1028 © *1993 The Chemical Society of Japan* *Bull. Chem. Soc. Jpn.*, ***66***, *1028—1031(1993)* [Vol. 66, No. 4

An NMR Study of Substituted Pyridine-Butyllithium Adducts

Akihiro YOSHINO, Norimasa NAKAMURA, and Kensuke TAKAHASHI*
Department of Applied Chemistry, Nagoya Institute of Technology, Gokiso-cho, Showa-ku, Nagoya 466

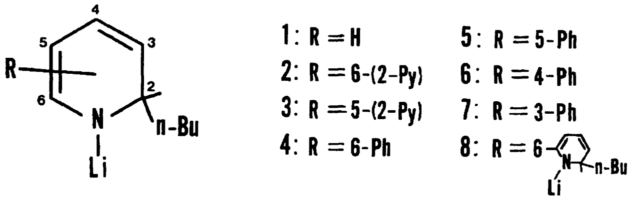
(Received October 15, 1992)

The ^{1}H and ^{13}C NMR spectra of the title adducts have been observed in THF and HMPA solutions. The charge distributions in the adducts calculated from the ^{13}C chemical shifts indicated that the 2-pyridyl ring accommodated at least about 25% negative charge at the 6-position of the adduct skeleton, while the phenyl ring gave only a 4% change at the same position. For the 2,2′-bipyridine-butyllithium adduct two isomers (*E* and *Z*) were confirmed by ^{1}H and ^{13}C NMR, indicating that the bond between the two rings has a partial double-bond character. However, for phenylpyridine–butyllithium adducts, the rotation of the phenyl group was not restricted, even at −80°C.

Substitution on the aromatic compounds, such as pyridine, has long been an important subject in organic chemistry, and a variety of methods have been reported. One of the simple methods is to use organolithium compounds. For example, in the reaction of pyridine with butyllithium, 2-butylpyridine is obtained in good yield. Pyridine with such substituents as oxazoline derivatives also reacts with butyllithium to yield some isomers having substituents at different positions.[1)] These reactions proceed via the σ-complex as an intermediate, which can be explained by an addition-elimination mechanism.[2)] On the other hand, alkylsubstituted pyridines react with butyllithium to give complex and/or picolyl-type carbanion whose charge distributions and ion pair structures have been investigated.[3)] Thus, the substitiuents affect the reactions of pyridine with organolithium in various ways; little is known about why this occurs. NMR is a useful and efficient technique for investigating many aspects of anionic intermediates in solutions. Structural studies of such intermediates should lead to a deep understanding of organic synthetic chemistry.[4)] To obtain some insight into these problems we investigated the structures, charge distributions, and effects of the pyridyl and phenyl groups regarding the adducts produced in reactions of substituted pyridines with butyllithium using ^{1}H and ^{13}C NMR. The prepared adducts are numbered from **1** to **8**, and are shown in Scheme 1.

Experimental

The pyridine, bipyridine, and phenylpyridine used as starting materials and butyllithium were commercially available. These starting materials were dried over calcium hydride and degassed by the freeze-pump-thaw procedure, and then stored in sealed ampules with a break seal. Tetrahydrofuran (THF) and THF-d_8 were dried over sodium, and then stored on a sodium–potassium alloy. Hexamethylphosphoric triamide (HMPA) was dried over calcium hydride and then stored in a sealed vessel with a break seal.



Scheme 1.

All of the preparations of the adducts were carried out in vacuo. The starting material (0.25—0.50 mmol) reacted with an equimolar amount of butyllithium in hexane or hexane/THF at −78°C. After the solvent was distilled off until almost dry, the residue was dissolved in a solvent such as THF, THF-d_8, or HMPA. The solution was then introduced into an NMR sample tube, which was sealed under a vacuum. The concentration of the sample solution was approximately 1 mol dm^{-3}.

The ^{1}H and ^{13}C NMR spectra were recorded on a Varian XL-200 spectrometer equipped with a variable-temperature probe operating at 200 and 50.3 MHz, respectively. ^{1}H–^{13}C COSY spectra were recorded on a Varian UNITY-400 spectrometer and performed using the standard sequence;[5)] 32 transients were accumulated for 128 values of evolution time. The ^{13}C NMR spectral width was 15043 Hz with an acquisition time of 0.068 s and a delay of 1.000 s. The ^{1}H NMR spectral width was 2859 Hz, and 256×2048 data points were sampled. ^{1}H and ^{13}C NMR chemical shifts were referred to the more shielded peak of the solvent, and then converted to the values from TMS by taking 1.79 or 1.75 for δ_H of THF or THF-d_8, 26.40, 25.40, or 37.00 ppm for δ_C of THF, THF-d_8, or HMPA, respectively.

Results and Discussion

^{1}H and ^{13}C NMR Chemical Shifts and Structures of the Adducts. Pyridine and substituted pyridines reacted with butyllithium and produced their adducts. The ^{1}H and ^{13}C NMR chemical shifts of the adducts are given in Tables 1 and 2. In the case of 2,2′-bipyridine, each ring has a reaction site. Therefore, 2,2′-bipyridine reacted with one or two molar amounts of butyllithium to produce **2** or **8**, respectively. However, 2,3′-bipyridine produced only **3**, and did not react with two molar amounts of butyllithium.

Fraenkel and Cooper reported that 20% of the negative charge in **1** is located at C_3 and C_5, and that the remainder is associated with either nitrogen or the N–Li bond.[2a)] Konishi et al. reported that δ_C of **1** is linearly correlated with the total calculated electron densities

Table 1. ^{1}H NMR Chemical Shifts of the Adducts in ppm in THF at 200 MHz

	H(2)	H(3)	H(4)	H(5)	H(6)	H(3′)	H(4′)	H(5′)	H(6′)	$(CH_2)_2$[a)]	CH_3	CH_2[b,c)]
1[d)]	3.53	4.22	5.74	4.38	6.57	—	—	—	—	1.23	0.86	2.00 0.77
2*E*[d)]	3.72[c)]	4.08[c)]	5.82	4.45	—	4.33	5.65	4.29	6.72	1.23	0.89	1.58 1.10
2*Z*[d)]	3.54[c)]	4.04[c)]	5.82	4.57	—	4.19	5.65	4.29	6.72	1.23	0.89	f)
3	e)	4.50	6.26	—	7.83	6.91	7.21	6.45	8.12	1.31	0.86	f)
						H(*o*)	H(*m*)	H(*p*)				
4	3.26	4.21	5.93	4.89	—	7.69	7.0 — 7.25			1.32	0.91	f)
5	3.79	4.46	6.41	—	7.37	6.98	6.87	6.36		1.32	0.90	1.61 1.19
6	e)	4.57	—	4.88	6.85	7.48	7.19	7.07		1.34	0.95	f)
7[c)]	4.51	—	6.56	4.56	6.99	7.22	7.42	6.59		1.32	0.90	f)
8A[d)]	3.43[c)]	3.91	5.84	5.22	—	—	—	—	—	1.32	0.89	1.72 1.51
8B[d)]	3.35[c)]	3.91	5.84	5.16	—	—	—	—	—	1.32	0.89	1.82 1.18

a) Center peak of complex multiplet. b) Methylene protons at the carbon bonded to C_2. c) Measured at 400 MHz. d) In THF-d_8. e) A resonance is obscured by the THF. f) Not observed.

Table 2. ^{13}C NMR Chemical Shifts of the Adducts in ppm at 50.3 MHz

	Solv.	C(2)	C(3)	C(4)	C(5)	C(6)	C(2′)	C(3′)	C(4′)	C(5′)	C(6′)	$(CH_2)_3$			CH_3
1	THF	57.16	98.11	126.29	91.05	150.03	—	—	—	—	—	34.68	28.44	24.43	14.98
	HMPA	57.99	92.02	126.91	85.36	151.25	—	—	—	—	—	36.54	28.53	24.08	15.00
2*E*	THF	58.31	97.04	127.68	86.78	168.26	170.57	106.33	124.35	89.92	148.65	37.49	26.22	24.87	15.97
2*Z*	THF	59.15	97.20	127.68	87.37	168.26	170.57	107.79	124.55	90.85	148.88	39.81	28.44	24.46	15.97
3	THF	34.87	101.75	139.06	103.89	146.30	162.21	113.91	134.99	114.50	149.16	38.99	28.38	24.30	14.98
							C(*i*)	C(*o*)	C(*m*)	C(*p*)					
4	THF	57.81	97.16	126.69	88.31	156.80	147.22	128.20	127.48	126.02		34.45	28.37	24.36	15.01
	HMPA	58.80	90.96	127.37	83.45	155.35	146.40	125.79	125.55	123.58		36.10	28.11	23.28	14.25
5	THF	58.58	101.24	124.27	99.97	150.59	144.49	117.40	128.45	116.22		38.23	28.62	24.37	15.00
	HMPA	59.05	99.78	124.47	96.32	151.90	144.46	115.17	127.78	112.28		38.89	28.62	23.96	14.91
6	THF	58.10	94.87	144.86	89.79	150.93	137.84	126.32	128.05	125.61		34.53	28.55	24.40	15.01
	HMPA	59.43	88.89	145.96	84.32	152.40	137.73	125.78	127.17	124.11		35.28	28.93	24.12	14.98
7	THF	57.78	97.37	124.00	91.21	151.19	145.10	122.19	128.28	119.29		32.09	29.24	24.64	15.00
	HMPA	57.67	92.22	124.64	88.96	152.30	145.14	120.47	127.50	116.09		31.95	28.83	24.23	14.40
8A	THF	59.25	97.10	129.13	88.59	159.19	—	—	—	—	—	39.94	29.92	24.52	14.89
8B	THF	58.86	97.10	128.53	88.06	159.01	—	—	—	—	—	38.65	29.44	24.44	14.89

on carbons.[4c)] However, the structures of these adducts have not yet been systematically studied.

The aim of this paper is to discuss the structures of these adducts. Figure 1 shows a CH COSY spectrum of **1**. As can be seen in Fig. 1, two methylene hydrogens, which bond to C_α, are nonequivalent (2.00 for H_α and 0.77 ppm for $H_{\alpha'}$). This is ascribed to the presence of a chiral carbon (C_2) in **1**. However, the difference of two δ_H is 1.23, which is quite larger than the generally accepted value of about 0.7.[6)] The coupling constants of two methylene hydrogens, H_α and $H_{\alpha'}$, with H_2 are 10.8 and 4.2 Hz, respectively. This is ascribed to the fact that the conformer given in Fig. 2 is more preferred than other conformers based on the magnitude of the vicinal coupling constants. To ascertain this situation an NOE experiment was carried out. Irradiation of an H_2 signal shows that H_2 is nearer to $H_{\alpha'}$ (2.2% NOE) than is H_α (0.3% NOE). This is consistent with Fig. 2.

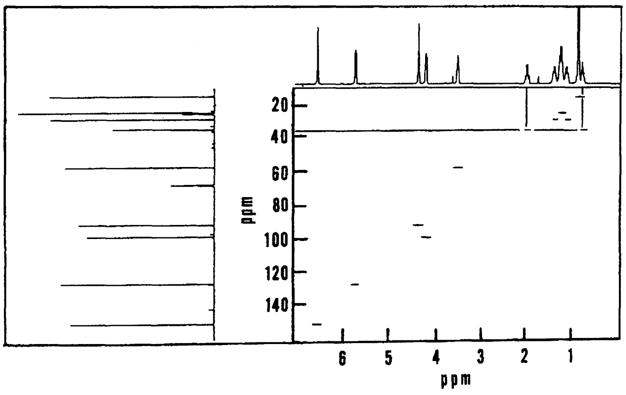


Fig. 1. ^{13}C/^{1}H COSY spectrum of **1** in THF-d_8.

Charge Distributions of the Adducts. The charge distributions of ionic species, such as carbocations or carbanions, are sometimes evaluated from their ^{13}C chemical shifts, compared with those of suitable references.[7,8)] In the present paper, suitable references can be considered to be water-quenched adducts in which a lithium atom in the adduct is substituted with hydrogen, since the structures of the references must be similar to the ionic species concerned. Table 3 shows the ^{13}C chemical shifts of the water-quenched adducts. Hereafter, the quenched adduct of **1** is called **1b** and

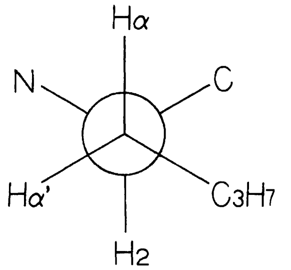


Fig. 2. Most preferable conformation around the C_α–C_2 bond of **1**.

so on. The ^{13}C chemical shifts increase in the order C_5, C_3, C_4, and C_6 in each adduct, except for C_5 of **3**. This fact means that the electron densities on the carbon atoms decrease in this order. The introduced substituents, however, only give a minor effect to the ^{13}C chemical shifts except for those of **3**, although the substituted carbons receive downfield shifts.

The excess negative charge distributions in the adducts are evaluated from a comparison of the corresponding chemical shifts between Tables 2 and 3. Generally, although the ^{13}C shifts of C_2, C_4, and C_6 of the adducts increase, those of C_3 and C_5 decrease, compared with those of the references. The changes are alternant at the position. This tendency is common in a charged conjugated-polyene system. The present system consists of five atoms, including nitrogen at the terminal. Therefore, the positions of N, C_3, and C_5 are electron-rich and those of C_4 and C_6 are electron-deficient. Large increase and decrease of the shifts were observed at C_6 and C_3 in the adducts, respectively. The sum of the chemical shift differences between each adduct and its reference for the ring carbons from C_3 to C_6 is rather small, except for that of **3**. The chemical shift of C_3 of **3** is almost the same as that of **3b**. This is quite different from the others. Another irregular behavior is found in the C_2 shift of **3**, which is 25 ppm upfield from the other C_2. The reason is not clear at present.

The migration of excess charge into the substituent from the adduct skeleton can be understood by comparing the C_p or $C_{5'}$ shift change in the phenyl or pyridyl substituent.[9] The shift changes become large in the order **7**, **5**, and **2**. The total sum of the carbon shift change of the pyridyl group of **2** is more than 40 ppm, which is equal to 0.25 unit of negative charge.[8] That of **3**, however, is about 7.1 ppm, which is equal to about 0.04 unit of charge. Therefore, the substituted position of the pyridyl group produces a big difference in the charge migration. Further, the large charge migrations of **2** and **8** are deeply connected with the restricted rotations around the C–C bonds, which are formed between the substituent and the ring skeleton in the adduct, as described in the next section.

It is well known that a polar solvent tends to prefer solvent-separated ion-pairs than contact ion-pairs. The interaction between the nitrogen and lithium atoms thus tends to be weakened in a polar solvent. Therefore, any excess negative charge is dispersed into the anions in a polar solvent. In fact, the C_3 and C_5 signals are more shielded in HMPA than in THF.

Internal Rotations. The C_6–$C_{2'}$ bond of **2** has a partial double-bond character, as previously described. Evidence concerning this double-bond character is that the ^{13}C signals of **2** appeared as two signals for each carbon, except for the quaternary carbon and C_4. Further, two signals were observed for each H_5, H_3, H_2, and $H_{3'}$ respectively. An expanded ^1H NMR spectrum of H_5 and $H_{3'}$ of **2** is shown in Fig. 3. Irradiation of the $H_{3'a}$ signal did not cause any change in the H_{5a} signal intensity. Irradiation of the $H_{3'b}$ signal, however, gave 7.3% NOE to the H_{5b} signal. This means that the two latter hydrogens are located nearer than the two former hydrogens. It is thus considered that two isomers, *E* and *Z*, were differentiated in the NMR time scale, as shown in Scheme 2. The integrated ratio of the 5a and 5b signals gave $E:Z=2:1$. This observation also applies to **8**. The assignment of the *E* and *Z* isomers of **8**, however, could not be determined because of its symmetric nature. The isomeric abundance of A and B of **8** was 56 : 44. Similar *E*–*Z* isomers have been previously observed in 2-(1-lithioalkyl)-pyridine[3b,10] and 2-(α-lithiobenzyl) pyridine.[11]

To evaluate the interconversion rate between *E* and *Z* of **2** and **8**, temperature-variable experiments were carried out from room temperature to 60°C. In this temperature range, however, since the H_5 signals of **2** and **8** did not show any change, no thermodynamical

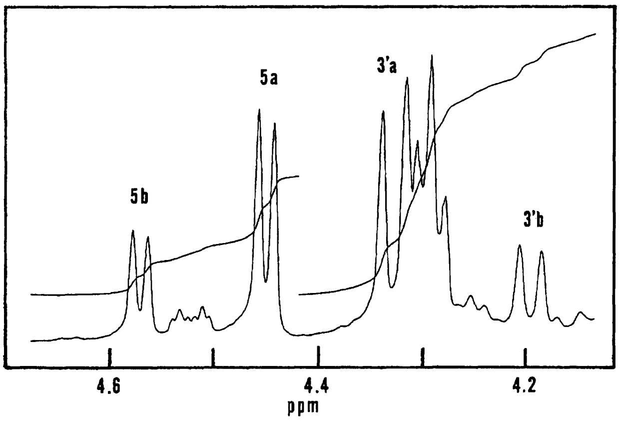
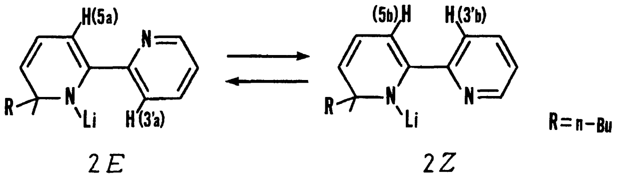


Fig. 3. ^1H NMR spectrum of H_5 and $H_{3'}$ of **2** in THF-d_8 at 400 MHz.



Scheme 2.

Table 3. ^{13}C NMR Chemical Shifts of the Quenched Compounds in ppm in THF at 50.3 MHz

	C(2)	C(3)	C(4)	C(5)	C(6)	C(2′)	C(3′)	C(4′)	C(5′)	C(6′)	$(CH_2)_3$			CH_3
1b	52.48	115.05	124.90	94.10	134.27	—	—	—	—	—	38.03	27.50	23.73	14.59
2b	52.99	118.90	125.04	94.68	141.72	157.32	122.94	136.54	119.72	148.94	37.92	29.96	24.55	14.93
3b	33.63	102.80	126.40	110.08	130.00	159.18	117.09	136.45	119.36	149.80	37.92	28.11	23.96	14.73
						C(*i*)	C(*o*)	C(*m*)	C(*p*)					
4b	53.22	115.59	121.96	94.67	143.97	138.97	126.31	129.01	128.77		37.61	27.43	23.77	14.65
5b	52.61	116.34	124.66	107.04	132.80	140.82	122.71	128.94	123.85		38.62	27.48	23.71	14.59
6b	53.16	111.96	137.06	94.42	135.33	141.93	126.19	128.83	127.41		37.97	27.64	23.33	14.58
7b	53.32	126.68	121.34	96.11	133.20	141.18	124.76	129.07	125.87		38.29	28.09	23.30	14.41
8b	52.89	121.04	124.73	97.80	141.98	—	—	—	—	—	37.73	28.63	23.78	14.54

parameters were obtained. If T_c of **2** is higher than 333 K, $\Delta G_c^{\neq}$ would be larger than 71 kJ mol^{-1}.[12] Since the *E* and *Z* isomers for **3** were not recognized, the C_5–$C_{2'}$ bond of **3** is more labile than is the C_6–$C_{2'}$ bond of **2**. In the cases from **4** to **7** two H_o in each phenyl ring are equivalent at room temperature. Therefore, the phenyl ring rotates freely around the C_i–C_p axis. This situation does not change even at −80°C.

The authors wish to thank Mr. Katsuhiko Kushida (Varian Co., Ltd., Tokyo) for measuring the two-dimensional NMR spectra, and Mr. Tetsuya Tashiro (Nagoya Institute of Technology, Nagoya) for his help with the low-temperature measurements.

References

1) a) A. I. Meyers and R. A. Gabel, *J. Org. Chem.*, **47**, 2633 (1982); b) A. E. Hauck and C. S. Giam, *J. Chem. Soc., Perkin Trans. 1*, **10**, 2227 (1984).

2) a) G. Fraenkel and J. C. Cooper, *Tetrahedron Lett.*, **1968**, 1825; b) C. S. Giam and J. L. Stout, *J. Chem. Soc., Chem. Commun.*, **1969**, 142.

3) a) T. S. Mansour, T. C. Wong, and E. M. Kaiser, *J. Chem. Soc., Perkin Trans. 2*, **12**, 2045 (1985); b) K. Konishi, H. Matsumoto, K. Saito, and K. Takahashi, *Bull. Chem. Soc. Jpn.*, **58**, 2294 (1985); c) K. Konishi and K. Takahashi, *Bull. Chem. Soc. Jpn.*, **56**, 1612 (1983); d) K. Konishi, A. Yoshino, M. Katoh, K. Takahashi, Y. Kawada, T. Sugawara, and H. Iwamura, *Bull. Chem. Soc. Jpn.*, **54**, 3117 (1981); e) K. Takahashi, K. Konishi, M. Ushio, M. Takaki, and R. Asami, *J. Organomet. Chem.*, **50**, 1 (1973).

4) a) G. Fraenkel, A. Chow, and W. R. Winchester, *J. Am. Chem. Soc.*, **112**, 2582 (1990); b) G. Fraenkel, A. Chow, and W. R. Winchester, *J. Am. Chem. Soc.*, **112**, 1382 (1990).

5) A. Bax, *J. Magn. Reson.*, **53**, 517 (1983).

6) For example: a) G. M. Whitesides, D. Holtz, and J. D. Roberts, *J. Am. Chem. Soc.*, **86**, 2628 (1964); b) E. I. Snyder, *J. Am. Chem. Soc.*, **85**, 2624 (1963).

7) J. B. Stothers, "Carbon-13 NMR Spectroscopy," Academic Press, New York (1972).

8) H. Spiesecke and W. Schneider, *Tetrahedron Lett.*, **1961**, 468.

9) E. Buncel, T. K. Venkatachalam, B. Eliasson, and U. Edlund, *J. Am. Chem. Soc.*, **107**, 303 (1985).

10) T. E. Hogen-Esch and W. L. Jenkins, *J. Am. Chem. Soc.*, **103**, 3666 (1981).

11) S. Bank and R. Dorr, *J. Org. Chem.*, **52**, 501 (1987).

12) Estimated from the following equation; $\Delta G_c^{\neq} = aT_c\{9.972+\log(T_c/\Delta\nu_{ab})\}$ where T_c, $\Delta\nu_{ab}$, and a are the coalescence temperature, the chemical-shift difference of two exchanging sites, and a constant of 19.14 J mol^{-1} respectively. The equation was cited from J. Sandström, "Dynamic NMR Spectroscopy, " Academic Press, London (1982), p. 96.