The Reduction of Pyridine to 1,4-Dihydropyridine by Lithiumtetrahydroborate in the Presence of Water

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In the presence of water lithium tetrahydroborate is capable of reducing pyridine to 1,4-dihydropyridine. The product, lithiumtetrakis(pyridine) tetrakis(1,4-hydropyridyl)borate, was isolated and characterized by NMR and IR spectroscopy and single crystal X-ray diffraction. $[Li(py)_4][B(pyH)_4] \cdot 2(1,4\text{-dioxane})$ crystallized in space group $P4_2/n$, $Z = 2$. Similarly, $NaBH_4$ can also reduce pyridine in the presence of water and equivalent amounts of LiCl or $ZnCl_2$.

*Key words:* Reduction of Pyridine, Tetrakis(hydropyridino)borate, X-Ray Structure

Introduction

F. A. Hochstein [1] discovered that $LiAlH_4$ is capable of reducing pyridine and F. Bohlmann showed that 1,4-dihydropyridine is formed [2]. Landsbury *et al.* [3,4,5] observed that "aged" solutions of $LiAlH_4$ in pyridine reduce carbonyl groups much more selectively than $LiAlH_4$ itself. They found that this is due to the formation $LiAl(pyH)_4$ (pyH = 1,4-hydropyridyl) [6]. This is now known as Landsbury reagent, used for many selective reductions [7,8]. Later the formation of $LiAl(pyH)_4$ was studied by NMR methods [9] and in 1999 also the X-ray structure of $[Li(py)_4][Al(pyH)_4]$ was published [10]. In contrast neither $NaBH_4$ nor $LiBH_4$ will reduce pyridine. The alkali metal ions of these tetrahydroborates simply coordinate pyridine as shown by the crystal structure of $LiBH_4 \cdot 3$ pyridine [11].

Results and Discussion

We have shown that pyridine can be used as a solvent to crystallize amine solvates of $LiBH_4$ [11]. This salt crystallizes from 1,4-dioxane as $LiBH_4 \cdot 2(1,4\text{-dioxane})$. However, no crystals suitable for a structure determination could be obtained in contrast to $LiBH_4 1,3$-dioxolane [12]. However, we found that crystals separate from a solution of $LiBH_4$ in pyridine and 1,4-dioxane after some months. Some of them were colorless and proved to be $LiBH_4 3$ py [11]. The others were orange and were shown by X-ray crystallography to be $[Li(py)_4][B(pyH)_4] \cdot 2(1,4\text{-dioxane})$.

Thus, reduction of pyridine has occurred. On the other hand, when $LiBH_4$ was treated with anhydrous pyridine no reduction was observed on heating the mixture for 18 h under reflux. Also, if rigorously dried pyridine and 1,4-dioxane were used, no reduction could be observed but if one equivalent of water was added and the mixture kept under reflux a sudden change in color from colorless to dark red was noted and small amounts of a colorless precipitate formed. After several hours ^{11}B NMR spectroscopy showed the presence of $LiB(pyH)_4$ and $B(pyH)_3$ in solution. The precipitate proved to be boric acid [13]. After removal of all volatile material $B(pyH)_3$ was extracted with hexane and $LiB(pyH)_4$ with THF. The lithium compound is very moisture sensitive. When it was dissolved in moist acetonitrile, boric acid was formed, which precipitated, while 1,4-dihydropyridine could be characterized in solution by its ^{1}H- and ^{13}C-NMR spectra [14]. Thus, in the presence of water the reaction

$$LiBH_4 + 4py \longrightarrow \underset{\mathbf{1}}{LiB(pyH)_4}$$
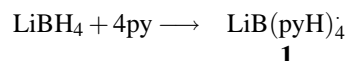
proceeds, and the isolated orange solid, which proved to be $LiB(pyH)_4 \cdot 4$ py, was isolated in 59% yield.

Single crystals of the lithium tetra(4-hydropyridyl)borate **1** were obtained from 1,4-dioxane solution as $\mathbf{1} \cdot 4$ py $\cdot 2$ $(C_4H_8O_2)$ (tetragonal, space group $P4_2/n$). Both the lithium atom as well as the boron atom are located on a site of symmetry $\bar{4}$. Therefore only one pyridine ring and one 1,4-dihydropyridine-1-yl ring are symmetry independent.
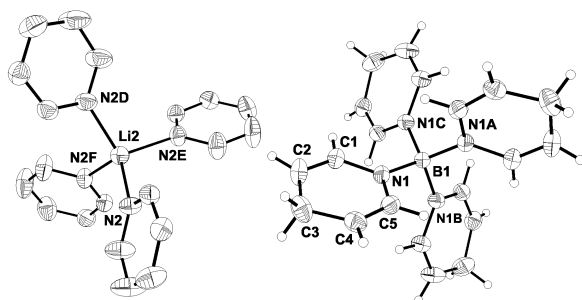
Fig. 1. Molecular structure of **1** · 4 py. Thermal ellipsoids are drawn at 25% probability level. Hydrogen atoms of the pyridine rings and the disordered 1,4-dioxane molecule are not shown for the sake of clarity. Selected atom distances in Å: Li1—N2 2.036(3), B1—N1 1.546(2), N1—C1 1.364(3), N1—C5 1.391(3), C1—C2 1.323(4), C4—C5 1.318(4), C2—C3 1.482(5), C3—C4 1.478(5). Selected bond angles in deg: C1—N1—C5 114.3(2), N1—C1—C2 124.3(3), C1—C2—C3 123.8(3), C2—C3—C4 109.2(3), C3—C4—C5 122.3(3), C4—C5—N1 125.5(3), N1—B1—N1A 107.5(2), N1—B1—N1B 110.48(8), N2—Li2—N2D 105.7(2), N2—Li2—N2E 11.38(8). Symmetry operations used for equivalent atoms: A: $-x+1/2$, $-y+1/2$, z; B: y, $-x+1/2$, $-z+1/2$; C: $-y+1/2$, x, $-z+1/2$; D: $-x+3/2$, $-y+3/2$, z; E: y, $-x+3/2$, $-z+1/2$; F: $-y+3/2$, x, $-z+1/2$.

The structure of the cation and the anion is shown in Fig. 1. The two dioxane molecules are site disordered but are not involved in coordination. Hydrogen atoms at the pyridine and the hydropyridyl moiety were located by difference Fourier analysis.

The crystal structure of **1** · 4 py proves beyond doubt, that reduction of pyridine by the tetrahydroborate has taken place. The average distance between $C_{ortho} - C_{meta}$ of the hydropyridyl ligand is 1.321 Å and lies well in the range of 1.310 Å to 1.323 Å in which C=C double bonds of *cis*-(R)(H)C=C(R)(H) compounds have been recorded [15]. In the pyridine molecules that coordinate to the lithium the average $C_{ortho} - C_{meta}$ distance is 1.362 Å. The average distance between C_{meta} and C_{para} in pyH anion is 1.480 Å. This is 0.127 Å longer than the corresponding distance in the Li-coordinated pyridine. Also the angle of 109.2(3)°between $C_m - C_p - C_m$ in the pyH moiety indicates that C_p is tetra-coordinated. The corresponding angle in the coordinated pyridine is found to be 118.3(3)°. The B—N distance of 1.546(2) Å lies in the same range as found in sodium and potassium tetrakispyrazolylborate (ranging from 1.531(4) to 1.545(5)) [16].

To confirm these results a DFT calculation of the B(pyH)$_4$ anion was carried out with the program pack-

Table 1. Comparison between the calculated bond length (Å) and angles (deg) and the mean values obtained by X-Ray diffraction for B(pyH)$_4^-$.

	calcd.	found
$B - N$	1.569	1.546(2)
$N - C_{ortho}$	1.393	1.378(3)
$C_{ortho} - C_{meta}$	1.345	1.321(4)
$C_{meta} - C_{para}$	1.510	1.480(5)
$C_{ortho} - N - C_{ortho}$	114.1	114.3(2)
$N - C_{ortho} - C_{meta}$	125.1	124.9(3)
$C_{ortho} - C_{meta} - C_{para}$	122.8	123.0(3)
$C_{meta} - C_{para} - C_{meta}$	108.9	109.2(3)

age Gaussian 98 [17]. The theory level B3-LYP [17] in combination with a 6-311++G(d,p) triple-ζ basis set was used. The symmetry of the B(pyH)$_4$ anion was fixed to D_{2d}. The calculated bond lengths and angles are in very good agreement with the experimental data (Table 1).

^{1}H and ^{13}C NMR data of LiB(pyH)$_4$ are consistent with the data obtained for the analogous aluminum compound [9]. The ^{11}B NMR shift of -0.8 ppm is typical for a tetra-coordinated boron species. For the tetrapyrazolylborate anion, for instance, δ was determined as 1.0 [18].

The mechanism of the formation of the tetrakis(hydropyridyl)borate is still obscure. Several attempts to carry out the reduction in dry pyridine failed. When the reaction was performed with half an equivalent of water, the reduction took place but the ^{11}B NMR spectra of the solution indicated the presence of BH$_4^-$. Using two equivalents of water resulted in no change of color, and the ^{11}B NMR spectra of the solution showed only the resonance of BH$_3$·pyridine (δ^{11}B $= -12.5$) and an unknown species with a chemical shift of $\delta = -15.4$ (quartet, 92 Hz, about 10% relative abundance). This species could be BH$_3$OH$^-$, which was first observed by J. A. Gardiner and J. W. Collat [19] as an intermediate in the hydrolysis of BH$_4^-$. It is also known, that the reactivity of BH$_4^-$ can be increased by the use of methanol. In this case the suggestion was made that BH$_3$OMe$^-$ might be responsible for this enhancement [20,21]. Several attempts failed to employ sodium tetrahydroborate instead of the lithium compound for the reduction of pyridine. But it is possible to carry out the reduction with sodium tetrahydoborate if stoichiometric amounts of lithium chloride or zinc chloride are added to the reaction mixture. If substoichiometric amounts are present the rate of reaction is slowed down, so it is doubtful whether the reduction can be carried out with catalytic amounts of metal salts.

Table 2. Crystal data and structure refinement of **1**.

Empirical formula	$C_{48}H_{44}BLiN_8O_4$
Form. Wght.	814.66
Cryst size (mm)	$0.20 \times 0.30 \times 0.30$
Cryst system	tetragonal
Space group	$P4_2/n$
a (Å)	12.62(1)
b (Å)	12.62(1)
c (Å)	14.57(2)
V (Å^3)	2320(4)
Z	2
P(calcd.), (Mg/m^3)	1.166
M[mm^{-1}]	0.075
$F(000)$	856
Index range	$-15 < h < 15$, $-9 < k < 9$, $-18 < l < 18$
2θ (deg) max	55.76
Temp (K)	193(2)
Reflns collected	12884
Reflns unique	2451
Reflns observed (4σ)	1213
R (int)	0.0883
No. variables	184
Weighting scheme^a x/y	0.1484 / 0.0459
GOF	1.033
Final $R1$ (4σ)	0.0786
Final $wR2$	0.2216
Largest.residual.peak (e/Å^3)	0.350

^{a} $w^{-1} = \sigma^2 F_o^2 + (xP)^2 + yP$; $P = (F_o^2 + 2F_c^2)/3$.

In contrast to the aluminum compound LiAl(pyH)$_4$ [9] the boron compound **1** shows an borane-borate equilibrium when dissolved in THF. This is indicated by ^{11}B NMR spectroscopy by a broad signal at $\delta = 25.4$. This result suggests that B(pyH)$_4^-$ is formed only after the reduction by a borane species. The pyridine borane adduct may indeed be an intermediate in the course of reduction of pyridine by LiBH$_4$. It had been shown that pyridine in THF and in the presence of an excess of NaBH$_4$ converts methylchloroformiate Cl-COOMe into N-carbomethoxy-1,4-dihydropyridine which was isolated in 35 – 40% yield. [22]. It is very likely that pyridine is activated by the carbonylation.

Further investigations will be necessary to understand the factors which are responsible for increasing the reducing power of tetrahydroborate in the presence of protic solvents.

Experimental Section

All experiments were performed in an atmosphere of dry nitrogen using Schlenk techniques. Solvents were made anhydrous by standard procedures and were kept in an atmosphere of N$_2$.

Materials: Commercial grade chemicals were pyridine, 1,4-dioxane and LiBH$_4$. Elemental analysis was performed at the microanalytical laboratory of the Department.

Physical Measurements: IR spectra were recorded with a Perkin-Elmer FT 370 instrument using a Nujol suspension except for B(pyH)$_3$. ^{1}H, ^{7}Li, ^{13}C and ^{11}B resonances were determined with a JEOL 400 spectrometer. TMS was used as internal standard for ^{1}H and ^{13}C, while BF$_3$·OEt$_2$ served as external standard for ^{11}B, and an aqueous solution of LiCl (1M) served as external standard for ^{7}Li.

Lithium Tetra(4-hydropyridyl)borate

To 0.512 g (23.5 mmol) of LiBH$_4$, dissolved in 60 ml of pyridine, 0.38 ml (0.38 g; 21 mmol) of water was added. The reaction mixture was stirred for 1 h at ambient temperature and kept at reflux for 12 h. During this time the pale, yellow solution turned dark orange and a white precipitate was formed. After all volatile material was removed *in vacuo*, the remaining solid was treated with hexane (150 ml). 100 ml of THF dissolved LiB(pyH)$_4$ leaving behind some boric acid. After removing THF from the filtrate *in vacuo* the dark red solid was dried *in vacuo*. The powder had the analytical composition LiB(pyH)$_4$. In the presence of moisture LiB(pyH)$_4$ was rapidly hydrolysed to boric acid and 1,4-dihydropyridine.

Yield: 4.73 g of LiB(pyH)$_4$ (59%); m.p. $> 200\ °$C; ^{11}B NMR (d^6-DMSO): $\delta = -0.8$; ^{1}H NMR (d^6-DMSO): $\delta = 3.00$ (m, 8 H, CH_2CH=CH-N), 3.79 (d, $J_{(H,H)} = 7.5$ Hz, 8 H, CH$_2$CH=CH-N), 5.69 (d, $J_{(H,H)} = 7.5$ Hz, 8 H, CH$_2$-CH=CH-N)); ^{13}C NMR (d^6-DMSO): δ 24.9 (CH$_2$), 92.2 (CH$_2$-CH), 134.9 (CHN); ^{7}Li NMR (d^6-DMSO): $\delta-1.1$; IR (nujol-mull): 1683, 1478, 1430, 1261, 1098, 1019, 800, 704 cm^{-1}. C$_{20}$H$_{24}$BLiN$_4$: (338.23): calcd. C, 71.03, H, 7.15, N, 16.57, found: C, 67.18, H, 7.80, N, 13.97.

The yellow hexane phase contained B(pyH)$_3$ (δ^{11}B = 27.5). After removal of the hexane from the solution a yellow oil was obtained, which was not purified any further but was characterized by its NMR spectra. A C$_6$D$_6$ solution of the oil showed the following signals: δ^1H = 2.98 (m, 6H, CH$_2$), 4.56 (m, 6 H, CH$_2$CH), 6.05 (m, 6H, CH=CH-N); – δ^{13}C = 23.1 (CH$_2$), 101.1 (CH$_2$-CH), 130.0 (CH=CH-N); δ^{11}B = 25.4. – IR (cm^{-1}, recorded as oil): 3055 (m), 2931 (St), 2814 (st), 1683 (St), 1626 (st), 1444 (broad), 1353 (st), 1323 (st), 1264 (st), 1206 (st), 1032 (m), 986 (st), 804 (st), 725 (m), 658 (m), 514 (st), 499 (st).

Crystallography

Data collection was performed with Mo-K$_\alpha$ radiation employing a graphite monochromator at 193 K on a Siemens P4 diffractometer equipped with a low temperature device LT2 and a CCD area detector. Crystals were transferred from the

cold mother liquor into precooled perfluoroether oil. The selected crystal was mounted on a glass fiber and rapidly put on the goniometer head cooled with a cold stream of N_2. The size of the unit cell was calculated from data on 15 frames each and at 5 different settings by changing φ by $0.3°$ between each frame. Data were collected in the hemisphere mode of the program SMART [23] with 10 s/frame exposure time. Two different χ settings were used and φ changed by $0.3°$ per frame. Data on a total of 1290 frames were reduced with the program SAINT [24]. The structure was solved by direct methods (SHELX97) [25]. Non-hydrogen atoms were refined anisotropically. The hydrogen atoms bound to the 1,4-dihydropyridyl-1-yl ring were revealed in the Fourier difference map and were refined freely with isotropic thermal

parameters. The hydrogen atoms at the pyridine ring were put into calculated positions and refined using a riding model. The center of the dioxane molecule lies on a fourfold screw axis 4_2 and is, therefore, site disordered. The carbon atoms of the dioxane in split positions refined to SOF = 58:42. No hydrogen atoms were added to these carbon atoms. Table 2 shows data related to crystallography and structure solution.

Supplementary data related to the reported crystal structure determination are deposited with the Cambridge Cystallographic Data Centre. These may obtained free of charge at http://www.ccdc.cam.ac.uk.conts/retrieving.html or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK by quoting the authors, Journal and CCDC 202774, E-mail: deposit@ccdc.cam.ac.uk.

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