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BROMINATION OF PYRIDINE IN THE PRESENCE OF SOME LEWIS ACIDS

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The bromination of pyridine in the form of complexes with some Lewis acids and in the presence of catalytic amounts of the latter was studied. It is shown that bromination takes place readily at $\sim 100^\circ\text{C}$ in the presence of catalysts such as AlCl_3 , ZnCl_2 , CuCl_2 , SbCl_3 , InCl_3 , TeCl_4 , and HgCl_2 . The principal bromination products are 3-bromopyridine and 3,5-dibromopyridine. The problem of the possibility of so-called π back-bonding in the case of elements of the higher periods (particularly In, Te, and Sb) is discussed.

It is well known that specific difficulties are encountered in the case of electrophilic substitution in the pyridine series: electrophilic attack on the π -deficient system requires activation; however, the aprotic and protic acids that are ordinarily employed as catalysts form complexes with pyridines that are even more inert than the free bases. An increase in the amount of the catalyst most often has no effect, since, for example, in the case of bromination it promotes a shift not only in equilibrium (1) to favor the active electrophile particle, which is depicted in this case as a polarized complex of bromine with the Lewis acid, but also in equilibrium (2) to favor the deactivated π complex:



The utilization of salts of metals of higher periods, particularly and especially mercury, most often gives a positive effect, which is usually explained by so-called "back-bonding" [1], i.e., by transfer of the electron density from the central metal atom to the π system of the pyridine ring. It should be emphasized that the explanation of the catalytic effect of aluminum halides that is sometimes encountered in the literature (for example, see review [2, 3]) is absolutely invalid: The aluminum atom, being an element of the third period, simply does not contain in its outer shell free electrons that could be transferred to the π system of the pyridine ring.

The aim of the present research was to study the catalytic activity in the bromination of pyridine of a number of Lewis acids, the central atoms of which belong to different periods of the Mendeleev system.* In the first stage of this research we studied the bromination at $80\text{--}100^\circ\text{C}$ of previously prepared complexes in which, depending on the nature of element M, the MX_n :pyridine ratio was 1:1 or 1:2. The results of the experiments are presented in Table 1.

*The contents of this paper were presented in part in [4].

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TABLE 1. Bromination of Complexes of Pyridine with Some Lewis Acids (for a pyridine:bromine molar ratio of 1:1.5 at 100°C)

Composition of the complex (salt)	Composition of the mixture after bromination, %			
	pyridine	3-bromo-pyridine	3,5-dibromo-pyridine	other substances
HCl · C ₅ H ₅ N*	100,0	—	—	—
BF ₃ · C ₅ H ₅ N	100,0	—	—	—
AlCl ₃ · C ₅ H ₅ N †	84,5	12,4	3,1	—
FeCl ₃ · C ₅ H ₅ N	100,0	—	—	—
FeCl ₂ · C ₅ H ₅ N	90,2	7,3	2,5	—
CoCl ₂ · 2C ₅ H ₅ N	82,7	15,8	1,5	—
NiCl ₂ · 2C ₅ H ₅ N	95,4	3,8	0,8	—
CuCl ₂ · 2C ₅ H ₅ N	56,7	27,1	5,0	11,2
ZnCl ₂ · 2C ₅ H ₅ N	61,9	21,7	11,8	4,6
ZrCl ₄ · 2C ₅ H ₅ N	100,0	—	—	—
InCl ₃ · 2C ₅ H ₅ N	34,8	21,4	43,1	0,7
SnCl ₄ · 2C ₅ H ₅ N	95,8	—	4,2	—
SbCl ₃ · 2C ₅ H ₅ N	69,7	28,2	0,7	1,4
TeCl ₄ · 2C ₅ H ₅ N	45,5	18,9	34,1	1,5
HgCl ₂ · 2C ₅ H ₅ N	52,7	18,5	27,0	1,8
BiBr ₃ · C ₅ H ₅ N	100,0	—	—	—

*According to the data in [5], the bromination of pyridine hydrochloride at 160–200°C gives 18.9% 3-bromopyridine and 6.1% 3,5-dibromopyridine.

†Pearson and co-workers [6], who used 2.6 moles of AlCl₃ per mole of pyridine, did not observe the formation of products of bromination of pyridine at ~100°C.

It can be seen from the data in Table 1 that the formation of products of bromination of pyridine under relatively mild conditions (at ~100°C with 1.5 mole of bromine per mole of pyridine) was not observed in the case of 10 of the complexes. In this connection let us recall that in the absence of catalysts the bromination of pyridine is carried out at or above 300°C [7, 8]. Of the complexes that we studied, the complexes formed by aluminum, cobalt, copper, zinc, indium, antimony, tellurium, and mercury give the most interesting results. In particular, in the case of treatment of the InCl₃ · 2C₅H₅N complex with bromine bromination takes place even at room temperature [according to the data from gas-liquid chromatography (GLC), 1.7% 3-bromopyridine and 3.2% 3,5-dibromopyridine are formed after 3 h]. When the temperature is raised to 100°C, the overall yield of bromination products in the case of the InCl₃ complex exceeds 60% (see Table 1).

We have established that the bromination of pyridine can also be realized when catalytic amounts of various Lewis acids (~10% with respect to pyridine) are used. Activation of bromine in the presence of catalytic amounts of Lewis acids may be achieved either due to MX_n, which exists in equilibrium with the complex [Eq. (2)] or a ternary complex that includes bromine, pyridine, and MX_n. In the experiments under discussion we used from 0.8 to 2 moles of bromine per mole of pyridine; as a consequence of the formation of complexes of pyridine with bromine, the catalyst, and with the hydrogen bromide liberated in the reaction, the reaction mixtures could be heated in an open vessel above the boiling point of pyridine. The results of some experiments carried out at 100, 150, and 200°C with 1 and 2 moles of Br₂ per mole of pyridine are presented in Table 2.

The results obtained are of greatest interest in a preparative respect, and they can also be used in the discussion of the problem as to the form (the free base or the complex with MX_n) in which pyridine is brominated, depending on the catalyst used. One's attention is first and foremost drawn to the fact that, despite the prevailing opinion, pyridine is brominated in the absence of a catalyst at 100°C, although the yields are low (the yields presented in Tables 1 and 2 were determined by GLC). Free pyridine evidently undergoes bromination in the presence of AlCl₃. This is confirmed not only by the general concepts presented above regarding the impossibility for aluminum of π bonding, which activates the pyridine ring to electrophilic attack, but also by the experimental data [6], which constitute evidence that when excess AlCl₃ (2.6 moles per mole of pyridine), which prevents dissociation of the complex and at the same time creates extremely favorable conditions for activation of bromine, is used, bromination does not occur. When catalytic amounts of AlCl₃ are used, the yield of bromination products increases as the temperature is raised

TABLE 2. Yields of 3-Bromopyridine (I) and 3,5-Dibromopyridine (II) in the Bromination of Pyridine in the Presence of Catalytic Amounts of Lewis Acids

Lewis acid	Temp. °C	Yields, %, at pyridine : bromine molar ratios			
		1 : 1		1 : 2	
		I	II	I	II
—	100	6,6	0,6	12,8	0,8
	150	9,6	0,6	10,5	0,4
	200	6,8	2,2	4,8	20,5
AlCl ₃	100	8,5	1,8	6,8	7,0
	150	15,1	5,7	7,8	5,6
	200	9,6	22,2	16,0	22,4
ZnCl ₂	100	6,6	0,6	7,9	3,5
	150	8,9	2,2	16,3	13,9
	200	8,4	2,8	10,3	29,4
InCl ₃	100	16,5	3,7	13,9	5,4
	150	9,4	4,6	23,8	18,2
	200	12,8	6,2	23,2	55,5
SbCl ₃	100	10,4	3,2	8,2	6,5
	150	6,5	0,8	19,6	16,6
	200	10,0	11,5	19,4	40,9
TeCl ₄	100	11,7	3,6	9,7	20,5
	150	8,1	6,0	15,4	21,7
	200	10,5	5,7	14,7	31,5
HgCl ₂	100	6,0	2,0	12,4	3,2
	150	9,4	2,1	14,4	16,0
	200	13,8	11,6	20,1	34,1

(Table 2), and this is in agreement with an increase in the activity of the reagent. The situation is different in the case of InCl₃, TeCl₄, and SbCl₃, for which even a certain decrease in the yield is observed as the temperature is raised. This may be determined by the fact that the corresponding complex is brominated more readily than free pyridine: An increase in the temperature leads to dissociation of the complex, and a decrease in the activity of the substrate is "compensated" by an increase in the activity of the electrophilic agent, which does not occur immediately but only in the case of a further increase in the temperature.

We also studied the bromination of pyridine in the presence of catalytic amounts of a number of other Lewis acids, specifically iron, cobalt, nickel, copper, manganese, titanium, and tin chlorides, to which one of our future communications will be devoted. At present it is still difficult to interpret sufficiently adequately the results of bromination of pyridine in the presence of salts of elements of the higher periods, which, by the way, are not such effective catalysts of electrophilic substitution reactions in the benzene series as aluminum chloride. Whereas in the case of complexes of the transition elements (Fe, Co, Ni, and Cu²⁺) the possibility of d π -p π interaction of π bonding [9] and, consequently, activation of the ligand is widely accepted, this possibility is not evident in the case of nontransition elements with filled d shells (In, Sn, Te, Sb, Zn²⁺, and Hg²⁺) and requires additional study.

For preparative purposes, of the investigated catalysts, aluminum and zinc chlorides can be regarded as optimal catalysts from the point of view of their accessibility and catalytic effect. When they are used together with 1.5 moles of Br₂ per mole of pyridine, the overall yield of 3-bromopyridine and 3,5-dibromopyridine, the separation of which is rather simple, may reach almost 40% (~60% with allowance for the recovered pyridine). The use of copper chloride also gives similar yields; however, the process is less selective: In addition to 3-bromopyridine and 3,5-dibromopyridine, considerable amounts of other bromination products (see Table 1), the principal of which was 2,5-dibromopyridine, are also formed. One of the possible pathways of its formation may include (as a first step) bromination of pyridine in the 2 position. Let us point out in this connection that, according to recently published data [10], the complex of pyridine with palladium chloride is brominated at 0°C, and the chief point (~90%) is 2-bromopyridine.

EXPERIMENTAL

The reaction products were analyzed by GLC with a Tsvet-100 chromatograph with a flame-ionization detector, a 3 m by 3 mm stainless-steel column, and 10% PEG-1000 on Chromaton N-AW-HMDS, previously treated with 2% NaOH at 120°C, with helium as the carrier gas at a flow rate of 60 ml/min. The quantitative determinations were made with respect to an internal standard (dimethylformamide). The structures of the products of bromination of pyridine were confirmed by the identical character of their IR spectra (recorded with an IKS-22 spectrometer at 700-4000 cm^{-1}) and the spectra of samples with known structures. The 3,5-dibromopyridine and 2,5-dibromopyridine isolated from the reaction products, as well as 3-bromopyridine picrate, did not depress the melting points when they were mixed with genuine samples obtained by the methods in [5, 11].

Preparation of Complexes of Pyridine with Lewis Acids and Determination of Their Compositions. Complexes of pyridine with Lewis acids were obtained by the general methods described in [12-14]. The complexes were dried at 100-105°C for 2-3 h. The compositions of the complexes presented in Table 1 were established from the amount of pyridine liberated during decomposition of the dry complex with alkali; the pyridine was determined by weight and by potentiometric titration.

Bromination of the Complexes of Pyridine with Lewis Acids. A complex containing 0.1 mole of pyridine was treated with ~ 0.15 mole of bromine, and the mixture was heated to 100°C and maintained at this temperature for 5 h. It was then cooled, and the complex was decomposed with a concentrated solution of alkali. The crystalline dibromide was separated by steam distillation, and the filtrate was made alkaline to pH 10 and extracted with ether (five 30-ml portions). The extract was dried with KOH, the solvent was removed by distillation, and the mixture was analyzed by GLC (see Table 1 for the results).

Bromination of Pyridine in the Presence of Catalytic Amounts of Lewis Acids. A 25-g (0.155 mole) sample of bromine and 1.25 g of the Lewis acid were added successively with vigorous stirring and cooling (from -10 to 0°C) to 12.5 g (0.155 mole) of pyridine, after which the mixture was heated to the temperature indicated in Table 2 and maintained at this temperature for another 5 h while gradually adding (in experiments with a pyridine:bromine ratio of 1:2) another 0.155 mole of bromine. The subsequent workup of the mixture and analysis by GLC were carried out as described above for the bromination of the complexes. In the case of preparative isolation of the bromination products, after steam distillation and separation of the crystalline 3,5-dibromopyridine, the ether extract was evaporated, and the residue was distilled with isolation of the fractions with bp 100-115°C (primarily unchanged pyridine) and bp 160-175°C (mainly 3-bromopyridine). Pure 3-bromopyridine with bp 172-173°C can be isolated by repeated distillation of the latter fraction.

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