2), 2.92 (t, 4, J = 0.5 Hz, $PyCH_2CH_2N$), 3.08 (s, 6, OCH_3), 6.90–7.20 (m, 2, C-3 and C-5 H of pyridine), 7.37–7.70 (m, 1, C-4 H of pyridine), and 8.40–8.57 ppm (m, 1, C-6 H of pyridine).

Anal. Calcd for $C_{14}H_{24}N_2O$: C, 66.63; H, 9.59; N, 11.10. Found: C, 65.67; H, 9.28; N, 11.10.

A 5.0-g (0.02 mol) sample of this material was treated with 10.0 g (0.07 mol) of 70% perchloric acid, as described above, to yield 2.0 g (26%) of the diperchlorate of **3b**, after four recrystallizations from 85–90% ethanol, as a colorless solid: mp 189.5–190.5°; ir (Nujol) 2050 (ClO_4^-), 1670 ($C{=}N^+R_2$), 1640, 1620, and 1545 (pyridinium), and 980–1200 cm^{-1} (ClO_4^-); NMR (DMSO-d_6) δ 1.97–2.42 (m, 2, C-4 H of pyrrolinium), 2.45 (t, 3, J = 1.5 Hz, CH_3), 3.00–3.72 (m, 4, $PyCH_2$), 4.00–4.52 (broad, m, 4 $PyCCH_2N$), 7.83–8.27 (m, 2, C-3 and C-5 H of pyridinium), 8.43–9.00 (m, 2, C-4 and C-6 H of pyridinium), and 12.67–13.00 (broad, 1, NH).

Anal. Calcd for $C_{12}H_{18}Cl_2N_2O_8$: C, 37.02; H, 4.86; N, 7.19. Found: C, 37.04; H, 4.59; N, 7.21.

1-Phenyl-2-methyl-Δ^1-pyrrolinium Perchlorate (4b). From aniline and 5-chloro-2-pentanone dimethyl ketal, following the procedure described above, ***N*-phenyl-5-amino-2-pentanone dimethyl ketal** was obtained in 80% yield as a colorless oil: bp 105–108° (0.03 mm); ir (liquid) 3400 (N–H), 1600, 1500, and 695 cm^{-1} (Ar); NMR (CCl_4) δ 1.13 (s, 3, CH_3), 1.42–1.92 (m, 4, $CH_2CH_2CH_2CO_2$), 2.75–3.17 (m, 2, NCH_2), 3.03 (s, 6, OCH_3), 3.47 (s, 1, N–H), 6.52 (m, 3, C-2, C-4, and C-6 H of phenyl), and 7.07 ppm (m, 2, C-3 and C-5 H of phenyl).

Anal. Calcd for $C_{13}H_{21}NO_2$: C, 69.92; H, 9.48; N, 6.27. Found: C, 70.41; H, 9.45; N, 6.28.

A 3.65-g (0.016 mol) sample of this material was treated with 3 ml of 70% perchloric acid and 7 ml of water, and 1.20 g (27%) of the perchlorate of **4b** was obtained, after two recrystallizations from acetone–ether at −20°, as a colorless solid: mp 106–107°; ir (Nujol) 2030 (ClO_4^-), 1665 ($C{=}N^+R_2$), 1150–1100 (ClO_4^-), and 695 cm^{-1} (Ar); NMR (DMSO-d_6) δ 2.33 (s, 3, CH_3), 2.17–2.67 (m, 2, C-4 H of pyrrolinium), 3.48 (t, 2, J = 8 Hz, C-3 H of pyrrolinium), 4.53 (t, 2, J = 7 Hz, C-5 H of pyrrolinium), and 7.64 (s, 5, Ar–H).

Anal. Calcd for $C_{11}H_{14}ClNO_4$: C, 50.87; H, 5.40; N, 5.40. Found: C, 51.20; H, 5.30; N, 5.37.

1-Benzyl-2-methyl-Δ^1-pyrrolinium Perchlorate (5b). From benzylamine and 5-chloro-2-pentanone dimethyl ketal, following the procedure described above, ***N*-benzyl-5-amino-2-pentanone dimethyl ketal** was obtained in 58% yield as a colorless liquid: bp 97–100° (0.08 mm); ir (liquid) 3400 (N–H), 1610, 1500, and 690 cm^{-1} (Ar); NMR (CCl_4) δ 1.03 (s, 1, N–H), 1.17 (s, 3, CH_3), 1.33–1.75 (m, 4, $O_2CCH_2CH_2C$), 2.53 (t, 2, J = 5 Hz, NCH_2), 3.05 (s, 6, OCH_3), 3.68 (s, 2, $ArCH_2N$), and 7.60 ppm (s, 5, Ar–H).

Table IV. Optical Density Values

20% $HClO_4$ ($-H_0$ = 1.01)[23a]	pH 10	pH 1.98[a]	pH 1.48	pK_a
1.458	0.730	0.881		1.40
1.478	0.740	0.890		1.38
1.472	0.738	0.874		1.36
1.116	0.553		0.823	1.44
1.124	0.559		0.827	1.43
1.120	0.558		0.826	1.44
			Average	1.41 ± 0.06

[a] Determined spectroscopically with 4-nitroaniline (pK_a = 0.99[24b]).

Anal. Calcd for $C_{14}H_{23}NO_2$: C, 70.85; H, 9.77; N, 5.90. Found: C, 70.99; H, 9.66; N, 6.68.

A 3.8-g (0.016 mol) sample of this material was treated with 3 ml of 70% perchloric acid in 7 ml of water, and 1.25 g (30%) of the perchlorate of **5b** was obtained, after two recrystallizations from acetone–ether at −20°, as a colorless solid: mp 54–55°; ir (Nujol) 2020 (ClO_4^-), 1665 ($C{=}N^+R_2$), 1500 (Ar), 1020–1175 (ClO_4^-), and 700 cm^{-1} (Ar); NMR (acetone-d_6) δ 2.00–2.50 (m, 2, C-4 H of pyrrolinium), 2.70 (s, 3, CH_3), 3.43 (t, 2, J = 7 Hz, C-3 H of pyrrolinium), 4.08 (t, 2, J = 8 Hz, C-5 H of pyrrolinium), 5.13 (s, 2, $ArCH_2N$), and 7.48 ppm (s, 5, Ar–H).

Anal. Calcd for $C_{12}H_{16}ClNO_4$: C, 52.74; H, 5.86; N, 5.12. Found: C, 52.55; H, 5.78; N, 5.07.

N-Isopropylidenepyrrolidinium perchlorate was prepared by the literature procedure[3] and obtained as a colorless solid: mp 229–231° (lit.[3] 232–233°); ir (Nujol) 2010 (ClO_4^-), 1680 ($C{=}N^+R_2$), and 1000–1200 cm^{-1} (ClO_4^-); NMR (DMSO-d_6) δ 1.83–2.33 (m, 4, $CH_2CH_2CH_2CH_2$), 2.43 (q, 6, J = 2 Hz, $(CH_3)_2C$), 3.67–4.17 ppm (broad, m, CH_2NCH_2).

1,2-Dimethyl-Δ^1-pyrrolinium perchlorate was prepared by the literature procedure[4] and obtained as a colorless solid: mp 239–241° (lit.[4] 239–240.5°); ir (Nujol) 1700 ($C{=}N^+R_2$) (lit.[4] 1701 cm^{-1}) and 1000–1200 cm^{-1} (ClO_4^-); NMR (DMSO-d_6) δ 1.80–2.50 (m, 2, $CH_2CH_2CH_2$), 2.37 (s, 3, $N{=}CCH_3$), 2.95–3.50 (m, 2, $N{=}CCH_2$), 3.40 (s, 3, NCH_3), and 3.82–4.33 ppm (t, 2, J = 7.5 Hz, NCH_2).

pK_a Determinations. Employing methods described in the literature, the pK_a values were determined by a spectrophotometric method[23a] and/or a titrimetric method.[23b] With the spectrophotometric method the extinction coefficients for the protonated form were measured at a pH at least two pK units below the pK_a of the compound, and those for the unprotonated form were measured at a pH at least two pK units above the pK_a of the compound. A typical example is provided by the data in Table IV for compound **2b**.

For the potentiometric titrations the following procedure was used. A known amount (calculated to bring the final concentration to 2.5 − 5.0 × 10^{-3} M) of the compound to be measured was weighed into a 10-ml volumetric flask. To this was added 8 ml of carbon dioxide-free water and 10–50 μl of a 1.00 N sodium hydroxide solution, and the volume was brought to 10 ml. From the measured pH of the solution the pK_a was calculated from the expression pK_a = pH + log [HA]/[A^-] where [HA] = $[HA]_{initial} - [OH^-]_{added}$ and [A^-] = $[OH^-]_{added}$.

Deuterium Exchange Experiments. The rate of exchange of hydrogen for deuterium in the methyl group of compounds **1–5** was measured by NMR spectrometry, the position of the methyl resonances for these compounds being δ 2.20 for **1**, δ 2.63 for **2**, δ 2.45 for **3**, δ 2.33 for 4, and δ 2.70 for **5**.

Method for Fast Reactions. To an accurately weighed amount of compound in a medium thickness wall NMR tube was added 50 μl of dimethyl sulfoxide-d_6. These materials were forced to the bottom of the tube, and 200 μl of the appropriate acidic or basic D_2O solution was then added in such a fashion that it remained near the top of the NMR tube, separated from the dimethyl sulfoxide solution at the bottom. The tube was placed in the probe and allowed to stand for 20 min to attain the temperature of the probe (41°). It was then removed, the upper and lower solutions were quickly mixed, and it was put back in the probe. Measurements of the area of the methyl resonance at 2–10 min intervals were made until 90% or more of the methyl protons had been exchanged. The resonance from the aromatic protons was used as an internal standard in the integration of the area of the methyl resonance. The tube was then removed from the probe and kept at 40–50° for 24 hr to obtain an infinity reading.

Table V. Data for Determination of Exchange Rates

Time, min	Area CH_3[a]	Area − area$_\infty$	log (area − area$_\infty$)	Area Ar–H
0	65.5	31.5	1.50	29
2	63.5	29.5	1.47	27
4	62.5	28.5	1.45	26
6	59	25	1.40	27
8	56.5	22.5	1.35	26
10	55	21	1.32	27
15	49	15	1.18	25
20	46	12	1.08	26
30	40.5	6.5	0.81	26
40	37	3	0.48	26
600	34	0		26

[a] The integration in this instance includes a portion of a CH_2 resonance, this accounting for the rather large infinity value.

Method for Slow Reactions. To an accurately weighed amount of compound contained in the NMR tube was added 50 μl of dimethyl sulfoxide-d_6 followed by 200 μl of the appropriate acidic or basic D_2O solution. The solution was allowed to attain the temperature of the probe (41°), and the measurements then made in the manner described above at 15–40 min intervals.

Method for Very Slow Reactions. For very slow reactions the NMR tube was placed in a constant bath held at 41° and removed at 12–24 hr intervals for NMR determination.

Determination of Rate Constants for Exchange. The first-order rate constants were determined using a linear least-squares program[25] on a Hewlett-Packard 9100A calculator. A typical example is provided by the data (Table V) for the exchange reaction of compound **2b**. The least-squares treatment of these data gives k = 2.18 ± 0.08 × 10^{-2} min^{-1}.

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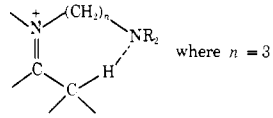

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Photoelectron Spectroscopy of Carbonyls. Urea, Oxamide, Oxalic Acid, and Oxamic Acid[1]

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Abstract: Photoelectron spectra are reported for urea, oxamide, oxalic acid, and oxamic acid. These spectra are interpreted in terms of a composite molecule model in which formaldehyde and formamide PES spectra play key roles. The correlative interpretation of the PES spectra of the larger molecules devolves on the manner of evolution of MO sets: n and π for H_2CO; n, π, and π_O for $HCONH_2$ and HCOOH; n, π, $\pi_\oplus$, and $\pi_\ominus$ for H_2NCONH_2; and n_+, n_-, $\pi_\oplus$, $\pi_\ominus$, π_+, and π_- for the three dicarbonyls. CNDO/s calculations are of considerable help in developing the composite molecule model and provide a remarkably good representation of experiment.

α-Dicarbonyl systems are of common occurrence[3] and they possess chemotherapeutic advantage[4] in cancer. Despite considerable work on the electronic structure of α-dicarbonyls,[5] no resolution of a number of important questions has been achieved. These questions relate to: (i) circular dichroism and chirality;[6] (ii) the nature of their low-energy electronically excited states;[7] (iii) their unique emission properties;[8] and (iv) their orbital energy level structure.[9] Photoelectron spectroscopy (PES) can provide some information on question iv and may be of indirect help in resolving questions i–iii.

The intent of this work is the analysis of the photoelectron spectra of oxamide and oxamic acid. The PES of the monocarbonyl analogs, formic acid and formamide, are available[10] but no data exist for their α-dicarbonyl counterparts. Additionally, in the correlative efforts which we undertook in order to relate the one-electron levels of these molecules, it seemed that urea occupied an important slot in the hierarchy $HCONH_2 \rightarrow H_2NCONH_2 \rightarrow H_2NCOCONH_2$. Hence, this work is also concerned with the PES of urea and its interpretation.

The discussion of oxalic acid given here consists of the presentation of an energy level diagram deduced from more detailed studies.[11] A general discussion ot PES data and assignments for monocarbonyls and α-dicarbonyls is available[12] and should be consulted for nomenclature. A summary of ionization data for monocarbonyls, α-dicarbonyls, and tricarbonyls is also available.[13]

Experimental and Computational

PES spectra were recorded on a Perkin-Elmer Model PS-18 photoelectron spectrometer with a 10-cm radius cylindrical electrostatic field deflection analyzer. A Bendix "Channeltron" Electronic Multiplier (Model CEM-4028) was used as a detector. The ionization energy was provided by the 584 Å (21.22 eV) HeI resonance line. Solid samples were sublimed in a heated probe, the temperature of which was adjusted for maximum count rate. The range of temperatures used for solid samples was 72 to 119°. Spectra were calibrated with regard to both energy and resolution using the $^2P_{1/2}$ and $^2P_{3/2}$ lines of xenon; the resolution was in the range 20–25 meV.

Oxamide (MCB), oxamic acid (MCB), and oxalic acid (Baker) were purified by recrystallization from water. Urea (Baker Reagent Grade) was used without further purification.

Semiempirical CNDO/s calculations were carried out for formaldehyde, formamide, urea, oxamide, oxalic acid, and oxamic acid in geometries appropriate to their ground states.[14] The MO notation used has been discussed previously[12] and is quite straightforward. The MO's of a monocarbonyl such as $HCONH_2$ are labeled n, π, and π_O. They have the following significance: n is a nonbonding σ MO with dominant amplitude on the carbonyl oxygen; π is the π MO of the carbonyl group in H_2CO, appropriately delocalized to embrace the nitrogen center in formamide; and π_O is a π MO with large amplitude on the amine group. In the case of formic acid, the n and π notations retain the same meaning as in formamide but π_O now refers to a π MO with large amplitude on the hydroxyl group. In a symmetric dicarbonyl such as oxamide, the MO notation is expanded, in a quite obvious way, to n_+, n_-, π_+, π_-, $\pi_\oplus$, and $\pi_\ominus$, where the extra +/− subscripts denote bonding/antibonding combinations of the constituent formamide MO's. This latter notation is inexact in the case of unsymmetrical dicarbonyls such as oxamic acid but, for want of a better notation, is used here. In the case of urea which may be supposed to consist of two amide groups, the single carbonyl entity doing double duty, the appropriate notation becomes n, π, $\pi_\oplus$, and $\pi_\ominus$ and should cause no confusion.

All PES spectra are supposed to consist of simple one-electron ionization events and are so interpreted. In the case of oxamide,