NMR Studies of Picolyl-type Carbanions. VIII.[1,2] Anions Produced by Reactions of Alkyl-substituted Pyridines with Butyllithium

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The ^1H and ^{13}C NMR spectra have been observed for the anions, produced from methyl-, ethyl-, and isopropylpyridines, in tetrahydrofuran (THF). Two kinds of anions are formed concomitantly by lithium-proton exchange and addition of butyllithium from 2-ethyl-, 2-isopropyl-, 4-methyl-, and 4-ethylpyridines. The former reaction tends to occur at the substituent bonded to the position adjacent to nitrogen, and the latter one occurs at the position adjacent to nitrogen without substituent. In the anions formed by the exchange from 2- and 4-ethylpyridines, a specific ring proton is coupled to the α-carbon, and, further, the *ortho*- or *meta*-protons (or -carbons) in the latter anion are nonequivalent respectively at room temperature. The α-carbons in these anions are virtually sp^2-hybridized.

It has recently been reported that two kinds of anions are produced by exchange and addition reactions of methyl-substituted quinolines with and without a 2-methyl group, with butyllithium, respectively, and that the former anions are picolyl-type carbanions, but the latter ones are ionic species having two of three basic characteristics on picolyl-type carbanions.[3] We now take up methyl-, ethyl-, and isopropylpyridines having at least two reaction sites (*i.e.*, the 2- and 6-positions) adjacent to nitrogen in a molecule, and present here some observations of the anions prepared from them.

Experimental

The starting materials, except for 2-, 3-, and 4-isopropylpyridines, used in this study were commercially available. 2- and 4-Isopropylpyridines were prepared by heating pyridine (10.60 g, 134 mmol) and 2-iodopropane (23.21 g, 137 mmol) at 200—240 °C for 16 h in an autoclave. A crude mixture (2.716 g) was obtained after removal of the recovered starting materials by distillation (101 kPa). A part of the mixture (1.267 g) was separated with thin-layer chromatography on silica gel using benzene–ether as a developing solvent to give 2-isopropylpyridine (R_f=0.71, 375 mg, 5%) and 4-isopropylpyridine (R_f=0.54, 515 mg, 7%). The structure of each pyridine derivative was confirmed by comparison of its physical properties with those of the authentic samples.[4,5] 3-Isopropylpyridine was prepared from 3-isopropenylpyridine by the method reported by Brown *et al.*[4] These starting materials were used after dried over calcium hydride and vacuum distilled.

The preparation of the anions was carried out *in vacuo*. About 1—3 mmol of a starting material was reacted with the equimolecular amount of butyllithium in hexane at 0—5 °C. After the completion of the reaction, all the volatile materials were trapped out and dried THF was introduced into the system. By solvent exchange, the solution became red or red-brown. The solution was then transferred into a NMR sample tube, and the tube was sealed off. The ^1H NMR spectra were measured at 200, 60, and 60 MHz on an Varian XL-200, Hitachi R-20B, and R-24B spectrometers respectively, and the ^{13}C spectra were measured at 50.3 MHz on a Varian XL-200. The proton and carbon chemical shifts were eval-

Table 1. The proton chemical shifts of the anions, in THF at 200 MHz, in ppm

Anion	Assignment										
	2-H	3-H	4-H	5-H	6-H	CH	CH_2		CH_3		
1 a		5.62	6.02	4.80	6.86		2.52				
b		5.42	6.13	4.70	6.81	3.11			1.41		
c$^{e)}$		5.35	5.83	4.42	6.82				1.45	1.54	
2 a	a)	4.22	5.78	4.33			1.29$^{b)}$		a)		0.89
b	a)	4.17	5.80	4.36			1.28$^{b)}$	a)	1.03		0.86
c$^{e)}$	3.54	4.01	5.80	4.28		2.02	1.28$^{b)}$		1.01	1.05	0.88
3 a	a)		5.52	4.26	6.41		1.27$^{b)}$		a)		0.86
b	a)		5.52	4.29	6.41		1.26$^{b)}$	a)	1.01		0.85
c$^{e)}$	3.63$^{c)}$		5.54	4.35	6.40	2.21	1.30$^{b)}$		0.96		0.85
4 a	a)	4.26	5.65		6.32		1.27$^{b)}$		a)		0.86
b	a)	4.29	5.71		6.36		1.26$^{b)}$	a)	0.92		0.85
c$^{e)}$	3.48	4.30	5.79		6.42	2.25	1.30$^{b)}$		0.96		0.85
5 a	6.39	5.28		5.28	6.39		2.64				
b	6.21	5.18		4.98	6.45	2.70			1.37		
c$^{e)}$	6.38	5.07		5.07	6.38				d)		
6 a	a)	4.03		4.26	6.57		1.28$^{b)}$		1.57		0.85
b	a)	4.07		4.31	6.57		1.27$^{b,c)}$	a)	0.97		0.86
c$^{e)}$	3.53	4.10		4.34	6.56	2.14	1.27$^{b)}$		0.98		0.87

a) Chemical shifts are not available because of overlapping of the large solvent peak. b) Center peak of complex multiplet. c) Assignment uncertain. d) Overlapping of large peaks. e) In THF-d_8.

Table 2. The carbon chemical shifts of the anions, in THF at 50.3 MHz, in ppm

Anion	Assignment 2-C	3-C	4-C	5-C	6-C	CH	CH_2				CH_3		
1 a	164.1	116.1	131.5	97.1	148.7		57.2						
b	155.9	109.9	132.0	95.1	149.6	66.9 (=C<)					12.5		
c[b)]	161.2[a)]	110.7	129.0	91.7	149.8	74.7					20.2	14.2	
2 b	57.2	97.3	127.2	87.3	161.5		35.6	28.3	24.3	31.7	14.7		15.0
c[b)]	57.5	94.7	127.3	83.4	166.1	37.0	35.0	28.5	24.4		25.5	23.2	15.1
3 a	62.2	106.6	121.9	89.5	146.9		34.1	29.9	24.8		23.6		15.0
b	61.8	113.0	119.4	89.5	147.0		33.9	29.7	24.8	29.8	14.1		15.0
c[b)]	60.6	117.5	117.9	89.4	146.9	34.0	34.0	29.6	24.8		23.6	22.9	15.1
4 a	57.3	98.7	128.9	96.8	147.9		35.5	28.6	24.5		19.4		15.0
b	57.5	98.7	127.6	105.4	147.0		35.1	28.6	24.5	28.1	18.1		15.0
c[b)]	57.7	99.1	125.8	110.3	145.0	32.7	35.4	28.8	24.6		25.4	25.1	15.1
5 a	143.8	109.9	149.8	109.9	143.8		65.8						
b	141.7	111.3	150.2[a)]	103.6	144.4	74.4					12.8		
6 a	58.0	96.8	133.5	93.0	150.1		35.5	28.5	24.5		21.6		15.0
b	57.8	95.2	140.0	91.7	150.2		35.4	28.5	24.5	29.3	15.0		15.0
c[b)]	57.6	93.9	144.6	90.7	150.2	34.2	35.6	28.6	24.5		23.8	23.4	15.0

a) Assignment uncertain. b) In THF-d_8.

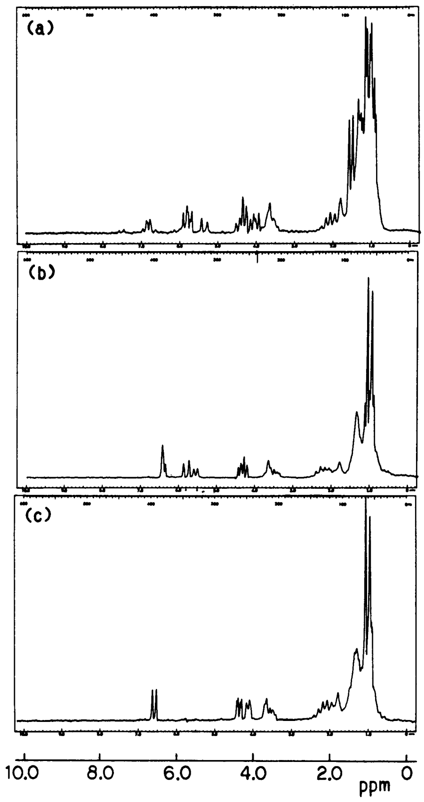


Fig. 1. ^{1}H spectra of the anions in THF-d_8 at 60 MHz; (a) **1c** and **2c**, (b) **3c** and **4c**, and (c) **6c**.

uated with the higher-field solvent peak of THF used as an internal reference and then converted to δ_H and δ_C values from TMS by taking 1.79 and 26.4 ppm respectively.

Results and Discussion

Typical ^{1}H NMR spectra of the anions produced from 2-, 3-, and 4-isopropylpyridines are shown in Figs. 1(a)—(c) respectively, and a typical ^{13}C spectrum of the anions produced from 2-ethylpyridine is shown in Fig. 2. The ^{1}H and ^{13}C NMR chemical-shift data are given in Tables 1 and 2 respectively.

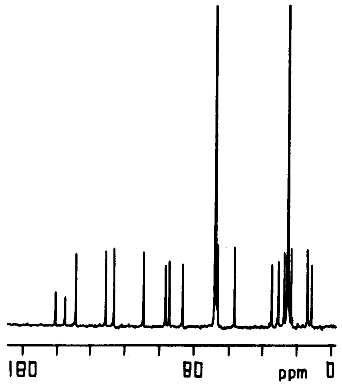
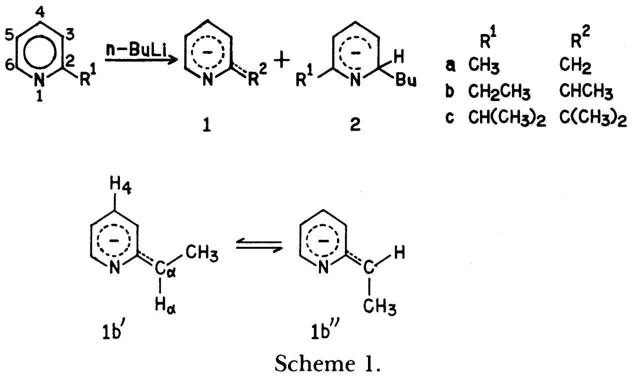


Fig. 2. ^{13}C spectrum of **1b** and **2b** in THF at 50.3 MHz.

First, it can be seen from Fig. 1 (a) that two kinds of anions, **1c** and **2c** (Scheme 1), are formed concomitantly by lithium-proton exchange and addition of butyllithium. In Fig. 2, eighteen signals, except for two large solvent peaks, are attributable to two kinds



Scheme 1.

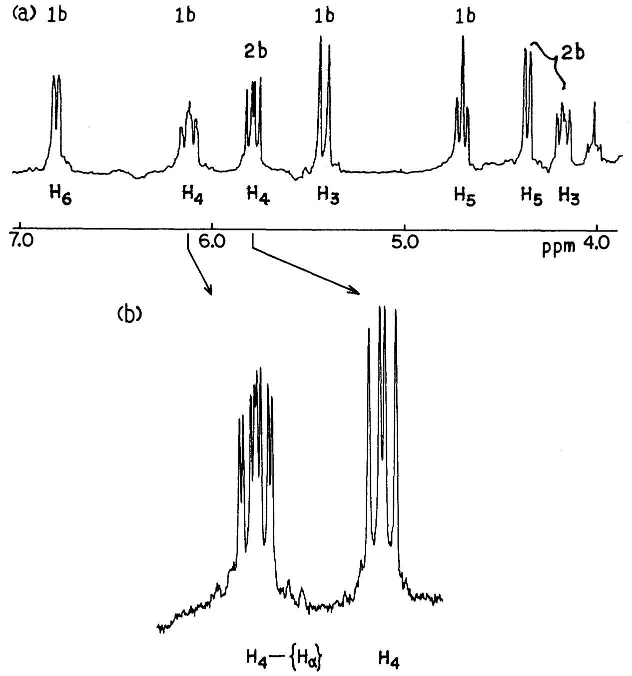


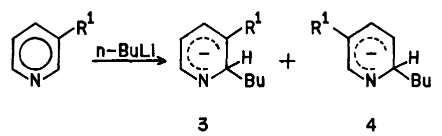
Fig. 3. (a) ^1H spectrum of the ring proton region of **1b** and **2b** in THF at 200 MHz, and (b) the expanded spectrum of the 4-proton peaks, where the 4-H of **1b** is decoupled to the α-H.

of anions, **1b** and **2b**. Thus, 2-ethyl- and 2-isopropylpyridines undergo both exchange and addition. 2-Methylpyridine appears to undergo only exchange to give **1a**, but, in a large scale preparation,⁶⁾ the presence of a small amount of **2a** was confirmed from a detailed inspection of the ^1H spectrum. Each of these two reactions occurs at a specific position as shown in Scheme 1. In any event, the 2-substituted pyridines undergo exchange to give **1**. The proportion of **1c** relative to **2c** is smaller than that of **1b** relative to **2b**, where **1b** and **2b** are in the ratio about 1:1. These facts indicate that the proton-releasing power of the α-carbon in the 2-substituted pyridines decreases in the order of methyl-, ethyl-, and isopropylpyridines.

In the ^{13}C spectra of **1**, the 5-carbon signal of each anion appears at a higher field in the order of **1a**, **1b**, and **1c**. The 5-carbon chemical shift is a well-defined index of negative charge delocalization, leading to the resonance stabilization, as stated before.⁷⁾ In the above order, therefore, these anions tend to take the resonance stabilization in a molecular plane. The resonance stabilization is enhanced by the α-positioned methyl group.

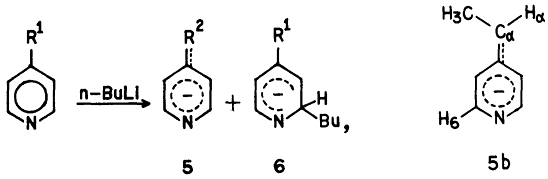
A typical ^1H spectrum of the ring proton region of **1b** and **2b**, prepared concomitantly from 2-ethylpyridine, is shown in Fig. 3. On the four signals assigned to **1b**, decoupling experiments show that the 4-H is coupled to the α-H with a coupling constant of 1.1 Hz.⁸⁾ This kind of long-range coupling was previously observed for **1a** at lower temperature.⁹⁾ Clearly, the α-carbon of **1b** is virtually sp^2-hybridized. These four signals for **1b** are attributable to the **1b′** isomer (Scheme 1). The presence of the **1b″** isomer could not be confirmed.¹⁰⁾ In **1c** and **2c**, the two methyl carbons bonded to the α-carbon of each anion show magnetic nonequivalence. The chemical shift difference between the two for **1c** is 6 ppm. This magnitude is appreciably larger than that for **2c** ($\Delta\delta_c$=2.3 ppm), whose α-carbon is in a sp^3 configuration.

Second, the 3-substituted pyridines undergo addition to give **3** and **4** (Scheme 2) concomitantly, but fail to do exchange. In **3c** and **4c**, as shown in Fig. 1 (b), the signals appearing as doublets at δ 5.54 and 5.79 are attributable to the 4-protons of **3c** and **4c** respectively. The ratio of the two peak areas is about 1:1.8, indicating that **3c** and **4c** are present in this ratio. In **3b** and **4b**, however, the ratio is about 1:1. This suggests that the 3-isopropyl group may tend to hinder the addition reaction occurring at the 2-position in the steric sense as compared with the 6-position.



Scheme 2.

Third, 4-methyl- and 4-ethylpyridines produce **6a** and **6b** (Scheme 3) together with **5a** and **5b** as by-products respectively. Further, 4-isopropylpyridine appears to produce **6c** only, as shown in Fig. 1(c), but the presence of a slight amount of **5c** was confirmed from a detailed inspection of the spectrum. In any event, the 4-substituted pyridines undergo exchange with difficulty, as compared with the 2-substituted ones. It was reported before by Zoltewicz *et al.* that 4-methylpyridine was more acidic than 2-methylpyridine.¹¹⁾ This implies that the proton-releasing power of the 4-methyl carbon is stronger than that of the 2-methyl one, that is, 4-methylpyridine tends to undergo exchange. In practice, however, **1a** is rather formed with ease as described above. This lithium-proton exchange reaction tends to occur at the substituent bonded to the position adjacent to nitrogen. This experimental result agrees with the observation of the anions produced from 2,4,6-trimethylpyridine,¹˒⁹⁾ and gives support to the view that the ring nitrogen (not α-carbon) can be regarded as the site where the anion–cation interaction takes place mainly in picolyl-



Scheme 3.

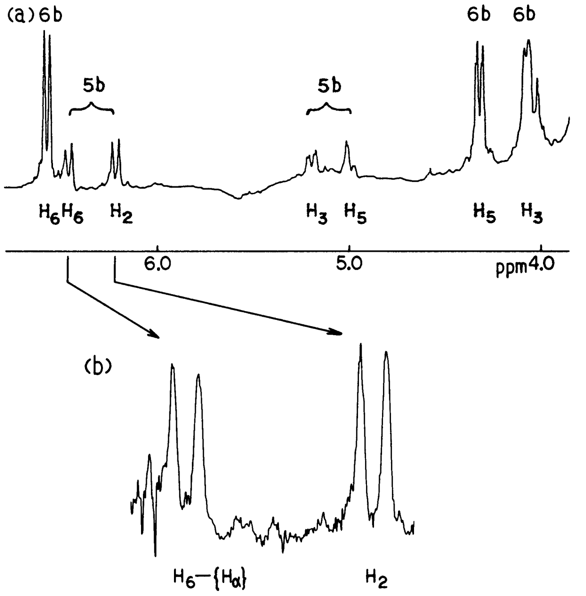


Fig. 4. (a) ^1H spectrum of the ring proton region of **5b** and **6b** in THF at 200 MHz, and (b) the expanded spectrum of the 6- and 2-proton peaks of **5b**, where the 6-H is decoupled to the α-H.

type carbanions with lithium as a counter ion.[3] The addition reaction also occurs at the position adjacent to nitrogen without substituent.

On the signals assigned to **5b** in Fig. 4, the *ortho*-protons (3- and 5-H) or *meta*-protons (2- and 6-H) are nonequivalent respectively at room temperature. Similar nonequivalence was observed before by Takahashi *et al.* for the α-methylbenzyl carbanion.[12] The *ortho*- or *meta*-carbons are also nonequivalent. This nonequivalence is explained by the restricted rotation around the bond between the ring and the α-carbon, caused by the resonance stabilization. Further, decoupling experiments show that the 6-H is coupled to the α-H (Scheme 3), and that the four signals appearing as doublets are attributable to the 6-, 2-, 3-, and 5-protons respectively in the upfield direction. The α-carbon of **5b**, as well as **1b**, is virtually in a sp^2 configuration.

In conclusion, two interesting facts should be noted. One is that two kinds of anions are formed concomitantly by lithium-proton exchange and addition of butyllithium from 2-ethyl-, 2-isopropyl-, 4-methyl-, and 4-ethylpyridines. The former reaction tends to occur at the substituent bonded to the position adjacent to nitrogen, and the latter one occurs at the position adjacent to nitrogen without substituent. Another is that a specific ring proton is coupled to the α-carbon in the anions formed by the exchange from 2- and 4-ethylpyridines, and, further, that the *ortho*- or *meta*-protons (or -carbons) in the latter anion are nonequivalent respectively at room temperature. The α-carbons in these anions are virtually sp^2-hybridized.

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