

Reduction of Pyridinoid Heterocyclic Compounds. A MINDO/3 Study

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A MINDO/3 study has been carried out on the anions that can be formed by addition of H^- to a number of pyridinoid heterocyclic compounds. Salts of such anions are formed when the parent heterocyclic compounds are treated with a hydride-transferring reducing agent. Correlation with earlier experimental results suggests that the product obtained with mild reducing agents, like ZnH_2 or $Zn(C_5H_5N)_2 \cdot 2C_5H_5N$, is the thermodynamically most stable one. The reduction of pyridine by the strong reducing agents MgH_2 and AlH_3 was studied by 1H n.m.r. spectroscopy, and it was found that a mixture of the isomeric 1,2- and 1,4-dihydro-1-pyridyl anions is formed initially. The final product, however, was a pure 1,4-dihydro-1-pyridyl derivative. This is discussed in terms of hydride exchange between reduced and unreduced substrate molecules co-ordinated to the same metal ion.

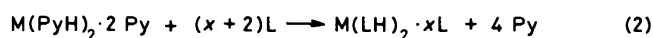
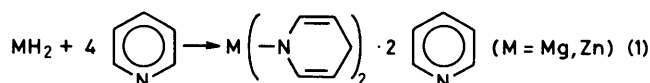
Magnesium hydride and zinc hydride react with pyridine to yield 1,4-dihydro-1-pyridyl derivatives as final products [equation (1)].^{1,2} These compounds in turn can be used to reduce pyridinoid heterocyclic compounds in a uniquely specific and selective way.³ In the reduction reaction, hydride is transferred from the dihydropyridyl group to the substrate L [reaction (2)]. In order to gain some insight into the factors governing this specificity, we have carried out a theoretical study of the anions LH^- actually formed in this reduction reaction, and of a number of isomeric anions. The MINDO/3 program⁴ was used for the calculations, since it has been shown to be well suited for calculations on similar compounds.⁵ The anions were taken as model compounds for the salts actually formed, since a calculation on a complete molecule of *e.g.* $Mg(C_5H_5N)_2 \cdot 2C_5H_5N$ would be prohibitively time-consuming.

Zinc hydride has been shown previously² to reduce pyridine to the 1,4-dihydro-1-pyridyl anion without the intermediate formation of a 1,2-dihydro-isomer. The reactions of the stronger reducing agents MgH_2 † and AlH_3 with pyridine have now been studied for comparison.

Experimental

Computational Procedures.—All calculations were carried out on the CDC Cyber-175 computer of the University of Utrecht Computer Center, using local versions of the MINDO/3⁴ and MNDO⁷ programs. Of all molecules studied the geometry was optimized with the following restrictions: (1) for both reduced and unreduced heterocyclic compounds, a mirror plane was assumed through the carbon skeleton of the molecule [except for some reduced bipyridyls; see (4)]; (2) for unreduced 2,2'- and 4,4'-bipyridyl, a mirror plane was assumed perpendicular to the C-C bond joining the two pyridyl rings; (3) for reduced bipyridyls, the unreduced ring was kept fixed in the geometry of the corresponding *symmetric* bipyridyl; and (4) for reduced bipyridyls in which the reduction site is the carbon atom to which the unreduced ring is attached, a planar carbon skeleton cannot be assumed. Instead, both rings were kept individually planar, and the planes of these rings were held perpendicular to the plane through $C_bC_aH_a$ (see Figure 1).

Restriction (1) is derived from the results of Bodor and Pearlman,⁵ who found that the dihydropyridyl anion skeleton is essentially planar. Restriction (3) seems reasonable, as the



e.g.

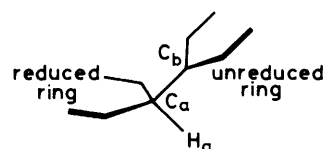
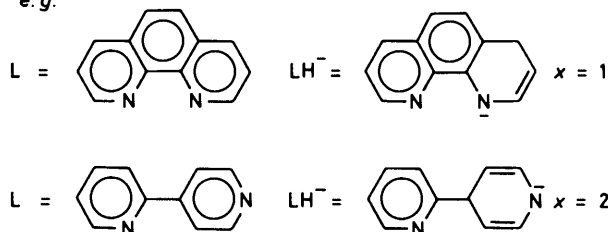


Figure 1. Configuration around the sp^3 carbon atom of non-planar reduced bipyridyls

geometry of a pyridyl ring would not be expected to depend strongly on the site of reduction of the dihydropyridyl ring to which it is attached. Restriction (4) is used to keep calculations on non-planar dihydropyridyl anions comparable to those on the planar ones.

Reactions of MgH_2 and AlH_3 with Pyridine.—All manipulations were carried out under nitrogen, with rigorous exclusion of air and moisture. Solvents were dried and distilled under nitrogen before use. MgH_2 ⁸ and AlH_3 ⁹ were prepared according to published procedures. To the hydride (1 g) was added pyridine (40 ml), and 1H n.m.r. spectra of the reaction mixture were recorded on a Varian EM-390 90 MHz spectrometer after 1, 4, 24, and 100 h stirring at room temperature. The reaction of MgH_2 with [2H_5]pyridine was carried out similarly, using MgH_2 (0.1 g) and deuteriated pyridine (5 ml).

† For a preliminary communication, see ref. 6.

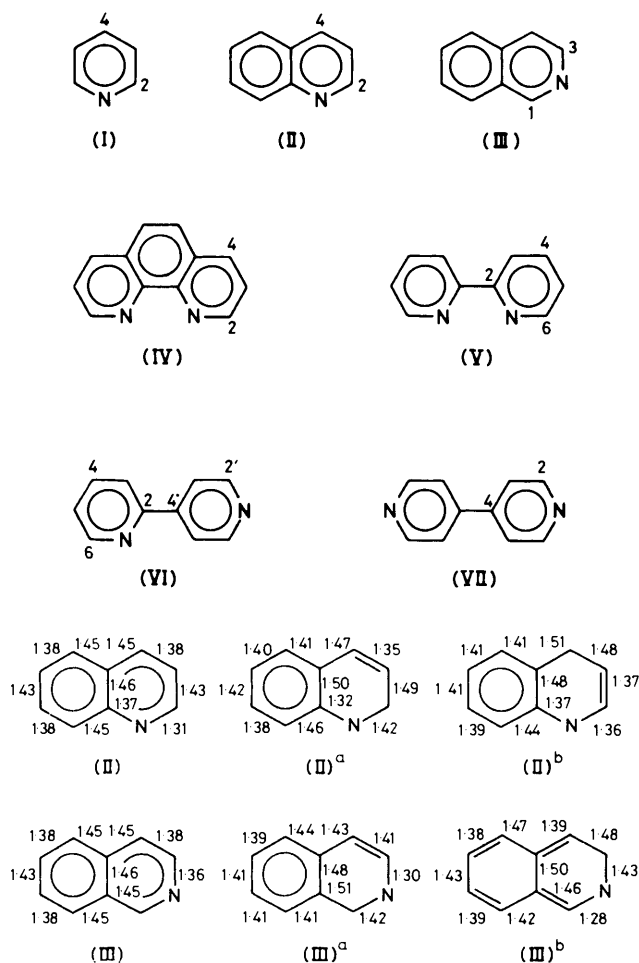


Figure 2. MINDO/3-optimized bond lengths (Å) for quinoline and isoquinoline and their reduction products

Results

MINDO/3 Calculations.—The reduction products of pyridine (I), quinoline (II), isoquinoline (III), *o*-phenanthroline (IV), 2,2'-bipyridyl (V), 2,4'-bipyridyl (VI), and 4,4'-bipyridyl (VII) were studied by the MINDO/3 method.⁴ Energies corresponding to the optimized geometries are given in Table 1, and calculated bond lengths for quinoline and isoquinoline and their reduction products are shown in Figure 2. Atomic positions corresponding to the MINDO/3 and MNDO-optimized geometries of (I)–(VII) are listed in Supplementary Publication No. SUP 23574 (28 pp.).* The results for pyridine and its reduction products agree with those of Bodor and Pearlman.⁵ The more recent and somewhat more accurate MNDO method⁷ was also used for calculations on pyridine and its reduction products; the MNDO-optimized geometries closely resemble the MINDO/3 results, and the energy difference between 1,4- and 1,2-reduction is approximately the same for both methods (see Table 1).

Reactions of MgH₂ and AlH₃ with Pyridine.—The reactions of MgH₂ and AlH₃ with pyridine were followed by ¹H n.m.r. spectroscopy. The n.m.r. spectra of the reaction mixtures after 1 h reaction time show absorptions due to both 1,2- and 1,4-

Table 1. MINDO/3 heats of formation at optimized geometries

Parent heterocycle	Reduction site	Molecule or anion	$\Delta H_f^\circ / \text{kcal mol}^{-1}$
Pyridine (I) ^a		(I)	(34.1/28.7) ^b
	2	(I) ^a	31.9/11.4 ^b
	4*	(I) ^b	26.7/7.5 ^b
Quinoline (II)		(II)	(54.1)
	2	(II) ^a	39.7
	4*	(II) ^b	33.1
Isoquinoline (III)		(III)	(60.1)
	1*	(III) ^a	44.3
	3	(III) ^b	47.9
<i>o</i> -Phenanthroline (IV)		(IV)	(73.8)
	2	(IV) ^a	55.8
	4*	(IV) ^b	51.8
2,2'-Bipyridyl (V)		(V)	(60.3)
	2	(V) ^a	62.0
	4*	(V) ^b	48.9
	6	(V) ^c	54.4
2,4'-Bipyridyl (VI)		(VI)	
	2	(VI) ^a	72.7
	4	(VI) ^b	60.6
	6	(VI) ^c	66.2
	2'	(VI) ^d	64.7
	4'*	(VI) ^e	66.5
4,4'-Bipyridyl (VII)		(VII)	(80.3)
	2	(VII) ^a	73.5
	4*	(VII) ^b	74.6

* Products corresponding to these anions are actually formed from unreduced ligand and M(PyH)₂·2Py.³

^a MINDO/3 calculations on pyridine and its reduction products have been carried out earlier⁵ and are included for comparison purposes only. ^b Second value is MNDO result.

dihydropyridyl isomers. The absorptions due to the 1,2-dihydropyridyl isomer disappear slowly, leaving only those due to a pure 1,4-dihydropyridyl derivative. The spectra of the AlH₃-pyridine reaction mixture after 1 and 100 h are shown in Figure 3, and n.m.r. data for the dihydropyridyl groups bound to magnesium and aluminium are listed in Table 2. From the time-dependence of the intensities of the absorptions, we conclude that the 1,2- and 1,4-dihydro-isomers are initially formed in approximately the statistical ratio 2:1. When MgH₂ was treated with [²H₅]pyridine, peaks due to both 1,2- and 1,4-dihydropyridyl groups appeared, but those of the 1,4-dihydro-isomer grew at the expense of those of the 1,2-dihydro-isomer. Eventually, all dihydropyridyl peaks disappeared as hydride exchange produced [²H₄]pyridine and fully deuteriated dihydropyridyl groups, as in the reaction of ZnH₂ with [²H₅]pyridine.²

Discussion

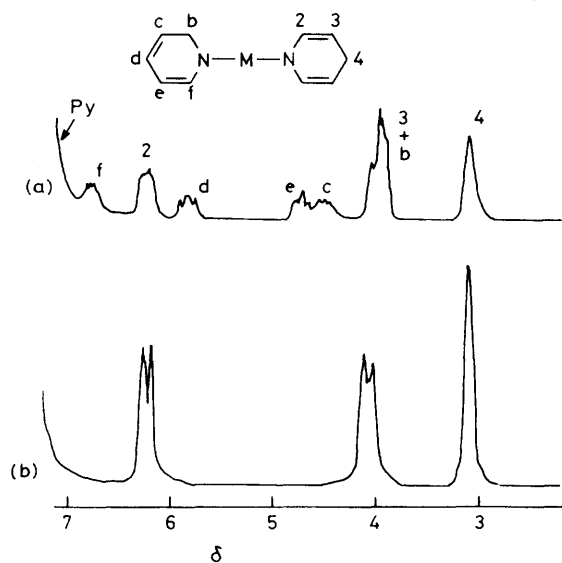
In Table 1, the anion corresponding to the product actually formed from the unreduced ligand and M(C₅H₅N)₂·2C₅H₅N (M = Mg, Zn)³ is indicated by an asterisk. Usually, this anion is the one calculated to be the most stable among its isomers. The most notable exception is 2,4'-bipyridyl (2,4'-Bipy), in which apparently the 'wrong ring' is reduced. Attack of hydride on the 4-position of the 2-substituted ring would produce the most stable anion (VI)^b. The product obtained

* For details of Supplementary Publications see Notice to Authors No. 7 in *J. Chem. Soc., Perkin Trans. 2*, 1983, Issue 1, p. xvii.

Table 2. Chemical shifts for dihydropyridyl groups bound to Mg and Al [in pyridine, δ (p.p.m. relative to internal Me₄Si)]. Numbering scheme is indicated in Figure 3

M	2	3	4	b	c	d	e	f
Mg	6.40	4.25	3.73	4.03	4.53	~6.4 ^a	5.20	≥7 ^b
Al	6.17	3.98	3.01	3.91	4.52	5.82	4.74	6.73

^a Obscured by absorptions of 2-H. ^b Obscured by absorptions of pyridine β -protons.

**Figure 3.** ¹H N.m.r. spectra of the AlH₃-pyridine reaction mixture after 1 h (a) and 100 h (b)

from M(PyH)₂·2Py and 2,4'-Bipy is not, however, a naked BipyH⁻ anion, but rather a salt in which the anion can be considerably stabilized by co-ordination of the negatively charged nitrogen atom to the positive metal ion. Such co-ordination is sterically impossible for the nitrogen atom of the 2-substituted ring; therefore, the other ring will be reduced.

In the other cases, no steric effects occur which might favour co-ordination of one isomeric anion over another, so that this co-ordination will not influence the reaction specificity. Inspection of Table 1 shows that 1,4-reduction (where possible) is favoured consistently over 1,2-reduction; the average energy difference $\Delta_{2,4}$ between 1,2- and 1,4-reduction is ca. 5.5 kcal mol⁻¹. However, a complication arises in the reduction of bipyridyls. In these cases, reduction at a carbon atom by which one pyridyl ring is bound to the other destroys the conjugative interaction between the two rings. This shows up as an elongation of the inter-ring C-C bond: the mean MINDO/3 inter-ring C-C distance is 1.505 Å for unreduced bipyridyls, 1.514 Å for conjugated reduced bipyridyls, and 1.552 Å for the non-conjugated reduced bipyridyls. The energy increase Δ_{conj} associated with this loss of conjugation can be estimated by comparing several analogous anions, e.g. (V)^a - (V)^c, (VI)^a - (VI)^c, or [(VII)^a - (VI)^b] - [(VII)^b - (VI)^a]. A value of ca. 7 kcal mol⁻¹ is obtained.

The two quantities $\Delta_{2,4}$ and Δ_{conj} appear to be the major factors governing the relative stabilities of the possible products. If only one of them is operative, or if both operate in the same direction, the most stable anion can be predicted immediately [(I)^b, (II)^b, (IV)^b, (V)^b], and this corresponds to the product actually formed in the reduction reaction (2). Also, predictions can be made for bipyridyls for which no calculations were carried out: 3,4'-bipyridyl is expected to be

reduced at the 4-position (this has indeed been observed³), while 2,3'-bipyridine should be reduced in the 3'-substituted ring (steric factor, analogous to the reduction of 2,4'-bipy) at the 4'-position. When, however, a 4-substituted ring is to be reduced [(VI) and (VII)], $\Delta_{2,4}$ and Δ_{conj} operate in opposite directions, and the reduction site will be determined by their relative magnitudes. The estimated difference of 1.5 kcal mol⁻¹ can, however, hardly be considered significant at the present level of approximation. The present study would indicate that $\Delta_{2,4} < \Delta_{\text{conj}}$ for the free anions, whereas the observed formation of (VI)^d and (VII)^a suggests that $\Delta_{2,4} > \Delta_{\text{conj}}$ for the salts M(LH)₂·xL. Possibly, the co-ordination of LH⁻ to M has some influence on the relative magnitudes of $\Delta_{2,4}$ and Δ_{conj} .

All in all, the specificity of the reduction of heterocyclic compounds by M(PyH)₂·2Py appears to correlate directly with the thermodynamic stability of the products formed. This could have been expected, because the reducing agents are mild, and therefore specific. Moreover, hydride transfer reactions to the 2- and 4-positions of the substrate are similar processes. Therefore, it is not likely that formation of the most stable product would be kinetically hindered. Similar arguments hold for the specific formation of the 1,4-dihydro-1-pyridyl anion from pyridine and ZnH₂, and ¹H n.m.r. studies using deuteriated pyridine have served to prove that no 1,2-dihydro-intermediate is involved.² Stronger reducing agents, e.g. MgH₂* or AlH₃, would be expected to be less specific. Indeed, we found that treatment of these hydrides with pyridine initially produced a mixture of 1,2- and 1,4-dihydropyridyl isomers, but spontaneous exchange of hydride occurred, leaving finally the pure 1,4-dihydro-isomer.

Formation of a mixture of 1,2- and 1,4-dihydropyridyl groups had been reported previously for the reduction of pyridine with LiAlH₄.¹⁰ In that case, however, no spontaneous isomerization occurred at room temperature. This can be rationalized by assuming that the hydride exchange occurs in an intramolecular reaction between a reduced and an unreduced pyridine molecule bound to the same central metal atom. In that way, facile isomerization would be expected for Mg(PyH)₂·2Py and Al(PyH)₃·Py, but not for Li[Al(PyH)₄]. In the latter case, hydride exchange must occur between a metal-bound PyH⁻ anion and a free, unco-ordinated pyridine molecule. Alternatively, a five-co-ordinated intermediate may be involved. Neither alternative seems very attractive, and in fact isomerization only occurs at elevated temperature (60 °C).¹⁰ Another support for this presumed intramolecular inter-ligand exchange is given by the observation that the reduction of *o*-phenanthroline by the strong reducing agent MgH₂ produces a product Mg(C₁₂H₉N₂)₂·C₁₂H₉N₂ containing 1,2- and 1,4-dihydrophenanthrolyl groups in the approximate ratio 3 : 2.³ We have pointed out earlier³ that the 'extra' phenanthroline molecule in the product is probably not co-ordinated to the central metal atom, but rather bound to the dihydrophenanthrolyl anions by a kind of charge-transfer interaction. In that case, hydride exchange between ligands

* See also ref. 6.

cannot take place, so that the energetically less favourable 1,2-dihydro-isomer, once formed, remains present.

Conclusions

Reduction of pyridinoid heterocyclic compounds with mild reducing agents like $\text{Mg}(\text{C}_5\text{H}_6\text{N})_2 \cdot 2\text{C}_5\text{H}_5\text{N}$ or ZnH_2 produces those products which are thermodynamically the most stable. These stabilities appear to be governed by the following rules: (1) the negatively charged nitrogen atom of the reduced ring must be sterically able to co-ordinate to the central metal ion; (2) 1,4-reduction is preferred over 1,2-reduction; (3) reduction takes place in such a way that conjugation interaction within the whole heterocyclic system remains undisturbed as much as possible.

Rules (2) and (3) are related to the stabilities of the anions formed, while rule (1) is derived from the stabilization resulting from co-ordination to the metal ion. Violations of rules (2) and (3) bring about increases in energy of $\Delta_{2,4}$ and Δ_{conj} , which are of the same order of magnitude (± 6 kcal mol^{-1} of heterocycle). When these rules conflict, no reliable prediction of the site of reduction can be made on the ground of the present work; earlier experimental work would suggest that rule (2) takes precedence. If a strong reducing agent, like MgH_2 , AlH_3 , or LiAlH_4 , is employed, a mixture of products will be obtained. Only if both reduced and unreduced substrate molecules are present together in the co-ordination sphere of the metal ion will intramolecular hydride exchange

eventually produce the thermodynamically most stable isomer.

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