[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF NOTRE DAME]

Electric Moments of Some γ-Substituted Pyridines[1]

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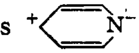
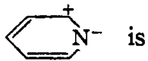
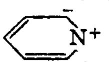
Electron diffraction studies have revealed[3] that pyridine has a structure nearly identical with that of benzene. The resonance energy of pyridine, 43 kcal. per mole,[4] compared to the value of 39 kcal. for benzene, indicates that the former compound is stabilized not only by Kekulé resonance, but also by the contribution of highly polar structures to the normal molecules. The large electric moment of pyridine, 2.2 debye units,[5] reveals that the contribution of the electromers  and  is appreciable, resulting in a low electron density at the 2 and 4 positions in the ring. This electron distribution is likewise evidenced by the rate and course of the great majority of substitution reactions of cationoid and anionoid reagents with pyridine. The formation of 2- and 2,6-derivatives in the halogenation of pyridine at high temperatures, however,[6,7] suggests the possible existence of the excited forms  and  having but six electrons in the nitrogen valence shell.

The electric moments of γ-substituted pyridines have now been obtained to determine the extent of resonance interaction of electron releasing and electron attracting groups with the pyridine nitrogen, and to clarify the structure of certain of these compounds. Dioxane was used as a solvent for those compounds which are but slightly soluble in benzene.

Experimental

Preparation and Purification of Compounds.—Reagent grade pyridine obtained from the General Chemical Co. was purified by repeated fractional freezings, refluxing over freshly heated barium oxide, and distilling through a column one meter in length packed with glass helices. Middle fractions having a constant index of refraction were used for physical measurements: $n^{20}{}_D$ 1.5094, $d^{20}{}_4$ 0.9832. Additional material was first purified by distilling off a low boiling fraction and treating the residue in the same manner as above, using calcium oxide as a drying agent; b. p. 114.5° (740 mm.), $n^{25}{}_D$ 1.5067, $d^{25}{}_4$ 0.9786.

γ-Picoline was supplied through the courtesy of the Reilly Tar and Chemical Co. The material was purified by fractional distillation. A middle fraction was converted to the hydrochloride and crystallized from hydrochloric acid. A water solution of the crystals was neutralized with excess potassium hydroxide and the picoline was extracted with ether, dried over potassium carbonate, refluxed over barium oxide and distilled; b. p. 143–145°, $n^{25}{}_D$ 1.5031.

Isonicotinic acid was prepared from γ-picoline in 45% yield by the procedure of Singer and McElvain[8] for obtaining picolinic acid. The concentrated aqueous solution of the acid was acidified with 6 *N* hydrochloric acid until all of the acid precipitated. The product was recrystallized from water; m. p. 317–318°.

Ethyl isonicotinate was prepared by esterifying the acid with absolute alcohol in the presence of concentrated sulfuric acid. The ester was distilled, heated over barium oxide at 100° for thirty minutes, and redistilled; b. p. 118–119° (25 mm.), $n^{25}{}_D$ 1.4990, $d^{25}{}_4$ 1.1003.

Isonicotinamide was prepared from the ester in 90% yield by refluxing an ethyl alcohol solution containing 20% ester by volume and bubbling a continuous stream of ammonia through the solution for twelve hours. The greater part of the alcohol was removed by distillation and the amide allowed to crystallize from the residue; m. p. 154°; recrystallized from benzene, m. p. 156°.

Isonicotinonitrile was prepared from isonicotinamide and phosphorus pentoxide by the method of LaForge.[9] The product was recrystallized from benzene; m. p. 78.5–80°.

4-Aminopyridine was prepared by adding isonicotinamide to a cold solution of potassium hypobromite. The mixture was kept at −5° with stirring until nearly colorless, then warmed to 70° for three hours. The resulting solution was neutralized to congo red with 6 *N* hydrochloric acid. A solid, isonicotinic acid, separated on standing. The mixture was filtered and the filtrate was evaporated to dryness under reduced pressure. The solid was extracted with warm 95% alcohol and the filtrate evaporated to dryness. The process was repeated with absolute alcohol to yield 4-aminopyridine hydrochloride. The hydrochloride was dissolved in a minimum volume of water and carefully neutralized with a concentrated solution of potassium hydroxide. The 4-aminopyridine (soluble in excess base) precipitated and was filtered, dried, and recrystallized from benzene; m. p. 159–160°.

4-Pyridol was prepared by a modification of the method of Koenigs and Greiner.[10] These authors heated a water solution of an intermediate, 4-pyridylpyridinium dichloride, for eight hours at 150° in an autoclave. We obtained the crude 4-pyridol in 60% yield from the dichloride by refluxing a water solution for sixty hours over a sand-bath, and treating the product in the manner these authors describe. For use in dielectric constant measurements the crude 4-pyridol was dissolved in alcohol, treated repeatedly with charcoal, and finally crystallized from alcohol and dioxane; m. p. 148°.

4-Chloropyridine was prepared from crude 4-pyridol by the method of Wibaut and Broekman.[11] Petroleum ether was used in place of diethyl ether to extract the product after steam distillation, because the last traces of ethyl ether could not be removed by distillation. The ligroin was removed by distillation from a flask equipped with a Vigreux column, the last traces being removed by reducing the pressure to 2 mm. with the distilling flask immersed in an ice-bath. The 4-chloropyridine was then distilled at 2 mm. and collected as a white solid in receivers immersed in a Dry Ice–acetone bath. Fractions having a constant refractive index $n^{20}{}_D$ 1.5315 were used in physical measurements. (This index checks an interpolated value obtained from the data of Wibaut and Broekman.) $n^{25}{}_D$ 1.5280, $d^{25}{}_4$ 1.2000, MR_D(calcd.) 29.03, MR_D (obs.) 29.13. The samples were packed in Dry Ice until the benzene solutions were prepared to avoid decomposition.

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(1) Presented in part before the Organic Division at the Cleveland meeting of the American Chemical Society, April, 1944.

(2) Present address: U. S. Navy.

(3) Schomaker and Pauling, THIS JOURNAL, **61**, 1769 (1939).

(4) Pauling, "The Nature of the Chemical Bond," Cornell University Press, Ithaca, N. Y., 1940, p. 137.

(5) Middleton and Partington, *Nature*, **141**, 516 (1938).

(6) Hertog and Wibaut, *Rec. trav. chim.*, **51**, 940 (1932).

(7) Wibaut and Nicolai, *ibid.*, **58**, 709 (1939).

(8) Singer and McElvain, "Organic Syntheses," Vol. 20, John Wiley and Sons, Inc., New York, N. Y., 1940, p. 79.

(9) LaForge, THIS JOURNAL, **50**, 2477 (1928).

(10) Koenigs and Greiner, *Ber.*, **64B**, 1049 (1931).

(11) Wibaut and Broekman, *Rec. trav. chim.*, **58**, 885 (1939).

4-Methoxypyridine was prepared from 4-chloropyridine and sodium methylate by the method of Haitinger and Lieben;[12] b. p. 102° (40 mm.), n^{25}_D 1.5176, d^{25}_4 1.0750, MR_D (calcd.) 30.89, MR_D (obs.) 30.74. The 4-methoxypyridine was precipitated from benzene solution as the hydrochloride and analyzed for chlorine.

Anal. Calcd. for C_6H_8ClNO: Cl, 24.35. Found: Cl, 24.33.

Reagent grade benzene obtained from the General Chemical Co. was refluxed over phosphorus pentoxide and distilled. Practical dioxane was purified by the method of Hess and Frahm.[13]

Measurements and Calculations.—The measurements of dielectric constants and densities and the calculation of solute polarizations at infinite dilution were carried out as previously described.[14] Measurements on solutions of 4-pyridol were made at 50° in order to obtain a sufficient concentration of solute. Densities of these solutions were measured in a 25-ml. pycnometer. All other data listed in Table I were obtained at 25°. Because of the very low solubility of isonicotinic acid in dioxane, and the consequent low precision of the dielectric constant increment, densities of these solutions were not measured. The Hedestrand equation[15] for calculating the solute polarization at infinite dilution has the form $P_{2\infty} = A + B\Delta d/\Delta c_2 + C\Delta\epsilon/\Delta c_2$ where A, B and C are constants characteristic of the solvent and solute. For most organic compounds the sum of the first two terms is very nearly equal to the distortion polarization of the solute, giving $c\Delta\epsilon/\Delta c_2 = P_0$, the orientation polarization.[16] The value of the third term of the equation for isonicotinic acid was determined as 148 ± 20, indicating a moment of 2.7 ± 0.2. Those molar refractions listed in Table II which are given to but three significant figures were calculated by subtracting the difference between the refractions of benzene and pyridine, 2.1, from the refractions of the corresponding substituted benzenes. The distortion polarization of each compound was taken as $1.1MR_D$, and the electric moment in debye units calculated from the relation $\mu = 0.0128\sqrt{(P_{2\infty} - 1.1MR_D)T}$.

TABLE I

DIELECTRIC CONSTANTS AND DENSITIES OF SOLUTIONS AT 25°

c_2	ε	d	c_2	ε	d
Benzene–Pyridine			Dioxane–4-Pyridol (50°)		
0.00000	2.272	0.8731	0.000000	2.176	0.9999
.01108	2.349	.8742	.000983	2.220	1.0002
.01615	2.385	.8749	.001140	2.227	1.0004
.02765	2.462	.8760	.001210	2.232	....
Dioxane–Pyridine			.001275	2.235	1.0006
0.00000	2.212	1.0281	Benzene–Isonicotinonitrile		
.01023	2.287	1.0279	0.00000	2.275	0.8736
.01605	2.318	1.0275	.01188	2.322	.8763
.02299	2.378	....	.01339	2.325	.8770
.02540	2.396	1.0273	.01721	2.342	.8778
Benzene–γ-Picoline			Benzene–Ethyl Isonicotinate		
0.00000	2.274	0.8734			
.02581	2.518	.8754	0.00000	2.274	0.8734
.02950	2.551	.8758	.01373	2.384	...
.03442	2.598	.8761	.01650	2.420	.8789
Benzene–4-Chloropyridine			.02471	2.491	.8817
0.00000	2.276	0.8729	Dioxane–Isonicotinamide		
.02000	2.302	.8799	0.00000	2.212	1.0281
.02137	2.303	.8801	.00836	2.396	1.0306
.02571	2.306	.8816	.01013	2.435	1.0309
Dioxane–4-Aminopyridine			.01192	2.491	1.0313
0.00000	2.212	1.0281	Dioxane–Isonicotinic Acid		
.00554	2.364	1.0290	0.000000	2.217	1.0276
.00865	2.451	1.0293	.000356	2.221	...
.00996	2.485	1.0296	.000494	2.222	....
Benzene–4-Methoxypyridine			.000684	2.224	....
0.00000	2.276	0.8729			
.00855	2.383	.8750			
.01361	2.445	.8764			
.01737	2.490	.8776			

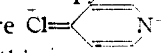
TABLE II

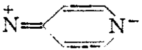
POLARIZATIONS AND ELECTRIC MOMENTS

	$P_{2\infty}$	MR_D	μ
Pyridine (benzene)	125.4	24.07	2.20
Pyridine (dioxane)	127.8	24.07	2.22
γ-Picoline	167.6	29.0	2.57
4-Chloropyridine	46.2	29.03	0.84
4-Aminopyridine	420.5	28.8	4.36
4-Methoxypyridine	211.7	30.74	2.94
4-Pyridol	704	25.8	6.0
Isonicotinonitrile	85.3	29.5	1.61
Ethyl isonicotinate	170.5	40.33	2.49
Isonicotinamide	345.3	34.0	3.88
Isonicotinic acid	...	...	(2.7)

Discussion of Results

The moments of the γ-substituted pyridines can best be analyzed by comparing them with values reported for the corresponding substituted benzenes. The difference between the moments of pyridine and γ-picoline, 0.37, is equal to the moment of toluene; it is somewhat small in the light of the reactive character (associated with positive residual charge) of the methyl hydrogens in γ-picoline.

The difference between the moments of pyridine, 2.2, and chlorobenzene, 1.55, is 0.65 debye unit. The moment obtained for 4-chloropyridine is 0.84, indicating that the structure  contributes to a greater extent in this compound than does the corresponding structure in chlorobenzene.

The moment calculated for 4-aminopyridine from the moments of pyridine and aniline in dioxane, 2.22 and 1.90,[17] assuming the latter vector to be in the plane of the ring, is 4.12. The observed moment, 4.36, indicates a strong contribution of the structure  to the normal molecule. Sidgwick[18] states that 4-aminopyridine can react in a tautomeric imine form

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[12] Haitinger and Lieben, *Sitzber. Akad. Wien*, **91**, 919 (1885); *Chem. Zentr.*, **56**, 488 (1885).

[13] Hess and Frahm, *Ber.*, **71**, 2627 (1938).

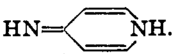
[14] McCusker and Curran, THIS JOURNAL, **64**, 614 (1942).

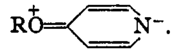
[15] Hedestrand, *Z. physik. Chem.*, **B2**, 428 (1929).

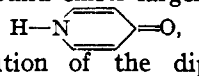
[16] The sum of the first two terms for ethyl isonicotinate in benzene, for example, is 41.5, and $1.1MR_D = 44.4$. $c\Delta\epsilon/\Delta c_2 = 129.0$ and $P_0 = 126.1$.

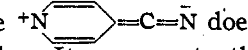
[17] Kumler and Halverstadt, THIS JOURNAL, **63**, 2182 (1941).

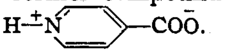
[18] Sidgwick, "The Organic Chemistry of Nitrogen," Clarendon Press, Oxford, 1937, p. 529.

 This tautomer would have a very low moment; its presence in any appreciable percentage in dioxane solution is ruled out by the large moment obtained for this compound.

Assuming the bond moments and bond angle postulated by one of the authors[19] for anisole, a moment of 2.8 has been calculated for methoxypyridine in the absence of resonance interaction between the methoxy group and the nitrogen. The observed moment, 2.94, reveals that the methoxy group likewise interacts with the ring nitrogen via the electromer .

The hydroxy group has about the same polarizability by resonance as the methoxy group. The moment calculated for 4-pyridol in dioxane assuming a resonance interaction similar to that in the ether is 3.5. The observed moment, 6.0, reveals that this compound exists largely as the 4-pyridone tautomer , with an appreciable contribution of the dipolar ion form  which is stabilized by Kekulé resonance. A large contribution of the dipolar ion form to the methyl derivative of this tautomer, N-methyl-4-pyridone, has been revealed by the typical aromatic absorption spectrum of this compound.[20,21] The high polarity of 4-pyridol accounts for its very low solubility in non-polar solvents.

The calculated moment for 4-cyanopyridine in the absence of resonance interaction, is 1.7, with the pyridine nitrogen as the positive end of the molecule. The observed moment, 1.61, reveals that the structure  does not contribute appreciably. It appears to the authors that if structures having but six electrons in the valence shell of nitrogen do not contribute to molecules of this type, they are probably not important in excited forms of pyridine itself. The lack of interaction between an electron attracting group and the pyridine ring is likewise revealed by a comparison of the calculated and observed moments, 2.6 and 2.49, of ethyl isonicotinate. The former value was calculated by assuming that the moment vector of the ester groups makes an angle of 74° with the pyridine ring.[22] The moment of isonicotinamide cannot be similarly analyzed at this time, because the exact direction of the moment vector of the amide group is not known.

The high melting point of isonicotinic acid, 318°, compared to that of benzoic acid, 122°, suggests that the former compound has a zwitterion structure . This is in line with the extremely low solubility of the acid in non-polar solvents. Water solutions of nicotinic acid, picolinic acid, and cinchonic acid (the quinoline analog of isonicotinic acid) all show[23] the large change in dielectric constant with concentration characteristic of zwitterions, and the dielectric increment for nicotinic acid is about equal to that of trigonelline, its N-methylbetaine. The low moment obtained for isonicotinic acid in dioxane, 2.7, indicates that in dioxane the acid is in the unionized form. Edsall and Wyman[24] have shown that the apparent moments of zwitterions in mixed solvents decrease with decreasing dielectric constant of the solvent. Oster[25] has attributed this decrease to the formation of a shell of the solvent constituent of higher dielectric constant around the dipolar ion, which serves as an electrostatic shield and thus decreases the effective moment of the ion. It is evident that this theory cannot account for the low moment of isonicotinic acid in dioxane.

Summary

Electric moments have been determined for several γ-substituted pyridines in benzene and dioxane. The values obtained are discussed in relation to the structure of these compounds and to their electron distribution.

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[19] Anzilotti and Curran, THIS JOURNAL, **65**, 607 (1943).

[20] Auwers, *et al.*, *Ber.*, **63B**, 2111 (1930).

[21] Riegel and Reinhard, THIS JOURNAL, **48**, 1334 (1926).

[22] Hobbs and Weith, *ibid.*, **65**, 967 (1943).

[23] Devoto and Ardissone, *Gazz. chim. ital.*, **65**, 1235 (1939).

[24] Edsall and Wyman, THIS JOURNAL, **57**, 1964 (1935).

[25] Oster, *ibid.*, **66**, 948 (1944).