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# CHEMIOSELECTIVITY[1] OF THE REDUCTION OF PHENYL-SUBSTITUTED α,β-UNSATURATED IMINIUM SALTS BY AN NADH MODEL[2]

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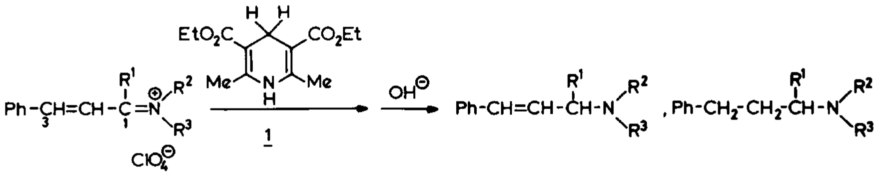
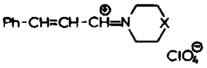
Abstract. Reduction of α,β-unsaturated iminium salts by 3,5-dicarbethoxy-2,6-dimethyl-1,4-dihydropyridine results in $>C=C<$ or $>C=\overset{+}{N}<$ (primary) reduction products, depending on the basicity of the amine component.

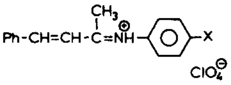
Several examples of the reduction of iminium salts and imines by 1,4-dihydropyridine derivatives (NADH models) have been reported from this laboratory[4]. The reduction of α,β-unsaturated iminium salts to the corresponding saturated iminium salts, by NADH models, provides a chemical precedence for the NADH-linked dehydrogenase-catalyzed reduction of α,β-unsaturated ketones to saturated ketones[5], it being recognized that the unsaturated and the saturated iminium salts are equivalents to the protonated Schiff bases of the corresponding ketones. In biological processes, Schiff base formation may involve an amino function at the active site In this communication we present results on the chemioselectivity of the reduction of phenyl-substituted α,β-unsaturated iminium salts with 3,5-dicarbethoxy-2,6-dimethyl-1,4-dihydropyridine 1 (Hantzsch ester, HE).



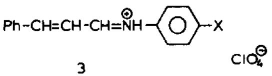
The iminium salts described in this investigation are readily prepared by the reaction of cinnamaldehyde or benzylidene acetone with the perchlorate salts of the various amines[6,7]. Reduction of the substrates is carried out by reaction with two equivalents of HE, in acetonitrile at room temperature, until the dihydropyridine has been consumed (3 min - 6 h). After evaporation of the solvent, the residue is taken up in a 1 M $Na_2CO_3$ solution and thoroughly extracted with chloroform. Separation and isolation of the product amines is achieved by column chromatography (silicagel, petroleum ether - ethylacetate gradient). All products are identified by $^1H$ NMR spectroscopy and by comparison with authentic samples. Product ratios are determined by GLC (SE-30, 0.5 m, 190-210°C). The use of two equivalents of HE is dictated by the fact that the primary products of reduction of the $>C=C<$ bond are rapidly (further) reduced to the fully saturated compounds. Any possible excess of HE is destroyed by acid-catalyzed disproportionation, since protons are available in the reaction mixture[8]. It has been established in separate experiments that the products of reduction of the $>C=N^{+}<$ bond are not reduced further by HE. The results of the reactions are summarized in Table 1. A study of the $NaBH_4$ reduction of the substrates has shown that the reaction uniformly leads to the formation of products which result from attack at $>C=N^{+}<$ [9].



2 a X = —
b X = O



4 a X = H
b = Br



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|  | X |  | X |
|---|---|---|---|
| a | $OCH_3$ | e | Br |
| b | $CH_3$ | f | $CO_2Et$ |
| c | F | g | CN |
| d | H | h | $NO_2$ |

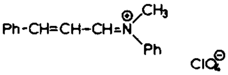

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Table 1

Chemoselectivity of the reduction of phenyl-substituted α,β-unsaturated iminium salts by Hantzsch ester

| substrate | X | $pK_a$ amine | $E\frac{1}{2}(V)$[a] | yield[b,c] | ratio[e] $>C=C<$ attack | $>C=N^{+}<$ attack |
|---|---|---|---|---|---|---|
| 2a | — | 11.27 | −0.75 | q | 100 | 0 |
| 2b | — | 8.33 | −0.66 | q | 100 | 0 |
| 3a | $OCH_3$ | 5.34 | −0.47 | 96% | 77 | 23 |
| 3b | $CH_3$ | 5.08 | −0.43 | q | 29 | 71 |
| 3c | F | 4.65 | −0.38 | q | 28 | 72 |
| 3d | H | 4.63 | −0.35 | q | 21 | 79 |
| 3e | Br | 3.86 | −0.32 | q | 10 | 90 |
| 3f | $CO_2Et$ | 2.46 | −0.22 | q | 0 | 100 |
| 3g | CN | 1.74 | −0.15 | 96% | 0 | 100 |
| 3h | $NO_2$ | 1.0 | +0.04 | q | 0 | 100 |
| 4a | H | 4.63 | −0.59 | q[d] | 100 | 0 |
| 4b | Br | 3.86 | −0.49 | 90% | 100 | 0 |
| 5 | — | 4.8 | −0.44 | q | 100 | 0 |

a In $CH_3CN$ (0.1 M $Et_4NClO_4$) relative to the saturated calomel electrode

b q = quantitative ≥97%

c determined in duplicate

d 95% $PhCH_2CH_2CH(CH_3)NHPh$ + 5% $PhCH_2CH_2C(=O)CH_3$

The α,β-unsaturated iminium salts are ambident electrophiles, which can undergo a formal hydride[10]-transfer from the dihydropyridine 1 to either C-1 or C-3 of the conjugated system. The substituents on both ends of the $>\underset{3}{C}=\overset{|}{C}-\underset{1}{\overset{|}{C}}=N^{+}<$ -chromophore would be expected to influence the ratios of the C-1 to C-3 attack. A substituent effect is indeed borne out by the data presented in Table 1.

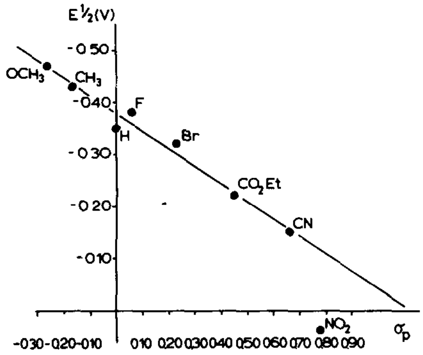

Figure 1

Plot of the polarographic reduction potential of $Ph{-}CH{=}CH{-}CH{=}\overset{+}{N}H{-}C_6H_4{-}X$ $ClO_4^-$ vs the $\sigma_p$ of X

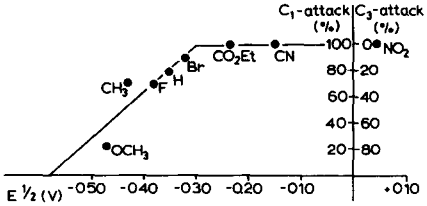

Figure 2

Plot of the preference for $\rangle C{=}\overset{+}{N}\langle$ attack by Hantzsch ester on $Ph{-}CH{=}CH{-}CH{=}\overset{+}{N}H{-}C_6H_4{-}X$ $ClO_4^-$ vs the polarographic reduction potential of the substrate

It has been recently shown that the results of the reaction of anionic nucleophiles with α-enones[11] are explicable in terms of the generalized perturbation theory, attack at C-α and C-γ (of the enones) being charge or frontier orbital controlled, respectively. Application of this approach to the reaction of HE with the conjugated iminium salts would predict that charge controlled reduction should result in $\rangle C{=}\overset{+}{N}\langle$ attack, while orbital controlled reduction would lead to $\rangle C{=}C\langle$ attack. Furthermore, substituents at or in the vicinity of the potential reaction sites of the substrate would be anticipated to display steric effects, in addition to their electronic influences.

Before considering the data in Table 1 it is pertinent to recall the experimental observation that $NaBH_4$-mediated reduction of <u>all</u> substrates results exclusively in products corresponding to attack on the $\rangle C{=}\overset{+}{N}\langle$ bond. This would imply a charge controlled reaction between the α,β-unsaturated iminium salts and $NaBH_4$. In this connection it should be mentioned that the stereochemical course of reduction of iminium salts, by $NaBH_4$, has also been explained on the basis of a charge controlled process[4c].

In the reaction between a series of iminium salts possessing varying energy levels for the lowest unoccupied molecular orbital (LUMO) (measured as half wave reduction potentials, E½) and Hantzsch ester, it has been shown that the stereochemistry of the reduction is relatable to the E½ values[4c]. In the case of unsaturated iminium salts 3a-h, the polarographic half wave reduction potentials (E½) exhibit a direct correlation with the $\sigma_p$ values[12] (Fig. 1) of the para substituents and $pK_a$ (Table 1) of the aromatic amine moiety. Since the half wave reduction potentials reflect the relative energies of the LUMO's of the substrates, it is interesting to examine the relationship between these potentials and the $\rangle C{=}\overset{+}{N}\langle / \rangle C{=}C\langle$ attack ratios (Table 1 and Fig. 2). Examination of Table 1 shows that for the substrates 2a,b and 3a-h with $E_{\frac{1}{2}}$ values below -0.59 V, $\gt C{=}C\lt$ attack is the preferred process, while in the case of the substrates exhibiting $E_{\frac{1}{2}}$ values above -0.30 V, the hydride[10] species is delivered to the $\gt C{=}N^{+}\lt$ group. In the reaction of the unsaturated iminium salts 3a-e which possess intermediate range $E_{\frac{1}{2}}$ values, the percentage of $\gt C{=}N^{+}\lt$ reduction displays a linear relationship with the reduction potential (Fig. 2). The salts 4a,b and 5 are of special interest since their reduction pattern reveals the steric influence of the substituents flanking the $\gt C{=}N^{+}\lt$ group. Thus, despite the reduction potentials of -0.49 V and -0.44 V for 4b and 5, respectively, both substrates exhibit an exclusive $\gt C{=}C\lt$ reduction.

While the aforementioned results show a distinct relationship between the chemioselectivity of reduction of α,β-unsaturated iminium salts by Hantzsch ester and the half wave reduction potential of the salts, attempts to correlate this selectivity with diverse calculated properties of the molecular systems are in progress.

## Acknowledgement.

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