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STEREOCHEMISTRY OF $\rangle C{=}N\langle^{\oplus}$ REDUCTIONS WITH NADH MODELS[1].

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Reductions of iminium salts by 1,4-dihydropyridine derivatives constitute model reactions for the reduction step of the $\rangle C{=}N- \rightleftharpoons \rangle CH-NH-$ equilibria mediated by pyridine nucleotide dependent dehydrogenases. In particular, such models illustrate the importance of electrophilic catalysis (a complete proton transfer, or metal cation coordination) of the presumed hydride transfer step[3] in the enzyme-coenzyme-substrate ternary complex. An example of a highly stereoselective reduction of the pyrrolidinium salts of 3-ketosteroids has been recently reported from this laboratory[4]. We now present results which throw light upon the stereochemical course of the reduction of iminium salts by NADH models.

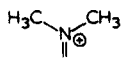
The iminium salts of 4-t-butylcyclohexanone are especially suitable substrates for the study of the stereochemical course of the abovementioned reduction reaction, because their isomeric reduction products can be easily characterized (spectra) and quantitatively analyzed (GLC).

The iminium perchlorates 1a-e were prepared by known procedures[5] and isolated as white, crystalline products[6]. The reduction reactions were carried out by refluxing the salts, under N_2, with Hantzsch ester (2)[7], in freshly distilled CH_3CN, until the dihydropyridine had been consumed (TLC). Evaporation of the solvent and washing of the residual solid with dry ether, to remove the oxidized Hantzsch ester (5), gave a mixture of the cis- and trans-ammonium salts (3a-e and 4a-e) in quantitative yield. The products were identified by ^1H- and ^{13}C-NMR spectroscopy, and by comparison with authentic samples. The latter were prepared by $NaBH_4$-reduction of 1a-e[8], followed by acidification with $HClO_4$. After liberation of the free amines from the salts, the isomer ratios were determined by GLC (SE-30, 0.5 m, 145-170°C). The results are presented in Table I. It was established that the isomer ratios did not alter in the course of the reaction or during the working-up of the reaction-mixtures. The isomer ratios may thus be regarded as the rate ratios of equatorial and axial approach of the Hantzsch ester to the substrates. Significantly, the $NaBH_4$-reduction of 1a-e yielded 4a-e as the main products.

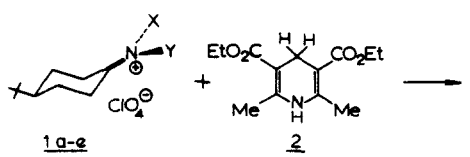
Although the stereochemistry of nucleophilic attack on iminium salts has been investigated[9], only a few studies concern themselves with the exocyclic $\rangle C{=}N\langle^{\oplus}$ bond[10]. Considerable attention, however, has been directed to the problem in the case of the analogous carbonyl function[11]. For unhindered ketones, in general, an axial approach to the carbonyl group is found to be the preferred mode of hydride transfer. This stereoselectivity has been explained on the basis of various steric

Table I

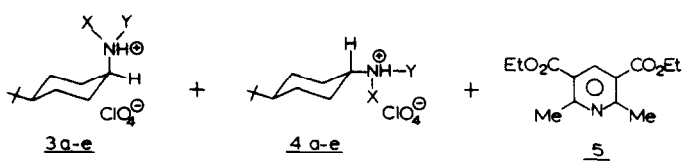
Stereochemistry of Reduction of Iminium salts by Hantzsch ester (5).

substrate	amine moiety	equatorial attack (%)[a]	axial attack (%)[a]	$E_{1/2}$ (V)[b]
1a		95	5	−1.66
1b		88	12	−1.60
1c		75	25	−1.62
1d		73	27	−1.58
1e		81	19	−1.46

a : The isomer ratios are based upon three runs.
b : In CH_3CN (0.1 M Et_4NClO_4) relative to the saturated calomel electrode



1a-e 2



3a-e 4a-e 5

X Y

a $-(CH_2)_4-$
b. $-CH_2-CH=CH-CH_2-$
c. $-CH_3$ $-CH_3$
d. $-(CH_2)_5-$
e $-(CH_2)_2-O-(CH_2)_2-$

factors (steric approach control, torsional strain) and, recently, it is suggested that electronic factors may influence the product isomer ratio. The molecular structure of the reducing agent plays a crucial role in the determination of the observed stereochemistry; as the size of the reductant becomes larger, equatorial attack is favoured over an axial attack[11]. Since the results in Table I show that the main product, viz. with the amino group in the axial position is formed in considerable excess, it would follow that in this reaction steric factors play a paramount role. Indeed, the least hindered approach of the Hantzsch ester is via the equatorial side, since an approach from the axial side encounters steric hindrance from the 3,5-diaxial hydrogens.

Steric factors alone do not suffice to account for the variation in stereoselectivity within the series. Consideration of "orbital" factors, however, leads to a satisfactory explanation. Nguyên Trong Anh and coworkers[12] have recently pointed out that, as a general rule - when all other interactions are equal - axial attack on a cyclohexanone system, by a nucleophilic agent, increases with increasing charge control of the reaction. Similarly, equatorial attack increases with increasing frontier orbital control. Therefore, we have determined the polarographic one-electron halfwave reduction potentials of the substrates 1a-e (Table I), which represent an experimental measure of the relative energies of the lowest unoccupied molecular orbitals (LUMO's). Since the reducing agent, Hantzsch ester, is the same for all substrates 1a-e, these relative values allow the reduction reactions to be arranged in an increasing order of charge control. Thus, the higher the energy level of the LUMO of the iminium salt, the more the expected axial attack by Hantzsch ester.

Nguyên Trong Anh et al. have also stressed the importance of antiperiplanarity[12,13]. If the cyclohexanone system is flattened, an axially attacking nucleophile becomes antiperiplanar to C_2-H_{ax}, and axial attack is therefore favoured over equatorial attack. Thus, the more flexible the iminium salt around $\geq C=N\leq^{\oplus}$, the more axial attack by Hantzsch ester will be observed.

Another way in which antiperiplanarity may be accomplished, is by pyramidalization of the carbonyl carbon atom[12]. Since this demands energy which is best compensated by equatorial attack, the latter is slightly favoured. Thus, the more stable the $\geq C=N\leq^{\oplus}$ bond, the more equatorial attack by Hantzsch ester.

These three, adapted rules enable us to rationalize the product isomer ratios in Table I. First, we compare the substrates 1d and 1e. The flexibilities and all other interactions of these two compounds may be considered equal, consequently we may expect more equatorial attack on 1e than on 1d, due to its lower LUMO energy-level. This, indeed, is the observed result. The dimethyl iminium salt 1c has a reduction potential comparable to that of 1d, its steric requirements around $\geq C=N\leq^{\oplus}$ are only slightly different, but the iminium bond itself is more stable[14]. Therefore, the isomer ratio of 75:25 is well within the limits of expectation.

The pyrrolidinium salt 1a has the highest reduction potential of the series, and therefore one is inclined to expect more axial attack than is actually demonstrated

The $\succ C=N\prec^{\oplus}$ bond in this compound, however, is much more stable than those in the other substrates, due to its exocyclic location to a five-membered ring[14]. Secondly, due to steric interactions between the methylene hydrogens flanking the $\succ C=N\prec^{\oplus}$ bond in both rings of this compound, no ring-flattening is possible. Thus, not only is equatorial attack slightly favoured because of the very stable $\succ C=N\prec^{\oplus}$ bond, but, more significantly, the axial attack is suppressed. This accounts for the almost stereospecific outcome of this reduction reaction.

The same holds for the pyrrolinium system 1b. The somewhat lower stereoselectivity may be accounted for by assuming hyperconjugative interactions between the $\succ C=N\prec^{\oplus}$ and the $\succ C=C\prec$ double bonds, which presumably facilitate pyramidalization.

Further experiments are being undertaken to test the general applicability of the abovementioned arguments to evaluate the stereochemical outcome of other model reduction reactions involving the $\succ C=N\prec^{\oplus}$ function.

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