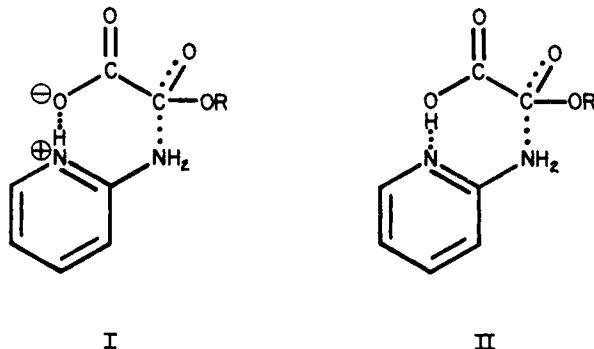


The exceptional reactivity of 2-aminopyridinium ion in its reaction with *o*-nitrophenyl oxalate ion, as indicated by the kinetic comparisons above, is attributed to the electrostatic stabilization of the quasi cyclic transition state as shown in I. The



similarity of the rate constants for the 2- and 4-aminopyridinium ions indicates that the stabilization of the transition state by long-range coulombic interactions has a relatively low sensitivity to variations in the steric relationships. It is, therefore, possible that a transition state similar to I can be drawn for the 4-aminopyridinium ion.

The kinetic expression for the rate of the reaction involving the anionic form of the ester and the cationic form of 2-aminopyridine (or 4-aminopyridine) is

$$\text{rate} = k_{\text{BH}^+} (\text{ester}^-)(\text{BH}^+)$$

This rate expression is equivalent to

$$\text{rate} = k' (\text{ester})/(\text{B})$$

where

$$k' = k_{\text{BH}^+} (K_{\text{ester}})/(K_{\text{BH}^+})$$

Using this relationship for the 2-aminopyridine case, k' is calculated to have a value of 1×10^4 l./mole sec. This large rate constant again can be explained by an interaction between the carboxyl group and the amine nitrogen in the transition state as shown in II.

The conclusion that there is an electrostatic interaction in the reaction of the aminopyridinium ions and *o*-nitrophenyl oxalate ion is confirmed by rate measurements with *o*-nitrophenyl acetate shown in Table II. The second-order rate constants for the reactions of pyridine with *o*-nitrophenyl acetate and with *o*-nitrophenyl hydrogen oxalate differ by a factor of about eight. However, no reaction whatsoever was observed between 2-aminopyridine and *o*-nitrophenyl acetate at pH 3.1 whereas an appreciable reaction was observed with 2-aminopyridine and *o*-nitrophenyl hydrogen oxalate under the same conditions. The lack of reaction between *o*-nitrophenyl acetate and 2-aminopyridine can be explained most easily in terms of the lack of the possible interactions described by I or II. The stabilization of the transition state in these systems may approximate the electrostatic interaction that occurs in enzymatic hydrolyses involving acetylcholinesterase.³⁰

Acknowledgment.—The comments of Professors T. C. Bruice, H. Morawetz and F. H. Westheimer on this manuscript are gratefully acknowledged.

(30) I. B. Wilson in "The Mechanism of Enzyme Action," W. D. McElroy and B. Glass, eds., Johns Hopkins Press, Baltimore, Md., 1954, p. 642; D. R. Davies and A. L. Green, *Adv. Enzymology*, **20**, 283 (1958).

CHICAGO 16, ILL.

[CONTRIBUTION OF THE DEPARTMENT OF CHEMISTRY OF CLARK UNIVERSITY]

Pyridoxine and Pyridoxal Analogs. II.^{1,2} Infrared Spectra and Hydrogen Bonding

BY DIETRICH HEINERT AND ARTHUR E. MARTELL

RECEIVED OCTOBER 17, 1958

Infrared spectra of pyridinecarboxaldehydes, *o*-methoxy- and *o*-hydroxypyridinecarboxaldehydes and of the corresponding substituted benzaldehydes are reported for the solid and liquid states and for dilute carbon tetrachloride solutions. Evidence is given that intramolecular hydrogen bonding exists in 3-hydroxy-4-pyridinecarboxaldehyde and 3-hydroxy-2-pyridinecarboxaldehyde in the liquid state and in solution, and the strength of chelation is correlated to the bond order in pyridine. Intermolecular hydrogen bonding is shown to occur in the crystalline 3-hydroxypyridinecarboxaldehydes, 3-pyridol and pyridoxal and a proposal for the structure of these substances is made accordingly. Improved methods are described for the synthesis and the purification of hydroxy- and methoxypyridinecarboxaldehydes.

This paper describes an extension of the work previously reported³ on the synthesis and study of analogs of pyridoxine and pyridoxal. Specifically, the new compounds under investigation as analogs of pyridoxal (I) are 3-hydroxy-4-pyridinecarboxaldehyde (II), 3-hydroxy-2-pyridinecarboxaldehyde (IV), 3-methoxy-4-pyridinecarboxaldehyde (III) and 3-methoxy-2-pyridinecarboxaldehyde (V). By the measurement of infrared spectra of dilute solutions as well as of the solid and liquid states,

it was hoped to obtain information on bond type in these compounds. A knowledge of the character of the carbonyl groups and of hydrogen bonds in these substances was considered desirable as a basis for a subsequent study of their interactions with metal ions and of the catalytic properties of the metal chelates formed.

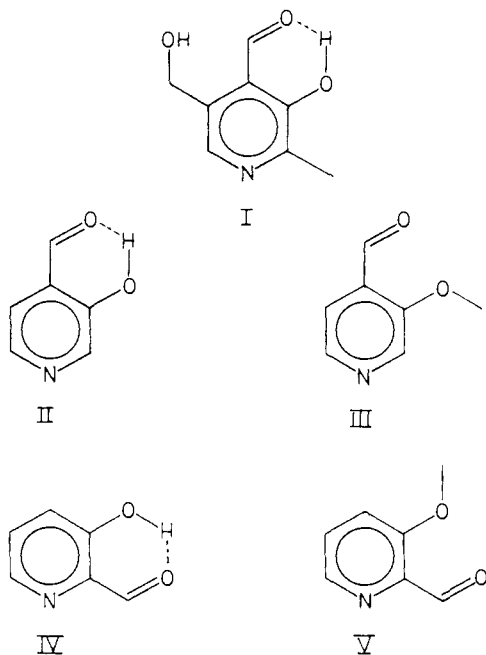
Experimental Part

Infrared Spectra.—The spectra were recorded in the region 4000–650 cm^{-1} with a Perkin-Elmer model 21 double beam spectrometer with sodium chloride optics. The liquid compounds and the methoxypyridinecarboxaldehydes were distilled *in vacuo* immediately before preparation of the solutions. The hydroxypyridinecarboxaldehydes and 2,6-pyridinecarboxaldehyde were purified by fractional sublimation. Solutions in Eastman spectro grade carbon tetra-

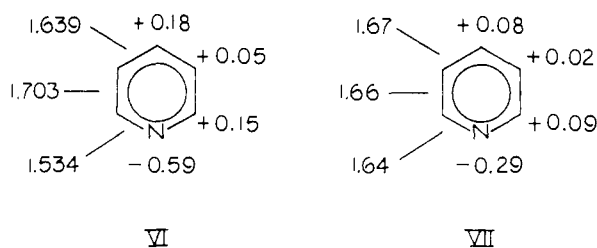
(1) This work was supported by a research grant, A-1307, from the National Institute of Arthritis and Metabolic Diseases, Public Health Service.

(2) Presented at the 134th Meeting of the American Chemical Society in Chicago, Ill., September, 1958.

(3) D. Heinert and A. E. Martell, *Tetrahedron*, **3**, 49 (1958).



chloride having 0.2, 0.1, 0.05 and 0.01 *M* concentrations were measured in sodium chloride cells of 0.1- and 1-mm. thickness under solvent compensation. Spectra of the crystalline compounds were obtained by means of the potassium bromide pellet technique.



Calibration in the 1700-1500 cm^{-1} region was performed with water vapor and methane gas. The probable error of the data was found to be $\pm 5 \text{ cm}^{-1}$ at 3000 cm^{-1} and $\pm 1 \text{ cm}^{-1}$ at 1700 cm^{-1} .

Oxidation of Substituted Pyridinemethanols to Pyridinealdehydes.—To a solution of the hydroxy- or methoxypyridinemethanol (0.01 mole) in water (150 ml.) heated with stirring to reflux temperature (60°) together with chloroform (200 ml.), manganese dioxide (0.03 mole, prepared by heating manganese carbonate for 12 hr. at 300°) was added. Sulfuric acid (0.005 mole for hydrochlorides, 0.01 mole for base) in water (50 ml.) was dropped into the reaction mixture over a 30-minute period. After 10 min. of additional refluxing the solution was slightly cooled, the layers were separated, and the aqueous layer was extracted with chloroform (three 35-ml. portions). The combined chloroform solution was dried for 6 hours over Na_2SO_4 and was cautiously evaporated at $30-40^\circ$ with a rotating film evaporator. After the product was freed completely from chloroform, III and IV remained as oils, which usually soon crystallized in an ice-bath, while II was obtained as a yellow solid. The hydroxyaldehydes then were purified by sublimation and were resublimed after the first small fraction was discarded. Compound IV was sublimed at $80-100^\circ$ under normal pressure, while II was sublimed at 20 mm. or at normal pressure and at 120° bath temperature. The methoxyaldehydes were purified by fractional distillation (III, b.p. ca. 89° (1 mm.); V, b.p. $106-108^\circ$ (3 mm.)) with an air condenser. The pure product crystallized immediately in the condenser in the form of long colorless needles. Yields and properties⁴ found are summarized in Table I.

(4) The melting points of compounds II and IV differ slightly from those reported in Part I (II, $126-128^\circ$; IV, $78-79^\circ$) because of the greater purity of the aldehydes now obtained by fractional sub-

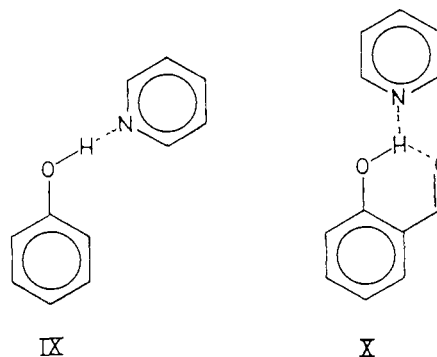
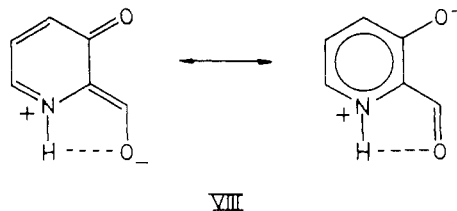
TABLE I

Compound	Yield, %	M.p., $^\circ\text{C}$.		Analyses, %		
II	50	133-134	Calcd.	C, 58.5	H, 4.1	N, 11.4
			Found	C, 58.4	H, 4.4	N, 11.1
III	64	36-37	Calcd.	C, 61.3	H, 5.2	N, 10.2
			Found	C, 61.3	H, 5.3	N, 10.2
IV	66	79-80	Calcd.	C, 58.5	H, 4.1	N, 11.4
			Found	C, 58.2	H, 4.1	N, 11.4

Compound V was obtained by the Grignard method described previously.³

Results and Discussion

Synthesis.—Since the yields of pyridinealdehydes obtained previously³ by manganese dioxide oxidation of the corresponding pyridinemethanols were low (generally about 40%), a series of oxidation experiments was conducted in order to determine the optimal reaction conditions. The intense band of the oxidation product, 3-hydroxy-2-pyridinecarboxaldehyde in the visible region at $374 \text{ m}\mu$, gave a satisfactory measure of the yield of aldehyde. In aqueous solution at room temperature the yield amounted to 36% after 6 hr. An increase of the reaction time to 17 hr. or an increase of the reaction temperature to 50 or 70° failed to increase the yield above 40%. Spectral shifts and previous observations by Barakat, *et al.*,⁵ indicated that the main reason for the low



yields of pyridinecarboxaldehydes was probably further oxidation to pyridinecarboxylic acids. Accordingly, the best yields (over 70%) were obtained by continuous extraction of the stirred suspension of MnO_2 in the aqueous pyridinemethanol solution (at 60°) with hot chloroform, while dilute sulfuric acid was added dropwise.

Spectra of Pyridinecarboxaldehydes, 2,6-Pyridinedicarboxaldehyde and the *o*-Methoxypyridine- limitation. When merely recrystallized from cyclohexane, II and IV gradually darken on exposure to air at room temperature, whereas the resublimed hydroxyaldehydes are perfectly stable in the dark over a long period of time and gave better analyses.

(5) M. Z. Barakat, M. F. Abdel-Wahab, and M. M. El-Saif, *J. Chem. Soc.*, 4685 (1956).

carboxaldehydes. 4000–2000 cm^{-1} Region in CCl_4 Solution.—In all of the aldehydes investigated the most characteristic absorption appears between 2870–2820 cm^{-1} in the form of a sharp band of high intensity. Since the aromatic C–H stretching frequencies of pyridine and benzene derivatives cause absorption only above 3000 cm^{-1} , this absorption band is assigned to the C–H frequency of the aldehyde group. In agreement with previous observations,⁶ it was found that the main band is always accompanied by a second band of considerably less intensity between 2765–2700 cm^{-1} . However, the assignment of two bands to the aldehyde hydrogen stretching cannot be justified on theoretical grounds. Of all the measured compounds, 2,6-pyridinedicarboxaldehyde showed the highest extinction, the band appearing at 2830 cm^{-1} as in 2-pyridinecarboxaldehyde. Except for a weak shoulder at 2770 cm^{-1} , no splitting could be observed in this case. The second aldehyde C–H band, however, seemed to be split into two components which appeared at 2705 and at 2675 cm^{-1} , as would be expected for the symmetric and asymmetric vibrations of the two formyl C–H groups (Fig. 1).

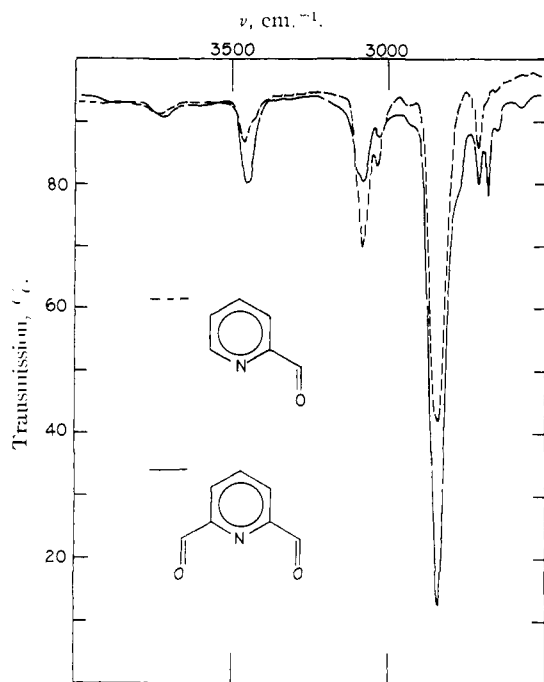


Fig. 1.—Infrared spectra of 2-pyridinecarboxaldehyde and 2,6-pyridinedicarboxaldehyde in 0.10 M CCl_4 solution; light path = 1 mm.

In the case of 3-methoxy-4-pyridinecarboxaldehyde (III) and 3-methoxy-2-pyridinecarboxaldehyde (V), the symmetric stretching vibration of the methyl group which was reported⁷ to occur near 2872 cm^{-1} would coincide partially with the C–H aldehyde vibration. Therefore, it is understandable that in the methoxyaldehydes, as well as in methoxybenzaldehyde, no separate band was found.

(6) A. Pozefsky and N. D. Coggeshall, *Anal. Chem.*, **23**, 1611 (1951).
 (7) J. J. Fox and A. E. Martin, *Proc. Roy. Soc. (London)*, **A176**, 208, 234 (1940).

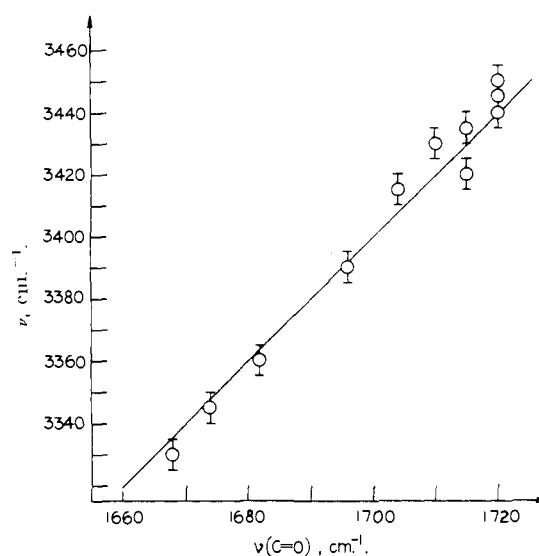


Fig. 2.—Variation of frequency of absorption band near 3400 cm^{-1} with the fundamental carbonyl stretching frequencies of various pyridinealdehydes and other aromatic aldehydes; — represents the theoretical value of the first overtone of the C=O band.

The asymmetric C–H stretching vibration of the methyl group (reported⁷ at 2962 cm^{-1}) however, was found as a clearly-defined doublet at 2980–2960 and at 2960–2940 cm^{-1} (Figs. 3 and 4),

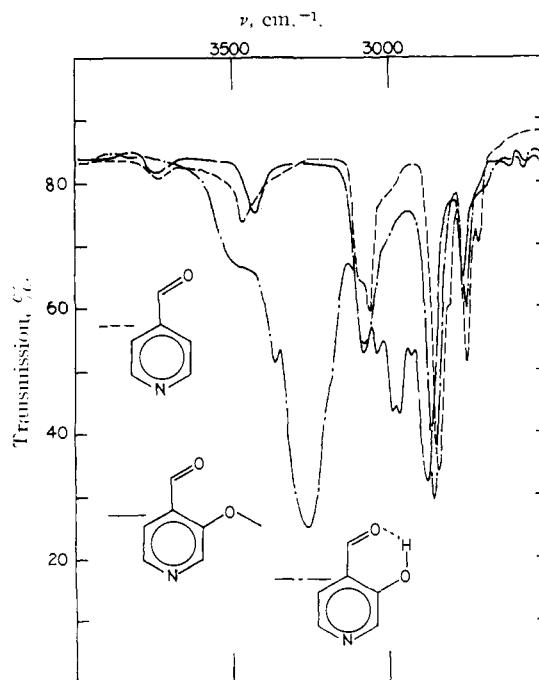


Fig. 3.—Infrared spectra of 4-pyridinecarboxaldehyde, 3-methoxy-4-pyridinecarboxaldehyde and 3-hydroxy-4-pyridinecarboxaldehyde in 0.10 M CCl_4 solution; light path = 1 mm.

between the aromatic C–H and the aldehyde C–H absorptions. Two bands of nearly constant frequency, which were observed in all of the compounds at 3095–3060 and at 3055–3010 cm^{-1} , are assigned to the aromatic C–H stretching vibrations.

^a A, 2-pyridinecarboxaldehyde; B, 3-pyridinecarboxaldehyde; C, 4-pyridinecarboxaldehyde; D, 2,6-pyridinedicarboxaldehyde; E, benzaldehyde; F, 3-methoxy-4-pyridinecarboxaldehyde; G, 3-methoxy-2-pyridinecarboxaldehyde; H, *o*-methoxybenzaldehyde; I, 3-methoxypyridine; K, 3-hydroxy-4-pyridinecarboxaldehyde; L, 3-hydroxy-2-pyridinecarboxaldehyde; M, salicylaldehyde; N, 3-hydroxypyridine; O, pyridine; P, benzene. ^b Average for substituted benzenes. ^c Bands 1-12 in carbon tetrachloride solution. ^d Bands 13-19 in liquid or crystalline state.

nitrogen produces two effects: 1, the inductive effect makes all the remaining carbon atoms somewhat more positive than those in benzene, but influences most strongly those adjacent to the N-atom; and 2, the resonance contribution of ionic forms accounts for a further decrease in π -charge equally at the α - and γ -carbon atoms, and an increase of π -charge at the ring nitrogen. In total therefore, the least π -charge would be expected at the α -positions, followed by the γ - and the β -positions.

Examination of the carbonyl stretching frequencies of the pyridinecarboxaldehydes revealed that 4-pyridinecarboxaldehyde and 2-pyridinecarboxaldehyde have identical frequencies (1720 cm^{-1}) and 3-pyridinecarboxaldehyde (1715 cm^{-1}) is closer to benzaldehyde (1710 cm^{-1}). This indicates that the π -charge at the β -position in pyridine is indeed smaller than in benzene, and also that it is still smaller but very similar in magnitude in the α - and γ -positions.

If two Kekulé and three ionic resonance forms of pyridine are taken into account, the bond orders 1.20, 1.60 and 1.40 are obtained for the 1,2, 2,3- and 3,4-bonds, respectively. The molecular diagrams as obtained by two different molecular orbital treatments of pyridine are given in VI and VII. The results of Longuet-Higgins and Coulson¹⁰ as well as of Wheland and Pauling¹¹ (VI) correspond in relative magnitude to the bond orders obtained by the valence bond method; however, the π -charges are calculated greater in the α -position than in the γ -position. The results of Orgel and co-workers¹² (VII) gave the reverse bond orders for the 2,3- and 3,4-bonds, but the expected relative π -charges. Chemical evidence¹³ as well as the results from the study of intramolecularly chelated hydroxypyridinecarboxaldehydes given below seem to correlate with the relative bond orders of VI, rather than VII. Other chemical evidence indicates the lower π -charge at the 2-position.¹⁴ It seems, therefore, that neither of the

(10) H. C. Longuet-Higgins and C. A. Coulson, *Trans. Faraday Soc.*, **43**, 87 (1947).

(11) G. W. Wheland and L. Pauling, *THIS JOURNAL*, **57**, 2086 (1935).

(12) L. E. Orgel, T. L. Cottrell, W. Dick and C. E. Sutton, *Trans. Faraday Soc.*, **47**, 113 (1951).

(13) Qualitative chemical evidence for the higher bond order of the 2,3-bond, suggested by referee II of this paper (I. M. Hunsberger), is given by the fact that 3-pyridol reacts with formaldehyde preferentially at the 2-position, and sulfonates preferentially at the 2-position. Furthermore, 3-methoxypyridine is nitrated preferentially at the 2-position, and 3-aminopyridine is chlorinated at the 2-position in high yield. The authors are indebted to Dr. Hunsberger for his careful review of this paper.

(14) For example, 2-aminopyridine is formed with NaNH_2 while 4-aminopyridine is formed only if both α -positions are blocked (Löffler, "Org. Reactions," Vol. I, John Wiley and Sons, Inc., New York, N. Y. 1942; Chapt. 4). Also, reaction with Grignard reagent gives (at 150°) 2-phenylpyridine and 2,6-diphenylpyridine [Evans and Allen, "Or-

m.o. calculations is able to account for all the known chemical facts. This is understandable in view of the fact that the coulomb integrals used for the calculations are chosen rather empirically, so as to give the best fit of the calculated dipole moments and resonance energies with experimental results. For the purposes of the present discussion, the identical frequencies of the 2- and 4-pyridinecarboxaldehydes may be interpreted as arising from the fact that the carbonyl group of the 2-aldehyde is adjacent to the 2,3-bond, which has the higher bond order. Therefore the effect of the increased positive charge at the α -carbon atom on the carbonyl frequency is compensated for by conjugation. The reverse is the case for the 4-pyridinecarboxaldehyde. If the bond order were higher in the 3,4-bond, however, and lower in the 2,3-bond, as is indicated by VII, the effect of charge at the α -carbons on the carbonyl vibrational frequency should be increased, and the two pyridinealdehydes would thus be expected to have markedly different carbonyl frequencies.

Introduction of a methoxyl group (compounds III, V and *o*-methoxybenzaldehyde) causes a decrease of the C=O stretching frequencies. If the shift, $\Delta\nu(\text{C}=\text{O})$, in going from a simple aldehyde to the *o*-methoxyaldehyde is considered, the lowering can only be attributed to the resonance interaction between the carbonyl and methoxyl groups. In the methoxypyridine aldehydes, if the bond order of the 2,3-bond is higher, one would expect greater interaction, and hence a greater $\Delta\nu(\text{C}=\text{O})$ value for V than for III. From the data given in Table II emerges, however, that III and *o*-methoxybenzaldehyde have greater shifts with $\Delta\nu(\text{C}=\text{O})$ equal to 15 cm^{-1} , whereas $\Delta\nu(\text{C}=\text{O})$ of V is only 5 cm^{-1} . This unexpected result may be interpreted on the basis that in III the carbonyl group can achieve coplanarity with the ring through a conformation opposite to that of the negatively charged methoxyl oxygen. In V, however, this conformation of the carbonyl group results in repulsion by the negatively charged nitrogen atom. Consequently, the carbonyl group of V either assumes a less coplanar conformation which would allow less resonance interaction despite higher bond order, or the polarization of the carbonyl group is reduced by the opposing effect of the other adjacent negative charges. This view is confirmed by the results of ultraviolet measurements in dioxane solution¹⁵ which show a hypsochromic shift of the π_1 -transition of V (307 $\text{m}\mu$, $\epsilon 5 \times 10^3$) as compared to that of III (322 $\text{m}\mu$, $\epsilon 4.3 \times 10^3$).

In 2,6-pyridinedicarboxaldehyde, coupling between the two carbonyl groups causes splitting of the carbonyl frequency into a very intense band at 1721 cm^{-1} and a strong shoulder at 1697 cm^{-1} , corresponding to the asymmetric and symmetric vibrations, respectively.

Condensed Phase.—In the 4000-2000 cm^{-1} region, the spectra of the liquid pyridinecarboxaldehydes, the crystalline methoxypyridinecarboxaldehydes and 2,6-pyridinedicarboxaldehyde are similar (see "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1943, p. 517).

(15) K. Nakamoto and A. E. Martell, *THIS JOURNAL*, **81**, in press (1959).

lar to the solution spectra, aside from a general broadening of the bands. The carbonyl stretching bands, however, which are sharp (half-band width about 15 cm^{-1}) in solution became very broad (half-band width about 30 cm^{-1}) for the solid and liquid states, and include several shoulders resulting from different intermolecular associated species. The main peak is shifted an average of 6–8 cm^{-1} toward lower frequencies (Table II). The strong pyridine bands reported¹⁶ at 1580, 1570, 1485 and 1440 cm^{-1} have been assigned to C=C and C=N ring stretching vibrations by Kline and Turkevich.¹⁶ These same bands are also reported in Table I for the pyridinecarboxaldehydes at 1602–1576, 1583–1562, 1490–1469 and 1454–1414 cm^{-1} , though they do not appear as strong bands in all cases. In the methoxyaldehydes III and V and in methoxybenzaldehyde, an additional strong band, observed at 1468–1460 cm^{-1} , is assigned to the symmetrical deformation vibration of the methyl group. This same absorption also is found in 3-methoxypyridine at 1462 cm^{-1} , and was reported¹⁷ to appear in other compounds with the grouping $-\text{OCH}_3$ at 1466 cm^{-1} . At 1395–1360 cm^{-1} a strong band with a relatively constant frequency, and which appears in all compounds investigated, may be due to a C–C stretching vibration, excited by the presence of the aldehyde group. A similar assignment was made previously¹⁸ for an absorption band at 1415–1350 cm^{-1} for aromatic aldehydes. All pyridinecarboxaldehydes and substituted aldehydes show a number of sharp absorption bands between 1400 and 900 cm^{-1} , which cannot be assigned unequivocally on the basis of information presently available.

Spectra of ortho-Hydroxypyridinecarboxaldehydes. 4000–2000 Cm^{-1} Region in CCl_4 Solution.—A new, relatively broad band of high intensity (half-band width 180 cm^{-1}) appears in the hydroxyaldehydes at 3250–3180 cm^{-1} (Figs. 3, 4). This band is similar to the band found in salicylaldehyde, but has no counterpart in the unsubstituted pyridinealdehydes and the *o*-methoxypyridinealdehydes, and is assigned to the O–H stretching frequency of the intramolecularly chelated O–H group. It has been suggested by several authors that the magnitude of the displacement of the O–H frequency in chelated compounds with respect to the free O–H stretching frequency should parallel the energy of the hydrogen bond.^{19–21} On the basis of the free O–H frequency which was reported for 3-hydroxypyridine¹⁸ as 3595 cm^{-1} , and for phenol²² as 3605 cm^{-1} (in CCl_4 solution), it appears that the hydrogen-bonded chelate rings in 3-hydroxypyridine-2-aldehyde ($\Delta\nu$ O–H 415 cm^{-1}) and salicylaldehyde ($\Delta\nu$ O–H 425 cm^{-1}) are about equally strong, whereas the corresponding effect in 3-hydroxypyridine-4-aldehyde is weaker ($\Delta\nu$ O–H 345 cm^{-1}). This conclusion

agrees with the observations in the carbonyl region where the greater accuracy of the measurements allows a more quantitative correlation.

2000–1500 Cm^{-1} Region in CCl_4 Solution.—It has been pointed out by several authors that properties which depend on the bond order in aromatic compounds should provide a means of detecting the magnitude of the bond order in different systems if a quantitative correlation can be established. Hunsberger^{19,23} showed for benzene, naphthalene and phenanthrene that a linear relationship exists between the bond orders and the shift of the carbonyl frequency, $\Delta\nu(\text{C}=\text{O})$, in going from a carbonyl compound such as an aldehyde, ketone or ester to the corresponding ortho-hydroxy-carbonyl compound. Also, Bellamy²⁴ established a similar relationship with the shifts in carbonyl stretching frequencies of aliphatic diketones. Compared to benzene, which has a bond order of 1.667 for all the C–C bonds,²⁵ the data in VI indicate that the 2,3-bond in pyridine has higher, and the 3,4-bond lower, double bond character. Since the molecular orbital bond orders of the 1,2-bond (1.73) and the 2,3-bond (1.60) in naphthalene²⁵ are distributed above and below the bond order of benzene by values which are greater than those given for the 2,3-bond (1.70) and 3,4-bond (1.64) of pyridine, substituted pyridine derivatives would be expected to show properties intermediate between those of the appropriate naphthalene and benzene derivatives. Examples of such derivatives may be found in 3-hydroxy-4-pyridinecarboxaldehyde (II) and 3-hydroxy-2-pyridinecarboxaldehyde (IV). In the spectra of II and IV in dilute carbon tetrachloride solution, the first strong band occurs at a position considerably lower than that of the corresponding simple pyridinecarboxaldehydes or methoxypyridinecarboxaldehydes (Figs. 5, 6). The same effect is observed for the analogous benzene derivatives. If the resonance effects of the hydroxy and the methoxy groups on the pyridine ring are considered to be of comparable magnitude, then the further weakening of the C=O bond can only be attributed to intramolecular hydrogen bonding. From the observed shift of the carbonyl stretching frequency, it follows qualitatively that because of the increased resonance contribution of the chelate ring made possible by the higher double bond character of the 2,3-bond, compound IV, $\Delta\nu(\text{C}=\text{O})$ 45 cm^{-1} , is more strongly chelated than is salicylaldehyde, $\Delta\nu(\text{C}=\text{O})$ 42 cm^{-1} , which in turn is more strongly chelated than II, $\Delta\nu(\text{C}=\text{O})$ 38 cm^{-1} . A plot of the $\Delta\nu(\text{C}=\text{O})$ values obtained for II, IV and salicylaldehyde (Table II) versus the respective bond orders in pyridine and benzene gives the linear relationship illustrated in Fig. 7. The $\Delta\nu(\text{C}=\text{O})$ values obtained in the same way from previously reported carbonyl frequencies^{19,23} of 1-hydroxy-2-naphthaldehyde (51 cm^{-1}), 3-hydroxy-2-naphthaldehyde (32 cm^{-1}) and 10-hydroxy-9-phenanthrenecarboxaldehyde (61 cm^{-1}): bond order

(16) C. H. Kline and J. Turkevich, *J. Chem. Phys.*, **12**, 300 (1944).

(17) L. J. Bellamy, "Ultrarot Spektrum und chemische Konstitution," Steinkopff, Darmstadt, 1955, p. 21.

(18) N. B. Colthup, *J. Opt. Soc. Amer.*, **40**, 397 (1950).

(19) I. M. Hunsberger, *THIS JOURNAL*, **72**, 5626 (1950).

(20) R. S. Rasmussen, D. D. Tunnicliff and R. R. Brattain, *ibid.*, **71**, 1068 (1949).

(21) D. Williams and W. Gordy, *ibid.*, **59**, 817 (1937).

(22) V. Keussler and G. Rossmly, *Z. Elektrochem.*, **60**, 136 (1956).

(23) I. M. Hunsberger, R. Ketcham and H. S. Gutowsky, *THIS JOURNAL*, **74**, 4839 (1952).

(24) L. J. Bellamy and L. Beecher, *J. Chem. Soc.*, 4487 (1954).

(25) C. A. Coulson and H. C. Longuet-Higgins, *Proc. Roy. Soc. (London)*, **A191**, 39 (1947).

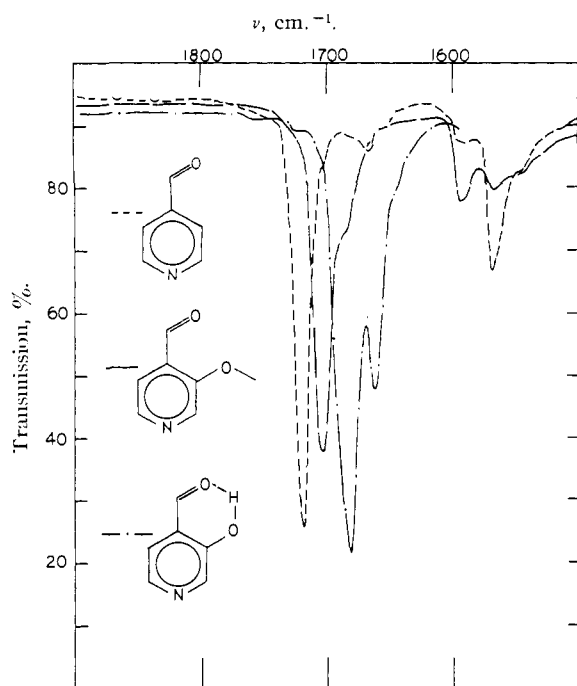


Fig. 5.—Infrared carbonyl bands of 4-pyridinecarboxaldehyde, 3-methoxy-4-pyridinecarboxaldehyde and 3-hydroxy-4-pyridinecarboxaldehyde in 0.01 *M* CCl_4 solution; light path = 1 mm.

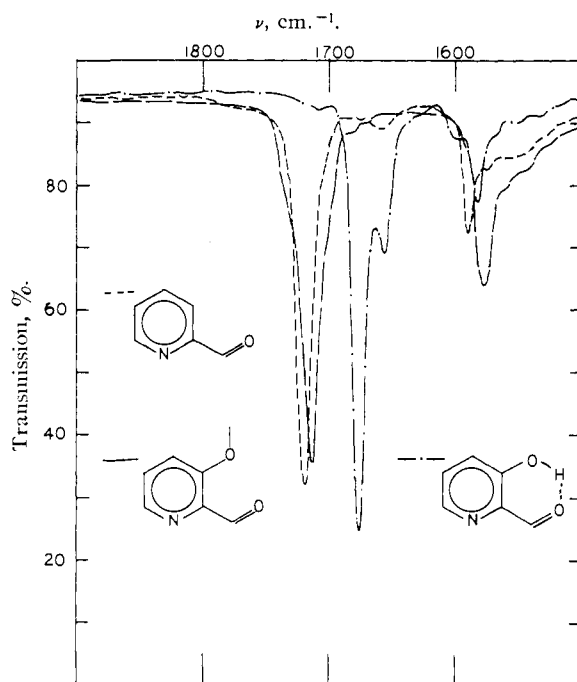


Fig. 6.—Infrared carbonyl bands of 2-pyridinecarboxaldehyde, 3-methoxy-2-pyridinecarboxaldehyde and 3-hydroxy-2-pyridinecarboxaldehyde in 0.01 *M* CCl_4 solution; light path = 1 mm.

1.775²⁶) also fit the linear relationship and occupy the predicted relative positions. Thus it seems that the bond order correlates with the $\Delta\nu(\text{C}=\text{O})$ values for simple aromatic as well as for heteroaromatic

(26) R. D. Brown, *Aust. J. Sci. Res.*, **A2**, 564 (1949).

compounds, and that the method could be used to determine bond orders in other heterocyclic systems. It should be noted, however, that the differences in bond order under consideration are small, as is obvious from the numbers given for the molecular orbital bond orders. Also the probable error in determining the $\Delta\nu(\text{C}=\text{O})$ values from two infrared measurements increases to $\pm 2 \text{ cm}^{-1}$, and that overlap between two adjacent uncertainty ranges occurs in almost all cases. In order to apply this method, therefore, it will be necessary

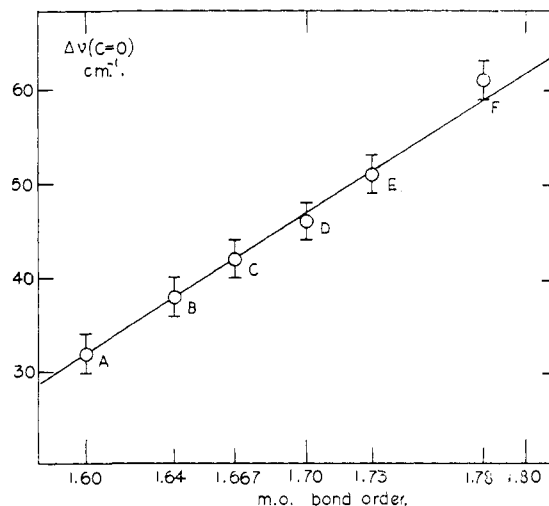


Fig. 7.—Variation of $\Delta\nu(\text{C}=\text{O})$ of *o*-hydroxyaldehydes with the bond order between the chelated groups: A, 3-hydroxy-2-naphthaldehyde¹⁹; B, 3-hydroxy-4-pyridinecarboxaldehyde; C, salicylaldehyde; D, 3-hydroxy-2-pyridinecarboxaldehyde; E, 1-hydroxy-2-naphthaldehyde¹⁹; F, 10-hydroxy-9-phenanthrenecarboxaldehyde.²¹ $\Delta\nu$ = shift of carbonyl frequency in going from a carbonyl compound to the corresponding *o*-hydroxycarbonyl compound.

to use a high resolution spectrometer and to determine all $\Delta\nu(\text{C}=\text{O})$ values with the same instrument and calibration, rather than to use literature values.²⁷ The results clearly indicate, however, that the order of the 2,3-bond is higher, and that therefore the molecular diagram VI represents the actual conditions in pyridine somewhat better than does VII.

Anomalous Absorption in the Carbonyl Region.—Attention should be drawn to the fact that in all three hydroxyaldehydes a characteristic second band of somewhat less intensity appears at the lower frequency side of the chelated carbonyl band (Figs. 5, 6) at 1661–1648 cm^{-1} .

The appearance of an anomalous second band in the carbonyl region already has been reported for several heterocyclic substances, as 2-pyridone,²⁸ 5-hydroxy-2-pyridone,²⁹ 3-hydroxy-4-pyridone,³⁰ 2-

(27) For example Hunsberger reported (ref. 17) a $\Delta\nu(\text{C}=\text{O})$ for benzene (from salicylaldehyde) of only 38 cm^{-1} .

(28) J. A. Gibson, W. Kynaston and A. S. Lindsey, *J. Chem. Soc.*, 4340 (1955).

(29) R. Adams and T. R. Govindachari, *THIS JOURNAL*, **69**, 1806 (1947).

(30) R. Adams, V. V. Jones and J. L. Johnson, *ibid.*, **69**, 1810 (1947).

pyrimidone,³¹ coumarone³² and various cyclopentenones.³³

The first interpretation for this phenomenon was only recently³⁴ obtained. All cyclopentenones with "two carbonyl frequencies" contained an ethylenic C-H adjacent to the C=O group which exhibits a C-H out of plane bending vibration of exactly half the frequency of the second C=O band. Thus, the appearance of the two bands could be ascribed to Fermi resonance between the first overtone of the C-H bending mode of vibration and the actual carbonyl vibration. Deuterated or alkyl-substituted compounds lacked the second absorption band. In the present case, however, neither salicylaldehyde nor IV show any absorption bands suitable for this interpretation, II being the only exception.

Studies in these laboratories¹⁵ indicate that II and IV are in equilibrium in aqueous solutions with dipolar ions of the type indicated by VIII, as is true of 3-pyridol and pyridoxal derivatives.³⁵ In methanol and ethanol the equilibrium is increasingly shifted in the favor of II and IV, and in solvents of still lower dielectric constant, such as chloroform, dioxane or carbon tetrachloride, the hydroxyaldehydes exist in the form of the non-ionic species exclusively. This result is confirmed by the infrared spectra of these compounds. In VIII, a tautomeric form of IV, one might expect the dipolar form to be stabilized by chelation of the carbonyl group with the pyridine ^+N-H . However, such chelate rings are known to be relatively weak, since the hydrogen bond tends to be linear. If the second frequency were due to the presence of this tautomer, then the ratio of the intensity of this band to that of the 6-membered chelated carbonyl band should increase in going from carbon tetrachloride to solvents of higher dielectric constant. The solution spectra in dioxane, chloroform and carbon tetrachloride obtained, however, were identical. Moreover, the second band was found for II, for which the stabilizing effect of the 5-membered chelate ring cannot occur, as well as for salicylaldehyde, where the formation of tautomers is impossible.

Since the unsubstituted aldehydes and the methoxyaldehydes in this region exhibit only very weak bands of varying frequency, it is reasonable to associate the occurrence of this second frequency with the presence of the hydrogen-bonded chelate ring. Thus, resonance in the chelate ring may cause the excitation of an additional C=C vibration or a splitting of the main carbonyl band into two components. Formation of a dimer or association in solution cannot be the reason for the appearance of the anomalous band, since the positions as well as the relative intensities of both bands remain unchanged in 0.1 and 0.01 *M* solutions. Even in the case of 3-hydroxy-2-pyridinecarboxaldehyde (IV), the solubility of which allowed the preparation of a 1 molar solution, no association

was observed. This latter observation is in agreement with results of cryoscopic measurements of intramolecular chelated naphthalene derivatives,¹⁹ where it was pointed out that even weak chelation is sufficient to retain monomeric character in moderately concentrated solutions. In contrast to this behavior, the unchelated pyridinecarboxaldehydes show downward shifts of the carbonyl frequency in solutions of concentrations higher than 0.02 *M*.

Spectra of *o*-Hydroxypyridinecarboxaldehydes, 3-Hydroxypyridine and Pyridoxal in the Crystalline State.

The O-H stretching frequency of crystalline phenol²² (3197 cm^{-1}) is considerably lower than the value obtained in dilute carbon tetrachloride solution (3605 cm^{-1}). This effect can be attributed to intermolecular hydrogen bonding of the O-H \cdots O type, similar to that found in aliphatic alcohols.³⁶ 3-Hydroxypyridine,³⁷ which has an O-H stretching vibration at 3595 cm^{-1} in CCl_4 , gives rise in the solid state to a broad absorption band at 2500 cm^{-1} (Fig. 8). This remarkable difference cannot be explained simply on the basis that in the crystalline state 3-pyridol exists in the form of a dipolar ion.^{37,38} Since molecules are generally arranged in solids so that the strongest hydrogen bonds are formed, it is reasonable to assign to this compound an intermolecular hydrogen bonded arrangement such as is illustrated in Fig. 10. Mason³⁷ concluded from the established relation between O \cdots O distance and strength of hydrogen bonding³⁹ that O-H \cdots O type of bonding should predominate in this compound rather than $\overset{+}{N}-H$

$\cdots \overset{-}{O}$ type. In order to further elucidate the type of bonding in these compounds, mixtures of phenol and pyridine were measured at various concentrations and at a mole ratio of 1:1. Pyridine in carbon tetrachloride solution showed only the aromatic C-H absorption, but no absorption below 3000 cm^{-1} regardless of concentration. Phenol in 1 *M* solution in CCl_4 showed a broad band at 3350 cm^{-1} characteristic of the intermolecular O-H \cdots O bonded species, a weak but sharp band at 3610 cm^{-1} (free O-H, st.) and the aromatic C-H absorption, but no absorption was found below 3000 cm^{-1} . In 0.1 *M* solution the O-H \cdots O band nearly vanished, and the free O-H stretching vibration was more intense. In 0.02 *M* solution only the latter band was present. In a liquid mixture of pyridine and phenol, as well as in a 1 *M* solution in CCl_4 , no free O-H was found, and the O-H \cdots O band of phenol was decreased in intensity. In addition, a series of strong bands overlapping to form a broad band from 2600 to 2810 cm^{-1} appeared. These bands are assigned to the O-H \cdots N intermolecular coordinated species IX. In 0.1 and 0.02 *M* solutions the free O-H band of phenol appeared again, and the O-H \cdots N band decreased proportionally in intensity, but was present even in the most dilute solution, indicating stronger intermolecular bonding in the species

(31) L. N. Short and H. W. Thompson, *J. Chem. Soc.*, 168 (1952).

(32) A. K. Bose and P. Yates, *THIS JOURNAL*, **74**, 4703 (1952).

(33) P. Yates, N. Yoda, W. Brown and B. Mann, *ibid.*, **80**, 202 (1958).

(34) P. Yates and L. L. Williams, *ibid.*, **80**, 5896 (1958).

(35) D. E. Metzler and E. E. Snell, *ibid.*, **77**, 2431 (1955).

(36) W. C. Coburn and E. Grunwald, *ibid.*, **80**, 1318 (1958).

(37) S. F. Mason, *J. Chem. Soc.*, 4874 (1957).

(38) Sensi and Gallo, *Ann. chim. (Italy)*, **44**, 232 (1954).

(39) K. Nakamoto, M. Margoshes and R. E. Rundle, *THIS JOURNAL*, **77**, 6480 (1955).

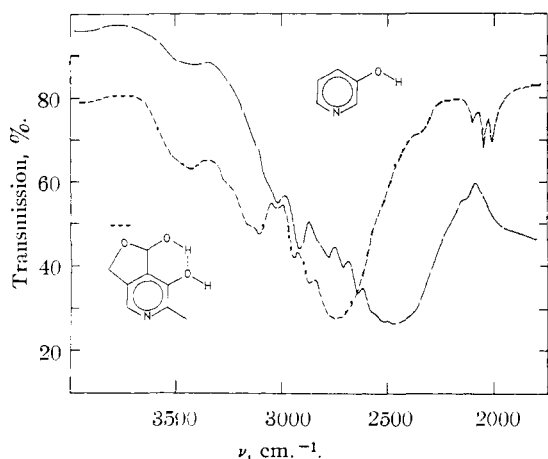


Fig. 8.—Infrared spectra of 3-hydroxypyridine, ———, and pyridoxal, - - - -; solid state, KBr pellet.

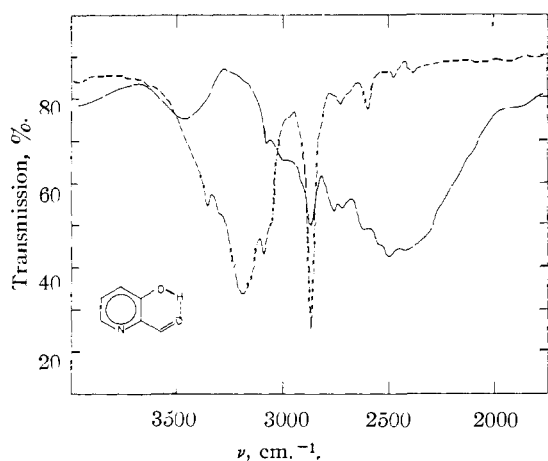


Fig. 9.—Comparison of the infrared spectra of 3-hydroxy-2-pyridinecarboxaldehyde in solution and in the solid state: ———, KBr pellet; - - - -, CCl₄ solution

IX than in phenol itself. Since IX is an analog of the crystal structure assumed for 3-pyridol, the 2400–2700 cm^{-1} band of the latter is assigned to $\text{N}-\text{H}\cdots\text{O}$ rather than $\text{O}-\text{H}\cdots\text{O}$ bonding. On the basis of infrared spectra alone no decision can be made as to whether the hydrogen is nearer the pyridine nitrogen or the oxygen. In Figs. 10, 11 and 12, therefore, the formal charges provide only a schematic indication of the charge distribution, and it is not possible to make a distinction between $\overset{+}{\text{N}}-\text{H}\cdots\overset{-}{\text{O}}$ or $\text{N}\cdots\text{H}-\overset{-}{\text{O}}$ type of bonding in these compounds, although X-ray evidence might indicate more precisely the nature of the intermolecular hydrogen bonds.

The spectra of *o*-hydroxypyridinealdehydes in the crystalline state are remarkably different from those in solution, as is indicated in Fig. 9. The $\text{O}-\text{H}\cdots\text{O}$ intramolecular bonded O-H frequency at 3200 cm^{-1} (half-band width 180 cm^{-1}) vanishes entirely and is replaced by a very broad absorption band at 2500 cm^{-1} (half-band width 500 cm^{-1}). The aromatic and aldehydic C-H frequencies are partially superimposed on this band and are therefore less sharp, but appear at the original frequencies. The presence of intermolecular as-

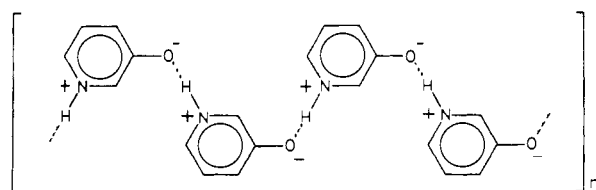


Fig. 10.—Proposed structure of crystalline 3-pyridol.

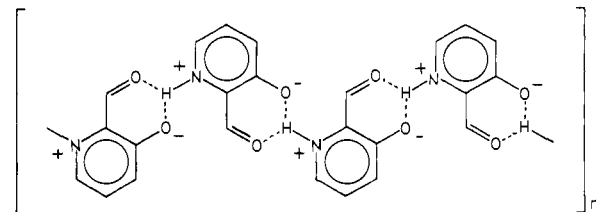


Fig. 11.—Proposed structure of crystalline *o*-hydroxypyridinecarboxaldehydes.

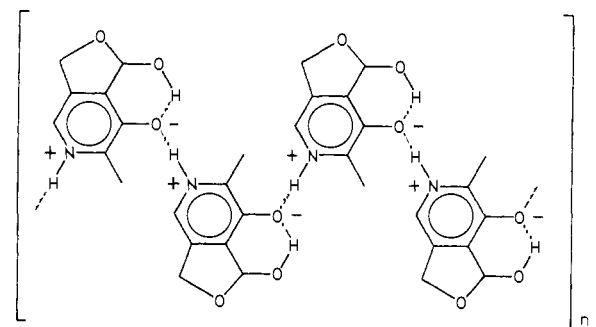


Fig. 12.—Proposed structure of crystalline pyridoxal (free base).

sociation similar to the type found in 3-hydroxypyridine is therefore indicated. The chelated carbonyl bands of II and IV show the same broadening as is described above for the unchelated aldehydes, but they appear at essentially the same frequencies in the crystalline state as in solution, and not at the frequency of the free pyridinecarboxaldehydes. Hence it follows that in the crystalline state the carbonyl group must still take part in hydrogen bonding, and the hydrogen atom may therefore be assumed to be only slightly displaced from its position in the monomeric chelated compound, but to be also bound to the pyridine nitrogen of a second molecule. Thus a bifurcated³⁹ hydrogen bond in which the hydrogen atom is bound by overlap with orbitals of two oxygen and one nitrogen atom is obtained, as is indicated in Fig. 11. Here also, evidence that $\text{N}-\text{H}\cdots\text{O}$ intermolecular hydrogen bonding is present rather than $\text{O}-\text{H}\cdots\text{O}$ type of bonding was obtained by the study of an analogous system pyridine/salicylaldehyde. Equimolar mixtures of these compounds in CCl₄ solution did not show any appreciable association, even in 1 *M* solution. But in a mixture of the pure liquids a new broad band assigned to species X appeared at 2550–2700 cm^{-1} , and a decrease of the intensity of the $\text{O}-\text{H}\cdots\text{O}$ intramolecular chelated band at 3200 cm^{-1} also occurred. This is quite analogous to that of the hydroxypyridinecarboxaldehydes.

Evidence was given above on the basis of solution spectra of hydroxypyridinealdehydes that intra-

molecular hydrogen bonding is much stronger in 3-hydroxy-2-pyridinecarboxaldehyde than in 3-hydroxy-4-pyridinecarboxaldehyde. If this knowledge is now applied to the arrangements suggested for the solid state, it seems that as intramolecular hydrogen bonding increases, the availability of the hydrogen as electron acceptor for the pyridine nitrogen decreases, and the strength of the intermolecular attraction in the crystalline state is decreased. A number of observations which have been made of the physical properties of the isomeric hydroxypyridinecarboxaldehydes are readily accounted for by this postulate. Thus, 3-hydroxy-2-pyridinecarboxaldehyde shows a much lower melting point (79–80°) than 3-hydroxy-4-pyridinecarboxaldehyde (133–134°), and even than 3-hydroxypyridine (129°). Compound IV sublimates slowly at room temperature and readily at 50°, whereas II sublimates with difficulty at over 100° (1 atm.). The solubility of IV in carbon tetrachloride is about 20 times higher than that of II. That intermolecular bonding is indeed replaced by intramolecular bonding in the fusion of these compounds was verified by the infrared spectrum of IV in the liquid state, which resembles its spectrum in CCl₄ solution (Fig. 4) very closely in that it has no absorption at 2500 cm.⁻¹ but has a band at 3180 cm.⁻¹, which is characteristic of the chelated O—H···O group. Similarly, no change in the O—H region is observed for IV in the series: liquid, 1 M solution, 0.1 M solution, 0.01 M solution.

The infrared spectrum of pyridoxal (base) in the crystalline state (Fig. 8) resembles that of 3-pyridol more than those of the hydroxypyridinecarboxaldehydes. In the 2000–1500 cm.⁻¹ region there is only one strong band at 1541 cm.⁻¹, undoubtedly arising from C=C/C=N ring vibrations, and only two very weak bands at 1621 and 1605 cm.⁻¹. 3-Hydroxypyridine exhibits the C=C stretching frequency at 1572 cm.⁻¹ and a weak band at 1613 cm.⁻¹. The absence of any carbonyl stretching frequency in pyridoxal indicates that in the crystalline state it is mainly in the form of the hemiacetal. The observations in the O—H region are in line with this result. The very broad band which appears in the spectrum of pyridoxal, as in those of 3-pyridol and of the hydroxyaldehydes, has a somewhat higher frequency (2735 cm.⁻¹), indicating weaker intermolecular hydrogen bonding than in 3-pyridol. This is understandable on the basis that the aliphatic hydroxyl group of the hemiacetal forms an intramolecular hydrogen bond with the phenolic oxygen, thus weakening the donor properties of the latter. This case resembles the intramolecular hydrogen bonding in *o*-hydroxybenzyl alcohol,⁴⁰ which has two O—H stretching frequencies, corresponding to a chelated hydrogen band at 3436 cm.⁻¹ and to a free hydroxyl group at 3605 cm.⁻¹. In the case of crystalline pyridoxal, however, no free O—H frequency is observed as the result of intermolecular hydrogen bonding, leaving one intramolecular (chelated) OH frequency at 3180–3100 cm.⁻¹, and an intermolecular O—H···N frequency at 2735 cm.⁻¹. On this basis the pro-

posed structure of crystalline pyridoxal indicated by Fig. 12 seems to be reasonable.

The three weak and sharp absorption bands of pyridoxal between 2100–2000 cm.⁻¹, and the absorption of 3-pyridol in this region, have been considered as further indication of the dipolar nature of these compounds in the crystalline state,^{37,41} since a band frequently is observed at this region for amino acids, amino acid hydrochlorides and amine hydrochlorides.⁴² The origin of the absorption at 2000 cm.⁻¹, however, which has been attributed to the group —NH₃⁺, is not certain. The fact that it is not found in the hydroxypyridinecarboxaldehydes is not inconsistent with the proposed structures in view of the difference in bond type between the ammonium groups in the dipolar forms of amino acids and pyridine compounds.

Spectra in the 900–650 Cm.⁻¹ Region in Condensed Phase.—The absorption characteristics of aromatic compounds in the 900–650 cm.⁻¹ region depend on the number and the relative position of the remaining hydrogen atoms attached to the nucleus. Thus it has been shown that pyridine,¹⁶ with five remaining hydrogen atoms, corresponds to a monosubstituted benzene, which absorbs at 770–730 cm.⁻¹ and at 700 ± 10 cm.⁻¹,⁴³ and that the absorption bands of the 2-, 3- and 4-picoline are similar to those of 1,2-, 1,3- and 1,4-disubstituted benzene derivatives,⁴⁴ respectively. A number of the substituted pyridines in this investigation correspond to 1,2,3- or 1,2,4-trisubstituted benzenes, as well as some simpler substituted compounds. In general, the known absorption characteristics for the corresponding benzene derivatives were found to apply with only small deviations, as is indicated in Table III. Thus benzaldehyde, as in the case of pyridine, shows strong bands near 750 and 700 cm.⁻¹. 2-Pyridinecarboxaldehyde, salicylaldehyde and *o*-methoxybenzaldehyde show only one strong band near 760 cm.⁻¹, as does 2-picoline.⁴⁵ The 1,3- and 1,2,3-substituted (respectively, pseudosubstituted) compounds are characterized by two very strong bands which appear at 800 and 700 cm.⁻¹ with little variation of position. In addition, the 1,3-substituted compounds as reported for benzenes¹⁷ and 3-picoline,⁴⁵ have a band of lower intensity at 920–880 cm.⁻¹. Since the 1,3- and 1,2,3-substituted compounds have none or only weak bands between 800 and 700 cm.⁻¹, they can definitely be distinguished from mono- and 1,2-substituted substances, which do not absorb at 800 cm.⁻¹. A number of 1,2,3-substituted compounds, however, have bands of medium intensity near 900 cm.⁻¹, while the 1,2-substituted compounds absorb near 710 cm.⁻¹, so that it is difficult to distinguish between members of each of the two substitution groups 1,2,3/1,3 and 1,2/mono. Finally, in the asymmetric 1,2,4-trisubstituted compounds a strong band appears near 830 cm.⁻¹ and a second band at 880 cm.⁻¹, but no ab-

(41) H. N. Christensen, *THIS JOURNAL*, **79**, 4073 (1957).

(42) N. Fuson, M. L. Josien and R. L. Powell, *ibid.*, **74**, 1 (1952).

(43) Reference 17, p. 219.

(44) H. Freiser and W. L. Glowacki, *THIS JOURNAL*, **70**, 2575 (1948).

(45) D. P. Biddiscombe, E. Z. Coulson, R. Handley and E. F. G. Herington, *J. Chem. Soc.*, 1957 (1954).

(40) A. E. Martin, *Nature*, **166**, 474 (1950).

TABLE III
 C-H IN PHASE OUT OF PLANE BENDING VIBRATIONS

Compound and substitution type	Absorption bands in the 900-650 cm^{-1} region				
Monosubstitution					
Monosubst. benzene ¹⁸				750s	700s
Pyridine ¹⁶	884w		807w	747s	710s
Benzaldehyde		827s		743s	685s
Average, C-H wagg. vibr.:				747s	698s
1,2-Substitution					
1,2-Subst. benzene ¹⁸				755s	
2-Picoline ⁴⁵	883w		798m	751vs	729s
2-Pyridinecarboxaldehyde		832s		764s	
<i>o</i> -Methoxybenzaldehyde		833m		757s	718w
Salicylaldehyde	883s			762s	712m
Average, C-H wagg. vibr.:				758s	
1,3-Substitution					
1,3-Subst. benzene ¹⁸	880m		780s		703s
3-Picoline ⁴⁵	923w		788vs		708vs
3-Bromopyridine	878m		795s	763m	700s
				748m	
3-Methoxypyridine	924m	900m	800s		705s
3-Hydroxypyridine	897m	847m	804s		703s
		831w			
3-Pyridinecarboxaldehyde		823s	798m		702s
Average, C-H wagg. vibr.:	900m		794s		704s
1,2,3-Substitution					
1,2,3-Subst. benzene ¹⁸			780s		703s
2,6-Lutidine ⁴⁵	889w		775vs	729m	716m
2-Chloro-3-hydroxypyridine	907w	864w	798s	727w	698s
2-Chloro-3-aminopyridine		852w	797s	734m	690m
2,6-Pyridinedicarboxaldehyde	912s		807s	787m	698s
				724w	
3-Methoxy-2-pyridinecarboxaldehyde		867m	803s	753w	735m
		855m			
3-Hydroxy-2-pyridinecarboxaldehyde	892s		812s	767m	703m
Average, C-H wagg. vibr.:			796s		706m-s
1,2,4-Substitution					
1,2,4-Subst. benzene	880m	830s			
3-Methoxy-4-pyridinecarboxaldehyde	898m	833s	794m	733w	
3-Hydroxy-4-pyridinecarboxaldehyde	888m	830m	813m		
Average, C-H wagg. vibr.:	889m	831s			

sorption was found at 750 or at 700 cm^{-1} . Therefore, it seems that the 3,4-disubstituted pyridines can be readily distinguished from the 3-substituted

and the 2,3-disubstituted pyridines by means of the infrared spectra in this region.

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