Nucleophilic Addition *versus* Metalation of 4- and 2-Methylpyridine studied by Multinuclear Magnetic Resonance Spectroscopy

Tarek S. Mansour, Tuck C. Wong, and Edwin M. Kaiser*
Department of Chemistry, University of Missouri-Columbia, Columbia, Missouri 65211, U.S.A.

Interaction of 4-methylpyridine with n-butyl-lithium in THF affords a 67:33 mixture of the 1,2-nucleophilic addition product and the laterally metalated derivative of the heterocycle, respectively, as shown by ^{13}C and ^{15}N n.m.r. spectroscopy. While mixtures were also obtained from 4-methylpyridine and methyl- or t-butyl-lithium, only metalation was realized with the lithium salts of di-isopropylamine and 2,2,6,6-tetramethylpiperidine. A regular trend was noted with other 4-alkylpyridines and n-butyl-lithium culminating in exclusive 1,2-addition on 4-n-butylpyridine. The ^{13}C n.m.r. spectrum from 2-methylpyridine and n-butyl-lithium also showed the presence of both addition and metalation derivatives; however, the former material was present only to the extent of 3%.

Alkylpyridines have long been known to react with strong basic reagents to undergo both nucleophilic addition to the aromatic ring to afford σ-complexes as well as lateral metalation of the side-chains to give picolyl-type carbanions. Thus, as early as 1914, Chichibabin and Zeide combined 2-picoline with sodium amide in the presence of methyl iodide to yield 2-amino-6-methylpyridine and its *NN*-dimethyl derivative.[1] In contrast, this same heterocycle was later found to be α-metalated by potassium amide as evidenced by alkylations with higher primary alkyl chlorides.[2] More recent metalations have been effected not only by sodium amide in liquid ammonia[3] but also by organolithium reagents.[4,5] On the other hand, 3-picoline undergoes addition readily with alkyl-lithiums,[6] but can be laterally deprotonated in good yields with lithium di-isopropylamine (LDA)–hexamethylphosphoramide (HMPA) in tetrahydrofuran (THF).[7]

Likewise, 4-picoline has been shown to undergo addition by n-butyl-lithium to afford, after air oxidation, 2-n-butyl-4-methylpyridine.[8] The interaction of this heterocycle with phenyl-lithium seems ambiguous since one set of workers described metalation with this base[9] while another found addition products including 4-methyl-2-phenylpyridine and 4-methyl-2,6-diphenylpyridine.[4] In contrast, 4-picoline is apparently only metalated by sodium amide in liquid ammonia[3] and by methyl-lithium.[4]

As part of a long-range study of the interaction of methylated nitrogenous heterocycles with organoalkali-metals, it was deemed of interest to ascertain which organolithium reagents would add to or metalate 4- and 2-methylpyridine. This paper reports such competitive pathways, conveniently studied by ^{13}C and ^{15}N n.m.r. spectroscopy.

Experimental

Unless otherwise specified, all n.m.r. spectra were recorded on a Nicolet NT-300 multinuclear spectrometer at 20 °C using 5 mm tubes for proton and 20 mm tubes for other nuclei. Usually 16—32 K data points were employed. The ^1H spectra were obtained at 300 MHz using as references the downfield peak of THF at δ 3.58 and the upfield peak at δ 1.73. ^{13}C Spectra were obtained at 75.45 MHz where approximately 50—200 transients were usually accumulated for each spectrum. Either [$^2H_8$]THF or D_2O was employed as the locking material and was placed in a 5 mm tube and fitted coaxially within the 20 mm tube. The downfield peak of THF at δ 67.4 p.p.m. was taken as a reference. Similarly, the ^{15}N spectra were obtained at 30.41 MHz and the shifts were relative to 1.0M-potassium nitrate ($K^{15}NO_3$) in D_2O contained in a 5 mm coaxial tube; D_2O was used as the locking material. ^{13}C Spectra were recorded before and after obtaining ^{15}N spectra to monitor any decomposition and long-term change which may have occurred.

All solvents used in this work were distilled and dried according to literature procedures. Tetrahydrofuran was refluxed for several hours over calcium hydride and distilled from it in a preliminary drying step. It was then stored over sodium–benzophenone ketyl under argon and refluxed for several hours before being distilled from the ketyl, just prior to use. Diethyl ether was distilled from iron(II) sulphate, then distilled over sodium, and finally refluxed and distilled from sodium–benzophenone ketyl under argon. Hexamethylphosphoric amide was refluxed for several hours over barium oxide, then distilled from it, and stored over molecular sieves size 4A in a dark bottle under argon. The methylpyridines were initially fractionally distilled under reduced pressure and stored for several days over potassium carbonate. The pyridines were then refluxed over calcium hydride and distilled from it under reduced pressure and stored over potassium hydroxide pellets at 0 °C under argon. Enough material was purified to conduct all the n.m.r. studies with the same lot thus excluding variations in the purity of the sample. ^1H And ^{13}C n.m.r. data further established the purity of these reagents. Similarly, the amines were distilled and stored over potassium hydroxide pellets under argon.

The determination of the solution concentrations of n-butyl-lithium in hexane (Aldrich), s-butyl-lithium in cyclohexane (Aldrich), t-butyl-lithium in pentane (Alfa), phenyl-lithium in cyclohexane–diethyl ether (70:30) (Aldrich), and methyl-lithium (0.055M chloride) in diethyl ether (Aldrich) was done by titration using the end point orange colour of the dianion of 1,3-diphenylacetone tosylhydrazone in THF as indicator.

The apparatus used to combine the heterocycles and the organolithiums consisted of a three-neck flask, a gas inlet, a gas outlet, and a magnetic stirrer. All glassware was dried in the oven and, after assembling, was flame-dried under vacuum. Argon was then passed into the system. All materials were introduced into the system by syringes previously dried in the oven and flushed with argon.

In a typical procedure 1.85M-n-butyl-lithium (5.5 ml, 10.2 mmol) in hexane was slowly added to a solution of the heterocycle (1.0 ml) in dry THF (7.0 ml) at 0 °C. After 15 min, the argon flow was replaced by a balloon and stirring was continued for an additional 20 min. The anion sample was then transferred from the reaction vessel to the n.m.r. tube by a syringe through a septum fitted on the tube after passing argon into it. This procedure to introduce the sample into the n.m.r. tube was done in all cases except with LDA, lithium tetra-

methylpiperidine (LiTMP), and n-butyl-lithium–tetramethylethylenediamine (TMEDA) complex. In the latter cases, the bases were prepared in the n.m.r. tube from the amines and n-butyl-lithium at 0 °C and were stirred for 30 min at 0 °C. The correct amount of the heterocycle was then added slowly at 0 °C. The concentration of the solutions was measured by determining the mmol of heterocycles per ml of solvent mixtures. Such measurements were performed after the current of argon was stopped and replaced by a balloon. Concentrations for entries reported in Table 2 were as follows: 0.82, 0.89, 0.78, 0.75, 0.80, and 0.78M, respectively.

Results and Discussion

The reaction of 4-methylpyridine (I) with one equivalent of n-butyl-lithium in THF gave a solution whose decoupled ^{13}C spectra (75.4 MHz) revealed the presence of nine signals *in the downfield region* ($\delta > 50$ p.p.m.), two of which appeared upfield from the aromatic region at δ 70.1 and 56.4 p.p.m., respectively, relative to the downfield peak of THF at δ 67.4 p.p.m. The coupled spectrum showed two singlets at δ 145.8 and 132.6 p.p.m. The signal at δ 70.1 p.p.m. was a triplet, and all the remaining peaks were doublets. Upon lowering the temperature to -100 °C, the singlet at δ 132.6 p.p.m. and four peaks subsequently assigned to (II) (Table 1) remained while the other four peaks broadened substantially but reappeared as sharp lines gradually upon raising the temperature.* The nine observed peaks are assignable to two different species, non-symmetrical organometallic (II) and symmetrical compound (III). That the charge resides on nitrogen in the latter compound has been proposed for many years.[3] The ^{13}C n.m.r. results are summarized in Table 1. The relative amounts of the two species were obtained at 20 °C by comparing the peak intensities of the two sharp methine signals at δ 96.6 and 109.3 p.p.m. *in the decoupled spectrum* assigned to the same carbon atom in (II) and (III), respectively.

4-Methylpyridine also reacted with other organolithium reagents as summarized in Table 2. Each entry in Table 2 was obtained by adding the alkyl-lithium to a solution of (I) in the desired solvent system at 0 °C except for the cases of LDA, LiTMP, and Bu^{n}Li–TMEDA where (I) was added to the organolithium. It should be noted that the ratio of (II) to (III) is dependent on the organolithium and the solvent. Thus, MeLi was found to be the least nucleophilic of the organolithiums studied, favouring deprotonation almost exclusively. The stronger bases Bu^{n}Li and Bu^{t}Li favoured both pathways in a variable ratio that reflect to some extent basicity factors. The use of Bu^{s}Li resulted in monoaddition as well as another side-reaction to afford a product which was not characterized. Furthermore, the ^{13}C spectra with LDA and LiTMP showed only the four signals with the same shifts and multiplicities as those assigned to (III) in the n-butyl-lithium reaction. The lithiated intermediate from LDA or LiTMP reacted with MeI at 0 °C to afford 4-ethylpyridine exclusively. Thus, only metalation was realized with these strong nitrogenous bases. In contrast, the lithiated intermediates from (I) and n-butyl-lithium were hydrolysed to give, after air oxidation, recovered (I) and the known 2-n-butyl-4-methylpyridine[8] (>92%). Incidentally, phenyl-lithium and (I) were reported by earlier workers to give a disubstitution product with no evidence of deprotonation at the methyl group.[4] The selectivity of LDA and LiTMP is interesting and not too surprising owing to their non-nucleophilic nature although the less bulky sodium amide effects nucleophilic addition to the pyridine nucleus.[2] Experiments with a deficiency (0.8 equiv.) or excess (1.6 equiv.) of LDA or LiTMP indicated no coupling or addition involving (I) as evidenced by the appearance only of the ^{13}C signals of (II), excess of (I), or excess of amide.[10] This selectivity of LDA and LiTMP is particularly useful in synthetic transformations.[5] Furthermore, in a related work, it has been shown that LDA deprotonates halogenopyridines cleanly with no metal–halogen exchange whereas alkyl-lithiums favour the other pathways.[11]

4-Ethyl-, 4-n-propyl-, and 4-n-butyl-pyridine also reacted with one equivalent of n-butyl-lithium in THF. By comparing the heights of the peaks at δ 96.6 and 109.3 p.p.m., the ratio of addition at position 2 *versus* deprotonation of the 4-alkyl group was found to change from 88:12 for 4-ethylpyridine to 90:10 for 4-n-propylpyridine to virtually 100:0 for 4-n-butylpyridine. The addition is thus substantially greater than the 67:33 ratio observed for 4-methylpyridine, a fact consistent with the inductive effects of the larger alkyl substituents which would have a tendency to destabilize carbanions α to the pyridine ring.

The reaction of Bu^{n}Li with 4-methylpyridine was studied further by varying the amount of base and the medium of the

* At -100 °C, species (III) slowly precipitated causing the ^{13}C peaks to broaden.

Table 1. Carbon-13 parameters of pyridyl anions[a,b]

Species	2-C	3-C	4-C	5-C	6-C	CH_2	CH_3
(I)	149.6	124.3	146.4	124.3	149.6		20.0
	(177.1)	(157.5)	Singlet	(157.5)	(177.1)		
(II)[c]	56.4	96.6	132.6	93.2	148.7		
	(132.5)	(154.8)	Singlet	(158.7)	(152.6)		
(III)	142.7	109.3	145.8	109.3	142.7	70.1	
	(160.4)	(153.3)	Singlet	(153.3)	(160.4)	(158.1)	
(III)[d]	143.6	107.4	147.1	107.4	143.6	63.2	
	(161.1)	(151.9)	Singlet	(151.7)	(161.1)	(152.3)	
(IV)	158.2	122.6	135.6	120.2	149.2		23.8
	Singlet	(159.5)	(161.5)	(161.5)	(179.2)		
(V)[e]	163.9	115.3	130.9	97.0	147.6	55.3	
	Singlet	(155.2)	(152.5)	(162.0)	(162.8)	(149.8)	
(VI)	154.6	98.8	126.4	90.7	55.7		
	Singlet		(151.6)	(155.5)			

[a] From Bu^{n}Li in THF, at 20 °C, relative to THF peak at δ 67.4 p.p.m. [b] Values in parentheses refer to $^1J(^{13}C-^1H)$ in Hz. [c] ^{13}C Shifts varied by *ca.* 1 p.p.m. at -100 °C. [d] In HMPA. [e] Varied by *ca.* 0.5 p.p.m. in THF–TMEDA at -100 °C.

Table 2. Variation of the ratio (II):(III) in THF at 20 °C[a]

Organolithium[b]	Ratio of (II):(III)
CH_3Li	5:95
Bu^{n}Li	67:33
Bu^{t}Li	20:80
LDA	0:100
LiTMP	0:100
Bu^{s}Li	(II) + other product
PhLi	mono- + di-substitution[c]

[a] Ratio calculated by comparing relative intensities of methine signals at δ 96.6 and 109.3 p.p.m., respectively, are $\pm 10\%$ accurate. [b] 1.0 Equivalent. [c] See ref. 4.

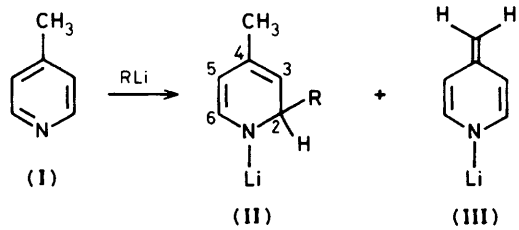


Table 3. Variation of the ratio of (II):(III) with solvent[a]

Solvent	Ratio of (II):(III)
THF	67:33
THF + LiCl	78:22
Et_2O	86:14
HMPA[b]	0:100
THF + TMEDA[c]	85:15
THF[d]	87:13
THF[e]	50:50

[a] Bu^nLi in hexane is the metalating agent; concentrations were 0.7—0.8M. [b] Deprotonation is not complete, *i.e.* some starting material is present. [c] TMEDA:Bu^nLi ratio 1:1. [d] 0.2 Equivalents of Bu^nLi. [e] 2.0 Equivalents of Bu^nLi.

reaction. The results are summarized in Table 3. Nucleophilic addition of Bu^nLi to (I) giving rise to (II) was found to be more favoured in ether and in THF saturated with lithium chloride than in THF. The presence of the donor ligand TMEDA also favoured addition. However, when HMPA was used as a solvent, no addition adduct was observed. With 0.2 equiv. of Bu^nLi in THF, both species (II) and (III) in addition to (I) were present. This observation reasonably removes the doubt that one pathway occurs prior to the other.

The above experiments reflect clearly the effect of aggregation of alkyl-lithiums on reactivity. In the polar aprotic solvent HMPA, Bu^nLi is probably in a deaggregated form. In contrast, this reagent is relatively more aggregated in ether or THF and either an aggregate or a complex in THF–LiCl. Contrary to our expectations with TMEDA, addition was favoured. The formation of the addition product (II) may be attributed to co-ordination of the organolithium aggregate with the ring nitrogen atom thus leading to reaction at the 2-position. The strength of this chelation effect is apparently dependent on the nature of the organolithium. Recently, it was proposed that such lithium complexation prior to metalation of 2,4-dimethylpyridines and -quinolines led initially to metalation of the less acidic 2-methyl group.[12] The regioselectivity observed in metalation of 3-fluoropyridines at position 2 or 4 has been similarly attributed to chelation between n-butyl-lithium and the heterocycle and is supported by theoretical quantum calculations using the CNDO/2 method.[12]* Complementary to this work, it has been shown recently that lithium halides and HMPA exhibit opposite roles on the marked stereoselectivity of carbonation of anions α to a chiral sulphoxide.[14]

The above results point out the importance of the organolithium reagent, the solvent, and the aggregation in reactions with substituted pyridines. It is worth noting that in the closely related *N*-acetylpyridinium salts, 1,2-addition across the C=N bond has been reported with alkenyl or alkynyl organomagnesium reagents.[15] Alkyl organomagnesium[15] and organocadmium reagents undergo both 1,2- and 1,4-addition to these salts in a variable ratio.[16] In contrast, organocopper[17] or organomagnesium reagents with catalytic amounts of copper(I) iodide[18] give exclusively the 4-substituted regioisomer.

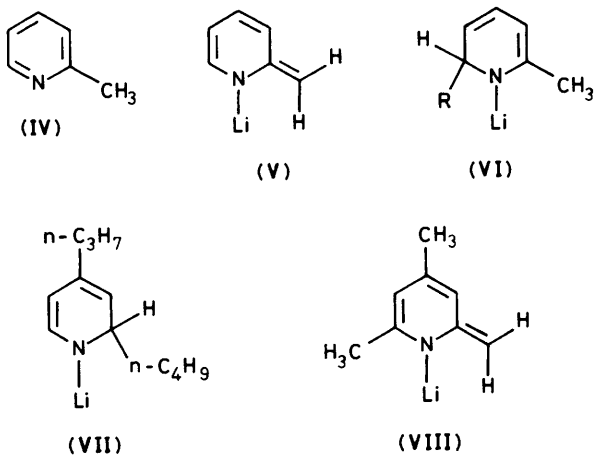
The above results show that only (III) exists in HMPA and thus permit the assignment of the ^1H n.m.r. spectrum of (III) in HMPA. The 300 MHz spectrum of (III) in HMPA shows two doublets at δ 6.58 and 5.27 with *J* coupling 7.0 Hz assignable to H-2, -6 and H-3, -5, respectively. This assignment in HMPA agrees with the assignments reported for the potassium salt of (I) in liquid ammonia[19] and complements ^1H n.m.r. assignments of other pyridyl anions.[20] Presumably, the previous lack of such ^{13}C and ^1H n.m.r. assignments of anions derived from (I) can be ascribed to the failure to recognize the presence of more than one species.

* Beak *et al.*[13] have recently detected a complex between s-butyl-lithium and *NN*-dimethyl-2,4,6-tri-isopropylbenzamide prior to metalation.

Table 4. ^{15}Nitrogen shifts of pyridyl anions[a]

Species	Shift
(I)	−71.0
(II)	−241.1[b]
(III)	−209.5[b]
(V)	−172.7[c]
(VII)	−242.0[c]
(VIII)	−173.9[d]

[a] Relative to 1.0M-$K^{15}NO_3$, negative shifts are upfield from reference. [b] 0.9M. [c] 1.1M. [d] Ref. 20.



The behaviour of 2-methylpyridine (IV) is quite different from that of (I). At 20 °C, the ^{13}C spectrum of 2-lithiomethylpyridine (V) formed from (IV) and n-butyl-lithium in THF showed the anion peaks whose shifts agreed well with those reported by Takahashi.[21] In addition, a set of peaks (Table 1) attributed to an addition adduct (VI) was observed but only to the extent of 3%. In contrast, LDA cleanly but not completely deprotonates the methyl group.[22]

Rather surprisingly, ^{15}N n.m.r. data on systems where nitrogen has some negative charge residing on it are rare. In the case of the reaction of (I) with n-butyl-lithium in THF, the presence of peaks at δ −241.1 and −209.5 p.p.m. relative to 1.0M aqueous $K^{15}NO_3$ were assigned to (II) and (III), respectively, since the related addition reaction of 4-n-propylpyridine and n-butyl-lithium in THF to afford (VII) gave a peak at δ −242.0 p.p.m. relative to the same standard. Furthermore, the ^{15}N spectra of (V) in THF showed a peak at δ −172.7 p.p.m. This chemical shift is very close to that of δ −173.9 p.p.m. previously assigned to (VIII) in [$^2H_{10}$]ether.[23] Table 4 summarizes the ^{15}N data. The variation in the ^{15}N shifts has to be interpreted very cautiously especially since there is no simple relationship between nitrogen shielding and electron density in heteroaromatic systems even if some local correlations are observed.[24]

The above work clearly demonstrates the importance of the choice of organolithium reagents in their reactions with alkylated nitrogenous heterocycles, especially those containing 4-alkyl moieties.

Acknowledgements

A portion of this work was supported by the Petroleum Research Fund, administered by the American Chemical

Society, on grant 11703-AC4. The Nicolet 300 MHz n.m.r. spectrometer was purchased through a grant from the National Science Foundation.

References

1 (*a*) A. E. Chichibabin and O. A. Zeide, *J. Russ. Phys. Chem. Soc.*, 1914, **46**, 1212 (*Chem. Abstr.*, 1915, **9**, 190). For isolation and ^{1}H n.m.r. characterization of some complexes, see (*b*) C. S. Giam and J. L. Stout, *Chem. Commun.*, 1969, 142; (*c*) G. Fraenkel and J. W. Cooper, *J. Am. Chem. Soc.*, 1971, **93**, 7228.
2 A. E. Chichibabin, *Bull. Soc. Chim. Fr.*, 1936, 1607.
3 H. C. Brown and W. A. Murphy, *J. Am. Chem. Soc.*, 1951, **73**, 3308.
4 C. Osuch and R. Levine, *J. Am. Chem. Soc.*, 1956, **78**, 1723 and references cited therein.
5 E. M. Kaiser, *Tetrahedron*, 1983, **39**, 2055.
6 I. Haiduc and H. Gilman, *J. Organomet. Chem.*, 1969, **18**, 5.
7 E. M. Kaiser and J. D. Petty, *Synthesis*, 1975, 705.
8 H. Gilman and H. S. Broadbent, *J. Am. Chem. Soc.*, 1948, **70**, 2809.
9 J. P. Wibaut and J. W. Hey, *Recl. Trav. Chim. Pays-Bas*, 1953, **72**, 513.
10 R. R. Fraser, A. Baignee, M. Bresse, and K. Hata, *Tetrahedron Lett.*, 1982, **23**, 4195.
11 F. Marais and G. Queguiner, *Tetrahedron*, 1983, **39**, 2009.
12 E. M. Kaiser, W. R. Thomas, T. E. Synos, J. R. McClure, T. S. Mansour, J. R. Garlich, and J. E. Chastain, *J. Organomet. Chem.*, 1981, **213**, 405.
13 M. Alaseer, P. Beak, D. Hay, D. J. Kempf, S. Mills, and S. G. Smith, *J. Am. Chem. Soc.*, 1983, **105**, 2080.
14 G. Solladie, R. Zimmermann, and R. Bartsch, *Tetrahedron Lett.*, 1983, **24**, 755.
15 R. Yamaguchi, Y. Nakazono, and M. Kawanisi, *Tetrahedron Lett.*, 1983, **24**, 1801.
16 R. E. Lyle, J. L. Marshall, and D. L. Comins, *Tetrahedron Lett.*, 1977, 1015.
17 K. Akiba, Y. Jseki, and M. Wada, *Tetrahedron Lett.*, 1982, **23**, 429.
18 D. L. Comins and A. H. Abdullah, *J. Org. Chem.*, 1982, **47**, 4315.
19 J. A. Zoltëwicz and L. S. Helmick, *J. Org. Chem.*, 1973, **38**, 658.
20 K. Takahashi, K. Konishi, M. Ushio, M. Takaki, and R. Asami, *J. Organomet. Chem.*, 1973, **50**, 1.
21 (*a*) K. Konishi, A. Yoshino, M. Katoh, H. Matsumoto, K. Takahashi, and H. Iwamura, *Bull. Chem. Soc. Jpn.*, 1981, **54**, 3117; (*b*) H. Matsui, A. Yoshino, T. Yoshida, and K. Takahashi, *ibid.*, 1984, **57**, 1052.
22 4-Methylpyridine has a lower pK_a than 2-methylpyridine: G. Seconi, C. Eaborn, and A. Fischer, *J. Organomet. Chem.*, 1979, **177**, 129.
23 K. Konishi, A. Yoshino, M. Katoh, H. Matsumoto, K. Takahashi, and H. Iwamura, *Chem. Lett.*, 1982, 160.
24 M. Alei, L. O. Morgan, and W. E. Wageman, *Inorg. Chem.*, 1978, **17**, 2288.

Received 25*th February* 1985; *Paper* 5/309