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# SPECIFIC AND SELECTIVE REDUCTION OF AROMATIC NITROGEN HETEROCYCLES WITH THE BIS-PYRIDINE COMPLEXES OF BIS(1,4-DIHYDRO-1-PYRIDYL)ZINC AND BIS(1,4-DIHYDRO-1-PYRIDYL)MAGNESIUM

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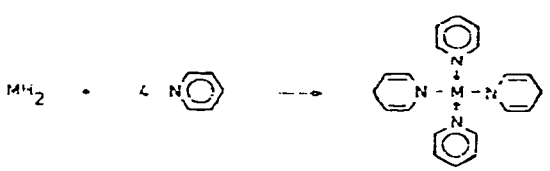
## Summary

Aromatic nitrogen heterocycles, e.g. quinoline, 2,2′-bipyridyl and 1,10-phenanthroline, are reduced in a uniquely specific and selective way by the bis-pyridine complexes of bis(1,4-dihydro-1-pyridyl)zinc and bis(1,4-dihydro-1-pyridyl)magnesium. The reactions occur by hydrogen transfer from the metal-bound 1,4-dihydropyridyl moieties to the substrates and yield zinc or magnesium salts of the 1,4-dihydroazaaromatic derivatives. Upon hydrolysis, the 1,4-dihydroazaaromatic compounds are liberated from the metal ions. The isolation and purification of several of the (novel) reduced compounds, e.g. 1,4-dihydroquinoline and 1,4-dihydro-1,10-phenanthroline, are described.

## Introduction

In an earlier paper [1] we described the preparation and characterization of stable pyridine complexes of bis(1,4-dihydro-1-pyridyl)zinc and bis-(1,4-dihydro-1-pyridyl)magnesium. These compounds were synthesized from pyridine and an active form of the corresponding metal hydride (eq. 1).




(1)

M = Zn : complex E *
M = Mg : complex D

* This notation is identical to that used in ref. 1 and ref. 2.

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One of the most striking properties of the complexes B and D is their selective reducing ability. The scope and the (stereo)selectivity of the reduction of carbonyl-containing substrates have been described previously [2], and it was noted that the bis(1,4-dihydro-1-pyridyl)metal complexes might provide convenient and stable starting materials for the generation of the unstable 1,4-dihydropyridine, and are potential reagents for the preparation of (novel) *N*-acyl-1,4-dihydropyridines. Hydrolysis of the complexes B and D yields, apart from the metal hydroxide, a mixture of equimolar amounts of pyridine and 1,4-dihydropyridine. This method of preparation of 1,4-dihydropyridine has the important advantage over those reported [3—5] that 1,4-dihydropyridine is the only reduced pyridine formed. In one of the attempts to isolate pure 1,4-dihydropyridine we tried to replace the two pyridine molecules in the parent compounds by non-volatile bidentate nitrogen ligands, e.g. 2,2'-bipyridyl and 1,10-phenanthroline, in order to obtain an easily separable mixture of 1,4-dihydropyridine and the bidentate ligand after hydrolysis, but the ligands used appeared to be reduced specifically to their 1,4-dihydro derivatives.

The very selective and specific reduction of nitrogen-containing heterocyclic compounds by the pyridine complexes of bis(1,4-dihydro-1-pyridyl)zinc and bis(1,4-dihydro-1-pyridyl)magnesium is the main subject of this paper. In addition the reductions of other compounds containing carbon—nitrogen multiple bonds, viz. nitriles and pyridinium salts, are described.

## Results and discussion

### *Reduction of aromatic nitrogen heterocycles*

A number of heterocyclic compounds (L) containing a pyridine ring system are reduced by the pyridine complexes of bis(1,4-dihydro-1-pyridyl)zinc and bis(1,4-dihydro-1-pyridyl)magnesium. These reduction reactions proceed according to eq. 2.

$$M(pyH)_2 \cdot 2\ py + (x + 2)L \rightarrow M(LH)_2 \cdot xL + 4\ py \qquad (2)$$

(M = Zn or Mg, L = nitrogen-containing heterocyclic compound, $x$ = 0, 1 or 2, depending on L)

The composition and colour of the complexes $M(LH)_2 \cdot xL$ obtained are given in Table 1. All the reductions proceed in a highly specific and selective way:

(i) The pyridine ring of the substrate L is reduced to one type of dihydropyridine exclusively. No isomers are formed, and no further reduction of the dihydropyridine ring takes place.

(ii) In the case of substrates containing more than one pyridine ring, e.g. 1,10-phenanthroline and the bipyridyls, only one of these rings is reduced.

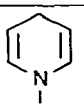
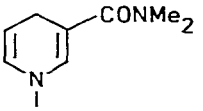
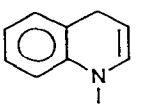
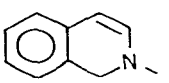
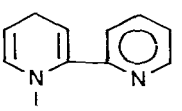
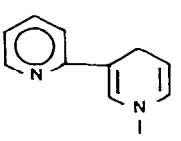
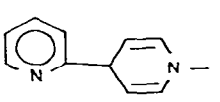
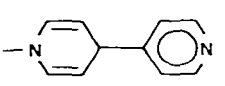
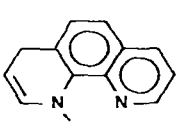
(iii) The substrates are generally reduced to the 1,4-dihydro derivatives. Only in the case of isoquinoline, where such a reduction would disrupt the aromaticity of both rings, does 1,2-reduction occur.

(iv) Hydrolysis of the complexes $M(LH)_2 \cdot xL$ yields L, $LH_2$ and the metal hydroxide. This procedure allows isolation of a mixture of the substrate and its 1,4-dihydro derivative with little or no complication from side reactions. The

*(Continued on p. 160)*

TABLE 1

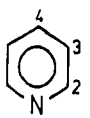
COMPOSITION AND COLOUR OF THE COMPLEXES $M(LH)_2 \cdot xL$

| Substrate | M | $x$ | Structure of LH | Colour of $M(LH)_2 \cdot xL$ |
|---|---|---|---|---|
| Pyridine | Zn<br>Mg | |  | yellow<br>yellow [a] |
| *N,N*-Dimethylnicotinamide | Zn<br>Mg | 0 |  | yellow |
| Quinoline | Zn<br>Mg | 2 |  | orange |
| Isoquinoline | Zn<br>Mg | 2 |  | orange-red |
| 2,2′-Bipyridyl | Zn [b]<br>Mg | 2 |  | brown |
| 2,3′-Bipyridyl | Zn<br>Mg | 2 |  | red |
| 2,4′-Bipyridyl | Zn<br>Mg | 2 |  | deep-brown |
| 4,4′-Bipyridyl | Zn<br>Mg | 2 |  | purple |
| 1,10-Phenanthroline | Zn<br>Mg | 1 |  | deep purple |

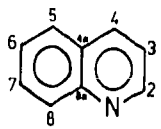
[a] The product $(pyH)_2Mg \cdot 2py$ is sometimes green. [b] The product could not be isolated pure.

TABLE 2

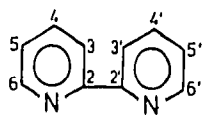
$^1$H NMR CHEMICAL SHIFTS [a] (in ppm relative to TMS) OF THE UNREDUCED AROMATIC NITROGEN HETEROCYCLES



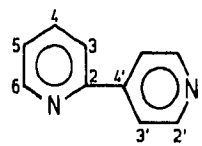

(I)



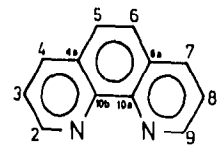

(III)




(V)




(VII)



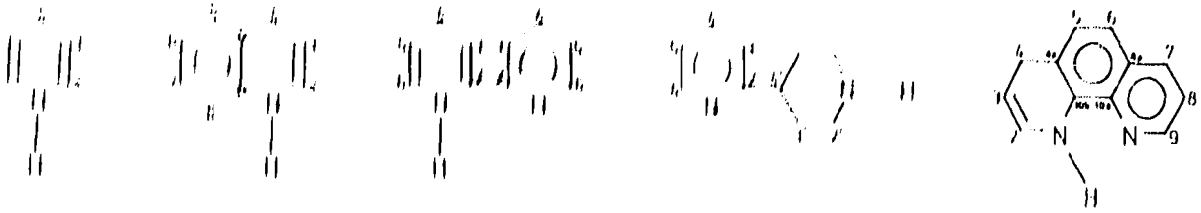

(IX)

| Compound | | H(1), H(2) | H(3) | H(4) | H(5) | H(6) | H(7) | H(8), H(2') | H(9), H(3') | H(4') | H(5') | H(6') | Reference |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Pyridine | (I) | 8.57 | 7.20 | 7.58 | 7.20 | 8.57 | | | | | | | |
| *N,N*-Dimethylnicotinamide | (II) | 8.67 | | 7.76 | 7.33 | 8.62 | | | | | | | |
| Quinoline [b] | (III) | 8.81 | 7.27 | 8.00 | 7.69 | 7.44 | 7.62 | 8.06 | | | | | 6 |
| Isoquinoline [b] | (IV) | 9.15 | 8.45 | 7.50 | 7.71 | 7.57 | 7.50 | 7.87 | | | | | 7 |
| 2,2'-Bipyridyl | (V) | | 8.40 | 7.74 | 7.23 | 8.65 | | | 8.40 | 7.74 | 7.23 | 8.65 | |
| 2,3'-Bipyridyl | (VI) | | 7.6 | 7.6 | 7.2 | 8.6 | | 9.24 | | 8.10 | 7.2 | 8.6 | |
| 2,4'-Bipyridyl | (VII) | | 7.73 | 7.26 | 7.73 | 8.7 | | 8.7 | 7.85 | | 7.85 | 8.7 | |
| 4,4'-Bipyridyl | (VIII) | 8.70 | 7.49 | | 7.49 | 8.70 | | 8.70 | 7.49 | | 7.49 | 8.70 | |
| 1,10-Phenanthroline | (IX) | 9.14 | 7.52 | 8.10 | 7.62 | 7.62 | 8.10 | 7.52 | 9.14 | | | | |

[a] Solutions in $CDCl_3$. [b] Solutions in $CCl_4$.

TABLE 4

PROTON CHEMICAL SHIFTS[a] (in ppm relative to TMS) OF THE REDUCED AROMATIC NITROGEN HETEROCYCLES



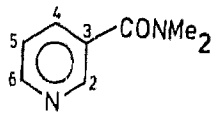
(III) (IIIIII) (IIV) (IIVII) (IIX)

| Compound | | H(1), H(1') | H(3) | H(4) | H(5) | H(6) | H(7) | H(8) | H(8), H(2') | H(9), H(3') | H(4') | H(5') | H(6') |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1,4-Dihydropyridine | III | 6.4[b] | 6.80 | 4.80 | 5.93 | 4.90 | 6.80 | | | | | | |
| 1,4-Dihydro-2,6-dimethyl-3,5-diethoxycarbonylpyridine | IIII | 6.6[b] | 6.61 | | 5.08 | 4.48 | 6.81 | | | | | | |
| 1,4-Dihydroquinoline | IIIII | 6.7[b] | 6.98 | 4.13 | 5.40 | 6.35 | (6.6 | | 7.1) | | | | |
| 1,4-Dihydroisoquinoline | IIII | 4.1[b] | 6.8[b] | 6.90 | 6.36 | (6.7 | | | 7.0) | | | | |
| 1,4-Dihydro-4-phenylpyridine | IV | 6.7[b] | | 6.10 | 5.08 | 4.39 | 6.09 | | | 7.40 | 7.25 | 6.96 | 8.34 |
| 1,4-Dihydro-4-(1-naphthyl)pyridine | IVI | 6.7[b] | | 6.08 | 7.3 | 7.3 | 8.38 | | 6.84 | | 3.28 | 4.64 | 5.98 |
| 1,4-Dihydro-4-(2-naphthyl)pyridine | IVII | 6.7[b] | | 6.11 | 6.90 | 7.63 | 8.50 | | 6.11 | 4.53 | 4.50 | 4.53 | 6.11 |
| 1,4-Dihydro-4-(2-pyridyl)pyridine | IVIII | 5.8[b] | 6.84 | 4.81 | 4.30 | 4.81 | 6.84 | | 8.51 | 7.23 | | 7.23 | 8.51 |
| 1,4-Dihydro-4-(2-hydroxyphenyl)pyridine | IVIIII | 7.1[b] | 6.80 | 4.50 | 5.71 | 7.03[c] | 7.06[c] | 7.88 | 7.17 | 8.61 | | | |

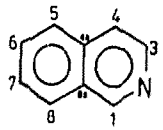
[a] Reference was HMDS. [b] Broad singlet. [c] Assignments may be reversed.

TABLE 4

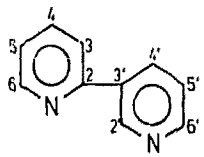
$^{13}$C NMR CHEMICAL SHIFTS [a] (in ppm relative to TMS) OF THE UNREDUCED AROMATIC NITROGEN HETEROCYCLES



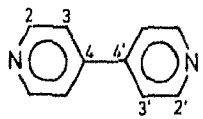

(II)



(IV)



(VI)

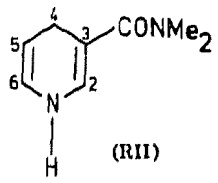


(VIII)

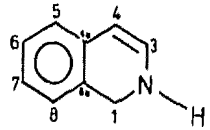
| Compound | | C(1), C(2) | C(3) | C(4) | C(4a), C(6a) | C(5) | C(6) | C(7), C(2′) | C(8), C(3′) | C(8a), C(4′) | C(9), C(5′) | C(10a–b), C(6′) | Reference |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Pyridine | (I) | 148.9 | 123.2 | 135.5 | | 123.2 | 148.9 | | | | | | |
| *N*,*N*-Dimethylnicotinamide | (II) | 146.8 | 131.0 | 133.5 | | 122.0 | 149.2 | | | | | | |
| Quinoline | (III) | 149.8 | 120.5 | 135.4 | 127.7 | 127.2 | 125.9 | 128.9 | 128.9 | 147.8 | | | 8 |
| Isoquinoline | (IV) | 151.9 | 142.4 | 119.7 | 135.0 | 125.8 | 129.6 | 126.5 | 126.9 | 128.0 | | | 8 |
| 2,2′-Bipyridyl | (V) | 155.7 | 120.6 | 136.4 | | 123.2 | 148.7 | 155.7 | 120.6 | 136.4 | 123.2 | 148.7 | |
| 2,3′-Bipyridyl | (VI) | 154.1 | 119.9 | 136.4 | | 122.9 | 149.4 | 147.7 | 134.2 | 133.6 | 122.3 | 149.4 | |
| 2,4′-Bipyridyl | (VII) | 153.6 | 120.0 | 136.2 | | 123.0 | 149.3 | 149.6 | 120.2 | 145.5 | 120.2 | 149.6 | |
| 4,4′-Bipyridyl | (VIII) | 150.1 | 120.8 | 144.8 | | 120.8 | 150.1 | 150.1 | 120.8 | 144.8 | 120.8 | 150.1 | |
| 1,10-Phenanthroline | (IX) | 149.4 | 122.2 | 135.1 | 127.8 | 125.7 | 125.7 | 135.1 | 122.2 | | 149.4 | 145.4 | 9 |

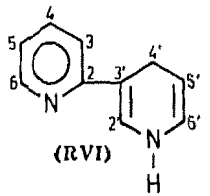
[a] Solutions in $CDCl_3$.

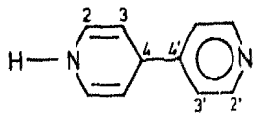
TABLE 5. $^{13}C$ NMR CHEMICAL SHIFTS [a] (in ppm relative to TMS) OF THE REDUCED AROMATIC NITROGEN HETEROCYCLES



(RII)


(RIV)


(RVI)


(RVIII)

| Compound | | C(1), C(2) | C(3) | C(4) | C(4a) | C(5) | C(6) | C(6a) | C(7), C(2′) | C(8), C(3′) | C(8a), C(4′) | C(9), C(5′) | C(10a), C(6′) | C(10b) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1,4-Dihydropyridine | (RI) | 126.9 | 96.1 | 21.8 | | 96.1 | 126.9 | | | | | | | |
| 1,4-Dihydro-*N*,*N*-dimethylnicotinamide | (RII) | 132.0 | 101.0 | 23.5 | | 99.2 | 125.4 | | | | | | | |
| 1,4-Dihydroquinoline | (RIII) | 126.5 | 95.3 | 26.2 | 119.0 | 113.6 | 120.7 | | 126.2 | 129.1 | 139.9 | | | |
| 1,2-Dihydroisoquinoline | (RIV) | 45.2 | [b] | 98.7 | [b] | [b] | [b] | | [b] | [b] | [b] | | | |
| 1,4-Dihydro-2,2′-bipyridyl | (RV) | 136.3 | 96.3 [c] | 23.3 | | 95.2 [c] | 127.5 | | 151.5 | 117.8 | 135.5 | 121.7 | 147.5 | |
| 1′,4′-Dihydro-2,3′-bipyridyl | (RVI) | 157.0 | 118.8 [c] | 135.7 | | 125.0 [c] | 148.1 | | 127.9 [c] | 104.9 | 23.6 | 99.4 | 116.1 [c] | |
| 1′,4′-Dihydro-2,4′-bipyridyl | (RVII) | 166.7 | 120.1 | 136.1 | | 122.0 | 147.9 | | 125.8 | 98.5 | 41.3 | 98.5 | 125.8 | |
| 1,4-Dihydro-4,4′-bipyridyl | (RVIII) | 126.3 | 99.4 | 38.6 | | 99.4 | 126.3 | | 149.6 | 122.6 | 157.5 | 122.6 | 149.6 | |
| 1,4-Dihydro-1,10-phenanthroline | (RIX) | 117.8 | 95.9 | 27.1 | 115.7 | 128.3 | 126.5 | 126.8 | 135.5 | 120.4 | | 147.5 | 136.7 | 135.9 |

[a] Solutions in $CDCl_3$. [b] No definite assignments of the resonances could be made; the signals lie between 122.1 and 135.2 ppm. [c] Assignments may be reversed.

reduced compounds $LH_2$, were identified by NMR spectroscopy. The $^1H$ and $^{13}C$ NMR chemical shifts of the reduced and unreduced aromatic heterocycles are given in Tables 2—5.

The composition of the very air- and moisture-sensitive complexes $M(LH)_2 \cdot xL$ was determined by $^1H$ NMR spectroscopy in HMPT, hydrolysis experiments and elemental analysis. HMPT appeared to be the only polar organic solvent in which all complexes dissolved without reaction. In the case of L = 4,4′-bipyridyl, the deep blue HMPT solutions exhibited paramagnetism, precluding $^1H$ NMR spectroscopy. All IR spectra of zinc and magnesium compounds containing reduced heterocyclic rings show absorptions in the 1500—1700 $cm^{-1}$ region, which can be assigned to the C=C or C=N stretching modes [10].

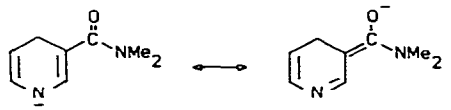
Although in all the reductions both the zinc complex B and the magnesium complex D give similar products, complex D is the preferred reagent because it reacts much faster and the final complexes are more stable. The reduction of 2,2′-bipyridyl by complex B is not complete and the reaction intermediates decompose in solution with separation of zinc metal.

*Nature of complexes $M(LH)_2 \cdot xL$*

When L is a monodentate nitrogen ligand, e.g. pyridine, quinoline or isoquinoline, the metal/nitrogen ratio in the complexes $M(LH)_2 \cdot xL$ is 1/4. In these cases the metal ion is presumably surrounded by four nitrogen atoms in a tetrahedral arrangement. It is noteworthy that in the complexes obtained from the reactions of either complex B or complex D with monodentate aromatic heterocycles, the coordinated pyridine molecules are replaced by quinoline or isoquinoline. The $\sigma$-donor strength of these ligands is lower than that of pyridine, but because of the potentially greater delocalisation of charge, quinoline and isoquinoline are stronger $\pi$-acceptors than pyridine. Apparently the latter factor predominates. This can only be explained in terms of charge transfer between the reduced and unreduced ligands.

The number of unreduced bidentate ligands ($x$) in the complexes $M(LH)_2 \cdot xL$ is not zero, e.g. $x = 1$ for L = 1,10-phenanthroline (M/N 1/6) and $x = 2$ for L = 2,2′-bipyridyl or 4,4′-bipyridyl (M/N 1/8). In these cases it is very unlikely that all the nitrogen atoms are coordinated to the central metal atom. The presence of monodentate 2,2′-bipyridyl or 4,4′-bipyridyl ligands is also not very likely. Therefore, other factors in addition to direct M—L coordination must be responsible for the bonding of the unreduced ligands. Presumably we are dealing with charge-transfer interactions, in which LH serves as a charge-donor and L as a charge-acceptor. Complexes between dihydropyridines and $\pi$-acceptors are known [11—13]. The stoichiometry of such charge-transfer complexes strongly depends on the nature of the charge-donor and charge-acceptor molecule. A characteristic feature of charge-transfer complexes is their intense colour, different from those of the charge-donor and charge-acceptor. Very intensive dark colours are, indeed, observed for the complexes $M(LH)_2 \cdot xL$, in which L is a bidentate nitrogen ligand. Another indication of the suggested type of bonding of the unreduced heterocycles in the complexes is found in the reactions of $M(LH)_2 \cdot xL$ (L = 1,10-phenanthroline) with diethylzinc. This Lewis acid is unable to remove the unreduced ligands from the complexes in which the metal atoms have already reached coordination saturation by the reduced heterocycles only.

The reaction between complex B or complex D and *N*,*N*-dimethylnicotineamide (Nic) yields $M(NicH)_2$. In this case the negative charge on the pyridine nitrogen atom in the anionic form of reduced Nic can be delocalized by an intramolecular charge-transfer:



$M(NicH)_2$, an insoluble solid, is presumably a coordination polymer in which the anion acts as a bidentate ligand. In this way the metal ion has reached the favoured four coordination, and the charge on the reduced substrate is delocalized, and binding of unreduced Nic would therefore not enhance the stability of the complex.

*Selectivity and specificity of the reduction reactions*

All the reductions of azaaromatic compounds by the complexes B and D proceed in a highly selective and specific way. When for example 1,10-phenanthroline, 2,2′-bipyridyl or 4,4′-bipyridyl is used as a substrate, only one of the nitrogen-containing rings is reduced (selectivity) and only 1,4-reduction occurs (specificity). The selectivity of the reductions is even more pronounced when asymmetric bipyridyls are used as substrates; 2,3′-bipyridyl and 2,4′-bipyridyl are both reduced exclusively to their 1′,4′-dihydro derivative.

The first step in the reduction process is probably a ligand-exchange (eq. 3),

$$(pyH)_2M \cdot 2\,py + nL \rightarrow (pyH)_2M \cdot nL + 2\,py \qquad (3)$$

($n$ = 1 for a bidentate nitrogen ligand, $n$ = 2 for a monodentate nitrogen ligand, M = Zn or Mg)

which brings the substrate into the coordination sphere of the metal ion. In an intra- or inter-molecular reaction the coordinated ligand is reduced by a metal-bound 1,4-dihydropyridyl group (eqs. 4 and 5).

$$(pyH)_2M \cdot nL \rightarrow [(LH)(pyH)M(n-1)L] + py \qquad (4)$$

$$[(LH)(pyH)M(n-1)L] \xrightarrow{L} (LH)_2M \cdot xL + py \qquad (5)$$

($x$ = 0, 1 or 2 depending on L)

The proposed reaction pathway (complexation followed by reduction of the ligand) is based on the mechanism found for the reduction of deuterated pyridine by the complexes B and D [1]. In the latter case hydride-transfer occurs from the 4-position of the metal-bound 1,4-dihydropyridyl group to the 4-position of the deuterated pyridine molecule, as shown by dynamic $^1H$ NMR spectroscopy. A similar hydride-transfer reaction is thought to occur in the reduction of the aromatic nitrogen heterocycles. During the reductions of the aromatic compounds ESR signals are observed; these signals come from the radical anions of the ligand involved, but differ from those of the same radical anions in the absence of metal ions [14]. We must therefore conclude that the reduction reactions proceed by an initial one-electron transfer in the coordination

sphere of the metal. The final metal complexes contain two equivalents of the reduced ligand and $x$ equivalents of the unreduced ligand, necessary to form the favoured charge-transfer complex.

The driving force for these reductions is, of course, the gain in the Gibbs energy. The azaaromatic compounds used have lower first and second reduction potentials than pyridine [14—16] and can therefore be reduced by an active form of reduced pyridine as present in the complexes B and D.

Obviously, reduction of pyridine by $ZnH_2$ and $MgH_2$ and the reductions of the azaaromatic compounds by complex B and complex D yield the thermodynamically favoured dihydropyridines. Theoretically, five isomeric dihydropyridines are capable of existence in addition to two possible bicyclic structures. Most of the known dihydropyridines, however, have either the 1,4- or 1,2-dihydro structure, except in a few cases where steric hindrance or the presence of certain stabilizing groups lead to 2,3- or 3,4-dihydropyridines [17]. A detailed MINDO/3 study was recently made of the formation, stability and behaviour of the various dihydropyridine isomers and related compounds [18]. The order of stability of the seven dihydro isomers is: 1,4 > 3,4 > 1,2 > 2,5 > 2,3>> the two bicyclic structures. These calculations are in good agreement with experimental observations [19]. It was shown that favourable electronic interactions (hyperconjugation, homoaromaticity) can account for the increased stability of the 1,4-dihydro isomers relative to the 1,2-dihydro isomers.

When a diazaaromatic compound is reduced by either complex B or complex D, only one of the nitrogen-containing rings is reduced. Although we cannot give a complete explanation for this selectivity, it is obvious that factors such as coordination behaviour and reduction potentials of both the unreduced and the partially reduced ligand, reaction mechanism, and charge-transfer formation must play an important role. The asymmetric diazaaromatic compounds, 2,3′-bipyridyl and 2,4′-bipyridyl are selectively reduced to their 1′,4′-dihydro derivatives. The pyridine ring attached to the 2-position of the other is reduced in both cases. Steric hindrance coordination of the 2-substituted pyridine to the metal ion probably causes this pronounced selectivity. In this context, we also tried to reduce 2-phenylpyridine by complex B or complex D. The electron-withdrawing phenyl group favours reduction of the substituted pyridine while steric hindrance will have a negative effect on coordination to the metal ion. The last factor apparently dominates and the substrate is not reduced.

Zinc hydride and magnesium hydride do not exhibit the specificity and selectivity of the complexes B and D. When e.g. 1,10-phenanthroline is treated with either $ZnH_2$ or $MgH_2$ in THF at room temperature, a mixture of 1,2- and 1,4-dihydro-1,10-phenanthroline derivatives is formed in a ≈3/2 molar ratio.

*Preparative applications; isolation of $LH_2$*

Hydrolysis of the complexes $M(LH)_2 \cdot xL$ (except L = Nic) yields a mixture of L and $LH_2$. In the case of L = Nic, pure $LH_2$ is obtained after hydrolysis.

A few of the compounds $LH_2$ described in this section, in particular for L = 1,10-phenanthroline or bipyridyl, were unknown. Photoreduction of 1,10-phenanthroline [20] yields dihydrophenanthroline. The dihydrophenanthroline, however, has neither been isolated nor characterized. Hydrogenation of 1,10-

phenanthroline with Raney nickel catalyst [21] affords 1,2,3,4-tetrahydro-1,10-phenanthroline and 1,2,3,4,7,8,9,10-octahydro-1,10-phenanthroline, no dihydrophenanthroline being obtained. The electrochemical reduction of 2,2'-bipyridyl [22,23] yielded four isomeric dihydropyridines, one of which possibly was 1,4-dihydro-2,2'-bipyridyl. The compound, however, could not be isolated; polymerization did occur on evaporating the solvent. Although 1,4-dihydropyridine, 1,4-dihydroquinoline and 1,2-dihydroisoquinoline are known, an easy separation procedure for the hydrolysis mixtures containing L and $LH_2$ would make the stable complexes $M(LH)_2 \cdot xL$ convenient starting materials for small scale syntheses of pure, isomer-free dihydropyridines.

A general method for the separation of L and $LH_2$, however, has not been found. The methods of separation tried are distillation, extraction, chromatography and selective complexation. The four separation methods were also applied to mixtures obtained on hydrolysis of complexes in which the unreduced ligands (L) had been replaced by other ligands (L'). The separations were hampered by the thermolability of the reduced compounds and their extreme sensitivity to oxygen, acids and sometimes bases.

Although distillation (in vacuo) is in principle applicable to the mixture of pyridine and 1,4-dihydropyridine, the difference in volatility of the components is so small that no separation could be obtained. The pyridine ligands in the zinc complex can be replaced by the nitrogen bidentate ligands tetramethylethylenediamine (TMED) or tetraethylethylenediamine (TEED) [1] (eq. 6).

$$(pyH)_2Zn \cdot 2\ py + TMED \rightarrow (pyH)_2Zn \cdot TMED + 2\ py \qquad (6)$$

TEED, in particular, has a lower vapour pressure than 1,4-dihydropyridine. After distillation in vacuo 1,4-dihydropyridine was obtained in 90% purity.

The extraction method worked very well in the separation of 1,10-phenanthroline and 1,4-dihydro-1,10-phenanthroline. In this separation process the mixture was treated with a water/pentane mixture. The unreduced ligand was found largely in the aqueous phase because of hydrate formation. After a triple extraction followed by recrystallization from hexane, 1,4-dihydro-1,10-phenanthroline was obtained in $\geq$95% purity. In the complexes $M(LH)_2 \cdot xL$ in which L is a monodentate nitrogen ligand, viz. pyridine, quinoline or isoquinoline, L can be replaced by *N*-methylimidazole (Nim). Upon hydrolysis of the resulting complexes a mixture of $LH_2$ and Nim is obtained from which the latter can be extracted with water. In this way the reduced monodentate ligand is obtained in 90% purity.

Chromatography, in particular LSC, was not a successful separation technique. Application of this method in most cases caused polymerization of the reduced products.

Separation of a mixture of L and $LH_2$ is possible when one of the components binds specifically to a metal ion, e.g. $Cu^{2+}$ under basic conditions preferentially binds pyridine. However, in this case the other component (1,4-dihydropyridine) reduces the metal ion. A pyridinechromium complex is obtained when a mixture of pyridine and 1,4-dihydropyridine is treated with $(CH_3CN)_3Cr(CO)_3$ [24]. This method, although very expensive, provides complete separation of pyridine and 1,4-dihydropyridine [25].

None of the separation techniques described above is applicable to mixtures

of L and $LH_2$ in which L is a bipyridyl. Isolation of pure 1,4-dihydrobipyridyls, therefore, has not yet been successful.

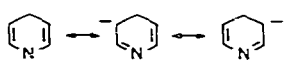
As an alternative, we tried to reduce metal-bound azaaromatic ligands. Also when, for example, complex B is treated with $Ph_2Zn \cdot L$ (L = 1,10-phenanthroline or 2,2′-bipyridyl), L is reduced. Hydrolysis of the reaction mixtures yields mainly the 1,4-dihydro derivative, but in these cases the hydrolysis mixture also contains the unreduced ligand (in non-stoichiometric amounts), while for L = 2,2′-bipyridyl even some polymerization products were present.

*Alkylation reactions*

In order to extend the applications of the complexes $M(LH)_2 \cdot xL$ to the synthesis of novel 1,4-dihydroazaaromatic compounds, we tried to alkylate the nitrogen atoms of the metal-bound 1,4-dihydropyridyl moieties (eq. 7). e

$$M(LH)_2 \cdot xL + 2\,RX \rightarrow MX_2 + xL + 2\,LHR \qquad (7)$$

However, these reactions are far more complicated than we had expected. Attack on the 3-position of the 1,4-dihydropyridyl group mainly took place, when $Zn(pyH)_2 \cdot 2$ py was treated with two mole-equivalents of methyl iodide in diethyl ether or THF. Acetyl chloride, on the other hand, did attack the 1,4-dihydropyridyl groups of complex B or complex D at the nitrogen atom, yielding *N*-acetyl-1,4-dihydropyridine. The difference in the place of attack between the alkylating and acylating agents is in agreement with the HSAB theory [26]. The negative charge on the $pyH^-$ anion is localized on nitrogen and the C(3) and C(5) atoms.



The "soft" alkylating agent $CH_3I$ will attack the "soft" C(3) atom, while the "hard" acylating agent, acetyl chloride, attacks the "hard" nitrogen atom. The reaction of complex B with $CH_3I$ yields a mixture of pyridine, 3-methylpyridine (minor product) and polymerization products (major components). The reactions between lithium tetrakis(*N*-dihydropyridyl)aluminate, prepared from $LiAlH_4$ and pyridine [27—29], and alkyl halides are convenient routes for the preparation of 3-substituted pyridines [30]. In these reactions, the dihydropyridyl moiety is also attacked at the 3-position although different experimental conditions are involved.

When methyl tosylate is used as alkylating agent for the 1,4-dihydropyridyl groups present in complex B or complex D, *N*-methyl-1,4-dihydropyridine is formed in low yields, but the main products are again those arising from attack at the C(3) atom. Using a "hard" electrophilic reagent, viz. triethyloxonium fluoroborate, only attack at the nitrogen atom of the 1,4-dihydropyridyl group bound to the metal takes place and *N*-ethyl-1,4-dihydropyridine is formed. Unfortunately, this reaction is not a useful procedure for the preparation of *N*-alkyl-1,4-dihydropyridines since *N*-ethyl-1,4-dihydropyridine reacts further with the alkylating agent. Quaternization of the nitrogen atom of the reduced substrate gives undesirable side products.

We must conclude that the methods described above are unsuitable for the preparation of *N*-alkyl-1,4-dihydropyridines. Electrophilic attack of an alkyl group on a 1,4-dihydropyridyl moiety bound to zinc or magnesium is in accord with the HSAB principle. Side and subsequent reactions, however, hamper the isolation of pure products arising from C or N alkylation only. Some of these undesired reactions are, depending on the reaction conditions, quaternization of the nitrogen atom(s) of the unreduced ligands, oxidation and reduction of the intermediate formed by the electrophilic attack at the C(3) atom, polymerization of unstable intermediates, quaternization of the reaction products, and electrophilic attack on the *N*-alkyl-1,4-dihydropyridines by the alkylating agent. *N*-Alkyl-1,4-dihydropyridines are not reduced further, under the conditions used, by the complexes B and D.

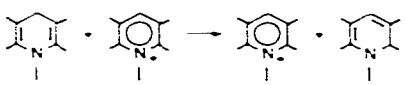
The complexes $M(LH)_2 \cdot xL$ ($L \neq py$) also failed to yield *N*-alkylated-1,4-dihydroazaaromatic derivatives on treatment with methyl iodide, methyl tosylate or triethyloxonium fluoroborate. The same problems were encountered as with $M(pyH)_2 \cdot 2\ py$, while in some cases, e.g. $Mg(LH)_2 \cdot L$ (L = 1,10-phenanthroline) and methyl tosylate no reaction at all took place.

*Other reductions*

In addition to aromatic nitrogen heterocycles, some other compounds containing carbon—nitrogen multiple bonds are reduced by the bis-pyridine bis-(1,4-dihydro-1-pyridyl)metal complexes.

*i. Reduction of nitriles.* The reaction of complex B or complex D with nitriles produces an addition product, which is readily hydrolyzed by acid to the corresponding aldehyde. Cyclohexanecarbonitrile and benzonitrile have been converted into the aldehydes in 70 to 85% yield. However, phenylacetonitrile is not reduced, but appears to react with the reducing agents preferentially through its acidic α-hydrogens. A similar reaction was found earlier by Brown and Garg [31].

*ii. Reduction of pyridinium salts.* Hydride transfer from a 1,4-dihydropyridine to a pyridinium salt is well-known [32,33]. This reaction, which sometimes leads to isomerization of the 1,4-dihydropyridine into its 1,2-isomer (eq. 8), is often encountered in enzymatic model reactions in which a substrate



is reduced by a 1,4-dihydropyridine. The autocatalytic conversion increases in rate as the concentration of the pyridinium salt (arising from reduction of the substrate) increases.

The complexes B and D reduce pyridinium salts derived from substituted pyridines containing electron-withdrawing groups; e.g. 1-propyl-3-carbamoylpyridinium iodide is reduced to the corresponding 1,4-dihydropyridine. Although no side products, such as 1,2-dihydropyridine, 1,6-dihydropyridine, and more highly reduced pyridines, are formed, the reaction gives low yields. The insolubility of the pyridinium salts in the reaction medium THF, together with the slight solubility of the complexes B and D, may be responsible for this.

## Experimental

*General*

All experiments were carried out under dry oxygen-free nitrogen. Solvents were carefully purified, dried, distilled, and stored under nitrogen. Solvents, solutions and liquid reagents were handled with syringes. NMR spectra were recorded on Varian EM 390, XL 100 and CFT 20 spectrometers. The $^{1}H$ $\delta$-values are believed to be accurate to ±0.02 ppm, $^{13}C$ $\delta$-values to ±0.1 ppm. Infrared investigations were carried out using a Perkin—Elmer 457 spectrometer. Spectra were recorded using Nujol suspensions between KBr disks. Elemental analyses were carried out under the supervision of Mr. W.J. Buis in the Analytical Department of the Institute for Organic Chemistry TNO at Utrecht.

*Starting materials*

The preparation of $ZnH_2$, $MgH_2$ and the pyridine complexes of bis(1,4-dihydro-1-pyridyl)zinc and bis(1,4-dihydro-1-pyridyl)magnesium has been described [1]. Commercially available nitrogen-containing substrates were purified before use by distillation, sublimation or recrystallization, as applicable. *N,N*-Dimethylnicotinamide was prepared according to Schindlbauer [34]. 2-Phenylpyridine was synthesized as described by Evans and Allen [35].

*Reduction of aromatic nitrogen heterocycles*

A general procedure of the reduction reactions is given. Details of each reaction will be given separately; some characteristics are indicated by Roman numerals and are presented in Table 6.

TABLE 6

SOME REACTION CHARACTERISTICS OF THE REDUCTION OF AROMATIC NITROGEN HETEROCYCLES BY THE PYRIDINE COMPLEXES OF BIS(1,4-DIHYDRO-1-PYRIDYL)ZINC AND BIS(1,4-DIHYDRO-1-PYRIDYL)MAGNESIUM

| Substrate (I) | Solvent (II) | Colour [a] (III) | Solubility (IV) | M(LH)$_2$ · xL (V) |
|---|---|---|---|---|
| *N,N*-Dimethyl-nicotinamide | THF | yellow | insoluble | $x = 0$ |
| Quinoline | THF<br>benzene | brown | soluble<br>soluble | $x = 2$ |
| Isoquinoline | THF | orange | soluble | $x = 2$ |
| 2,2'-Bipyridyl | THF<br>benzene | deep brown | soluble<br>slightly soluble | $x = 2$ |
| 2,3'-Bipyridyl | THF | red | soluble | $x = 2$ |
| 2,4'-Bipyridyl | THF | deep brown | soluble | $x = 2$ |
| 4,4'-Bipyridyl | THF<br>benzene | deep purple | insoluble<br>insoluble | $x = 2$ |
| 1,10-Phenanthroline | THF<br>benzene | deep purple | insoluble<br>insoluble | $x = 1$ |

[a] Final colour of the reaction mixture.

Five mol equivalents of the azaaromatic compound to be reduced (I) were added at room temperature to a suspension of 2—3 g of the pyridine complex of bis(1,4-dihydro-1-pyridyl)zinc or -magnesium in 75 ml of THF or benzene (II). In all cases a colour change (III) of the suspension occurred immediately. After two days the mixture was worked up.

When the reaction yielded a product insoluble (IV) in THF or benzene the solid was filtered off, washed three times with the same solvent and twice with pentane. After drying in vacuo the product (V) was usually obtained in 80—90% yield. In the cases where the product was soluble (IV) in THF or benzene, the solvent was evaporated in vacuo and the residue was washed three times with diethyl ether and twice with pentane. The product (V) was isolated after drying in vacuo in 75% yield.

*Hydrolysis experiments*

The general hydrolysis procedure utilized in the small-scale exploratory studies was as follows: to a suspension of 2—4 g $M(LH)_2 \cdot xL$ in 50 ml of benzene was added 1 ml of water or 1 ml of a 5% aqueous KOH solution. Hydrolysis of the compounds was usually complete within 5 minutes, recognizable by a colour change. The hydrolysis of complexes in which L = 1,10-phenanthroline took longer (15—30 minutes). The yellow benzene solution was decanted from the white metal hydroxide and the solvent evaporated in vacuo. The residue was usually a mixture of L and $LH_2$; only 1,4-dihydro-*N*,*N*-dimethylnicotinamide was obtained pure by this method.

When $D_2O$ was used in the hydrolysis, deuterium was incorporated into the reduced compounds at the nitrogen atom of the reduced pyridine ring.

*Separation of L and $LH_2$*

(i) Distillation (applicable to a mixture of 1,4-dihydropyridine and TEED). A mixture of 1,4-dihydropyridine and TEED, obtained from the hydrolysis of $(pyH)_2Zn \cdot$ TEED in pentane, was separated by distillation in vacuo. Although not all TEED was removed, 1,4-dihydropyridine was isolated in 90% purity.

(iia) Extraction (applicable to the mixture of 1,10-phenanthroline and 1,4-dihydro-1,10-phenanthroline). To 1 g of a mixture of 1,10-phenanthroline and 1,4-dihydro-1,10-phenanthroline 10 ml of water and 90 ml of pentane were added. After vigorous stirring the pentane layer was separated from the aqueous layer. Two more extractions were carried out and the combined pentane layers were evaporated to dryness in vacuo. The residue was recrystallized from hexane; 1,4-dihydro-1,10-phenanthroline was obtained in 95% purity.

(iib) Ligand exchange/extraction (applicable to isolation of 1,4-dihydropyridine, 1,4-dihydroquinoline and 1,2-dihydroisoquinoline). To a suspension of 5 g of $M(LH)_2 \cdot 2$ L (L = pyridine, quinoline or isoquinoline) in 50 ml of diethyl ether or benzene, 5 ml of *N*-methylimidazole (Nim) was added. After stirring for 1—2 h at room temperature the solvent was decanted and the sticky residue, $M(LH)_2 \cdot x$Nim, was washed twice with 50 ml of diethyl ether. The residue was then hydrolyzed in pentane with 4 ml of water. Evaporation of the pentane layer yielded the dihydro product in 90% purity.

(iii) Chromatography. All attempts to separate mixtures of the substrate and its dihydroderivative by LSC failed. The dihydro products are unstable under

the conditions used (S = silica gel or alumina, L = hexane, benzene or diethyl ether).

(iiii) Selective complexation (applicable to a mixture of pyridine and 1,4-dihydropyridine). To a mixture of pyridine and 1,4-dihydropyridine in pentane was added an equimolar amount of $(CH_3CN)_3Cr(CO)_3$ [25], (calculated on pyridine). After stirring the mixture for 30 minutes at room temperature, the pentane layer was decanted from the solid and the solvent evaporated in vacuo (15 mmHg); the residue was 1,4-dihydropyridine of 95% purity.

*Reduction of nitriles*

To a stirred suspension of 2—3 g of complex B or complex D in 50 ml of THF was added 1 mole-equivalent of the nitrile under investigation. After a period varying from 1—20 h a clear solution resulted, and this slowly changed again into a suspension. After 24 h the addition product was decomposed with 5 ml of 5 *N* sulfuric acid. The ether layer was separated and the solvent evaporated in vacuo (15 mmHg). The residue was analyzed by $^1H$ NMR spectroscopy and GLC.

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