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METAL ION CATALYSIS OF THE REDUCTION OF C=N LINKAGE BY NADH MODELS

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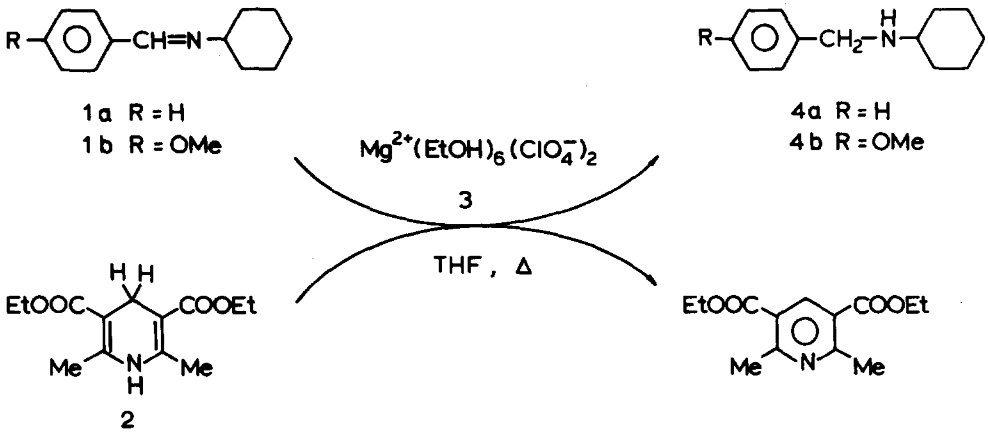
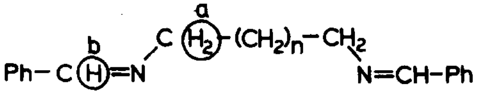
Several oxidoreductases which mediate the $>$C-N $\rightleftharpoons$ $>$C=N-equilibrium are dependent upon the pyridine nucleotide coenzymes (NAD, NADP). The enzyme L-glutamate dehydrogenase (1.4.1.3)[2] can utilize either of the two coenzymes for its operation and is furthermore known to have an essential zinc requirement[2].

In this communication we describe the reduction of imines and diimines by 1,4-dihydropyridine derivatives, in the presence of metal complexes, which serve as model reactions for the zinc dependent pyridine nucleotide linked glutamate dehydrogenase. Several examples of the use of metal ethanolate complexes in NADH model reductions have been reported from this laboratory[3a,b].

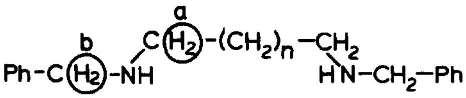
In orientation studies it was shown that when imines 1a,b were heated with Hantzsch ester 2 and magnesiumhexaethanolate perchlorate 3 (1:1:1), in THF (reflux, N_2), the reduction products 4a,b were formed in 50-55% yield. In the absence of 3 no analogous reduction could be demonstrated.

Since bidentate ligands possess highly effective chelating properties, we were prompted, especially in the light of the aforementioned results, to examine a diimine system to which a metal cation could simultaneously coordinate via the two functions. A suitable substrate for such a study may be recognized in diimines of type 5, which have been shown to undergo enhancement of hydrolysis in the presence of metals[4a,b]. An analogy may be drawn between the latter reaction and the reduction by NADH models, if it is assumed that the species being transferred from the dihydro pyridine system (such as 2), is a hydride ion. It would be expected that the reduction process will be enhanced if the metal cation would complex more strongly in the transition state[5] or with the product than with the starting material[6]. In order to evaluate the relative complexation of diimine 5a and its reduction product 6a, with metals, ^{1}H-NMR spectra of the compounds with increasing amounts of Mg^{2+} in the





5a n=0
5b n=1
5c n=2
5d n=4



6a n=0
6b n=1
6c n=2
6d n=4

form of its ethanolate complexes (3) were examined. The results are presented in Table I. These results show that in mixtures of 3 and 6a the maximum shifts were reached at a 3:6a ratio of about 1:1. Inspection of the latter Table suggests that while the product diamine 6a exhibits definite complexation, the starting diimine (5a) spectrum is not influenced by the addition of the complex (3). This does not imply an *absence* of complexation, but may reflect the presence of an undetectably low concentration of a complex, under the conditions of measurement. However, the results of Table I clearly show that the product diamine binds more strongly to the cation than the starting material, a condition which we have indicated is favourable for the operation of metal catalysis.

When a mixture of 5a-d and 2 (mole ratio 1:2) was heated in THF (reflux) for 66h, no reduction product could be detected in any of the reaction mixtures. In contrast, when 3 was added to a similar mixture the amines 6a-d were formed and could be conveniently isolated as their crystalline hydrochlorides. Basification of the salts gave the diamines in high yields, which were identified by their spectra and compa-

TABLE I

^{1}H-NMR Chemical Shifts (δ) of mixtures of 5a+3 and 6a+3 in CD_3CN

DiImine (5a)				DiAmine (6a)			
Ratio 5a/3	H_a	H_b	Ph(H)	Ratio 6a/3	H_a	H_b	Ph(H)
1 : 0	3.94	8.35	7.70–7.49	1 : 0	2.63	3.68	7.30m
1 : 0.25	n.c.	n.c.	n.c.	1 : 0.25	2.73	3.77	7.33m
1 : 0.5	n.c.	n.c.	n.c.	1 : 0.5	2.90	3.92	7.40m
1 : 1	n.c.	n.c.	n.c.	1 : 1	2.99	3.98	7.40m

n.c.=no change

TABLE II

Reduction of Diimines 5a–d in the presence of varying amounts of magnesium complex 3 (THF, 67°, 48h)

Diimine	Diimine / 3	Reduc. Prod. Yields (%)
5a	1 : 0.1	36
5a	1 : 0.5	100
5a	1 : 1	100
5b	1 : 0.5	100
5c	1 : 0.1	28
5c	1 : 0.5	100
5c	1 : 1	100
5d	1 : 0.1	22
5d	1 : 0.5	100
5d	1 : 1	100

TABLE III

Rate (k_{pseudo}) of reduction of Diimines 5a-d with Hantzsch ester (3) in THF; [20°, Diimine 1M, Mg-complex (3) 0.5M, Hantzsch ester (2) 0.05M]

Diimine	$k_{pseudo} \times 10^5$ (sec^{-1})
5a	2.32 ± 0.02
5b	4.25 ± 0.02
5c	0.83 ± 0.02
5d	0.67 ± 0.02

rison with authentic samples. The influence of the amount of metal complex on conversion is presented in Table II. The yields are based upon the crystalline hydrochlorides of 6a-d. Table II reveals that a ratio of diimine to 3 of 1:0.5 is adequate to bring about a complete conversion of the substrate. The essential role of the metal is undisputably established by the latter results.

An interesting question pertains to the influence of the ring-size of the complex upon the extent of activation of the reduction process. To investigate this point, kinetic studies were undertaken. The pseudo first order rates were measured by following the disappearance of the Hantzsch eser (372 nm). The results are described in Table III. Significantly, the fastest rate is observed for diimine 5b which would give a 6-membered ring upon complexation. Substrate 5a results in a slightly less effective 5-ring complex. Such a 6/5-ring order of stability of complexes has also been observed in the chelates of 4-imidazolylalanine and 4-imidazolylglycine[7]. With larger rings, namely the complexes of 5c and 5d, the activation effect gradually falls off. Further studies on the reduction of structurally varied imines with NADH models in the presence of other metals are in progress.

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