THE REDUCTION OF TRIFLUOROACETOPHENONE BY METHYL-SUBSTITUTED DIHYDRONICOTINAMIDES

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Abstract — In a series of methyl-substituted 1-(2,6-dichlorobenzyl)-1,4-dihydronicotinamides, compounds with a methyl group α to the pyridine nitrogen have a free energy of activation which is at least 7.5 kJ/mol lower than those without methyl or with methyl on the 5-position.

Introduction

The reductive properties of 1,4-dihydronicotinamides have been the subject of intense research in recent years. Few reports on kinetics, however, deal with variations on the dihydropyridine compound itself[13]. Even more scarce are reports that study variations other than in the substituent on 1 or 3 position[7].

We here report on the experimental results from the kinetics of the oxidation of 2-, 5- and 6-methyl-1-(2,6-dichlorobenzyl)-1,4-dihydronicotinamides by trifluoroacetophenone (TFAP)[1]. These compounds act as biomimetic models for the reduction of ketones by NADH (nicotinamide adenine dinucleotide in its reduced form).

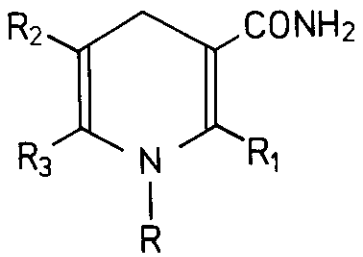
In another report these results will be used as a "benchmark" for existing quantum-chemical models[8,11,12]. The choice of reductants was dictated by quantum-chemical limitations : (1) the variation in reactivity has to be large enough to be accounted for by quantum-chemical methods, (2) comparison should be possible between the electronic energies of the compounds and (3) systematic errors, typical for the chosen calculation method should be minimised.

Whereas the first point maximises variation, the last two points minimise variation in geometry. A constant number of atoms covers the last two points, so a search was made for isomers with enough variation in reactivity.

Dommisse et al.[7] reported on the oxidation of 3,5-diethoxycarbonyl-2,6-dimethyl-1,4-dihydropyridine (Hantzsch ester) by chloranil in $CHCl_3$. However, unmethylated 3,5-diethoxycarbonyl-1,4-dihydropyridine did not react. This behaviour was observed throughout a series of analogues which were

only reactive when methyl groups were present at 2- or 6-positions.

In order to study the influence of a methyl group on the oxido-reduction behaviour of 1,4-dihydropyridines, a series of ring-substituted methyl-1-(2,6-dichlorobenzyl)-1,4-dihydronicotinamides were synthesized (Fig. 2) and subjected to reaction with a suitable substrate. As will be shown, the variation in reactivity was substantial. The 2,6-dichlorobenzyl (DCB) group turned out to be the only N-substituent for which as well the 2- and 5-methyl isomers as 6-methyl isomers could be synthesised, none of these showing many competitive reactions[5,23].



Ia : $R_1 = R_2 = R_3 = H$

Ib : $R_1 = CH_3$, $R_2 = R_3 = H$

Ic : $R_2 = CH_3$, $R_1 = R_3 = H$

Id : $R_3 = CH_3$, $R_1 = R_2 = H$

Fig. 2 : Structures of 1,4-dihydronicotinamides

Many substrates are reactive towards 1,4-dihydropyridines. Most of these are at least bifunctional. As it is our intention to use the results as a parametrisation for theoretical studies, it is imperative that the compounds studied should be as simple as possible. A suitable monofunctional ketone is 1,1,1-trifluoroacetophenone (TFAP). Its reaction with 1,4-dihydronicotinamides (see Fig. 3) has been well documented[5,18,21,22,23]. Although the reversible formation of a adduct between analogues of I_a (with R = benzyl or propyl, $R_1=R_2=R_3$ = H) and TFAP has been reported, the contribution of such a compound is not important in the case of 1-(2,6-dichlorobenzyl) derivatives, possibly due to steric hindrance[5,23].

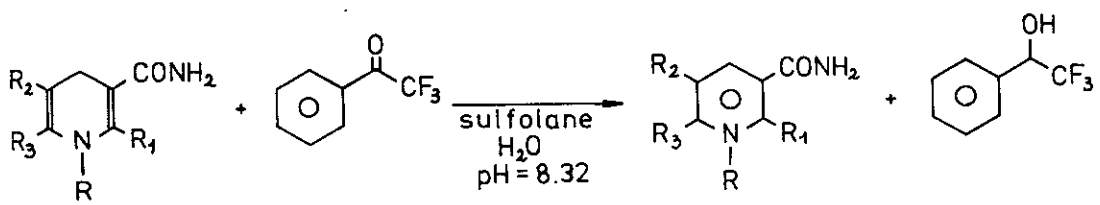


Fig. 3 : The reduction of TFAP by dihydronicotinamides (Ia-Id)

Results and discussion

The Choice of Substrates : The dihydronicotinamides were synthesised by sodium dithionite reduction

of the corresponding pyridinium salts. Attempts were made to reduce the corresponding 1-methyl pyridinium salts. However, neither reduction products nor starting materials could be isolated after the reaction was completed. It is likely that reduction took place, but that the reduction products were too labile in the medium (H_2O at pH=8) to be isolated. In a next attempt the 1-benzylpyridinium salts were subjected to the same reduction. All dihydropyridines could be isolated except the 1-benzyl-2-methyl-3-carbamoyl-1,4-dihydropyridine. Again no starting material could be recovered. In a third attempt it proved to be possible to reduce the 1-(2,6-dichlorobenzyl)-pyridinium salts and to isolate the corresponding dihydropyridines.

The pyridinium salts were derived from the corresponding nicotinamide homologues through alkylation. These nicotinamides were derived either from alkyl-substituted pyridines by oxidation or by ring closure procedures and subsequent derivatisation[4].

Kinetics : The reaction medium was chosen in analogy of Stuart et al.[21,22], i.e. aqueous solutions were used. The initial transformation rate of the dihydronicotinamides was determined spectrophotometrically. In principle the reaction is pseudo-first order in I(a-d)[5,18,21,22,23] in the presence of a large excess of TFAP. However, correction has to be made for the decomposition of I(a-d). Indeed, most 1,4-dihydropyridines are unstable in aqueous solutions as they undergo hydration[16].

The reaction was followed at 5 temperatures approximately 10°C apart in the range of 10°C to 50°C, with a stability of ±0.2°C. Exception was made for 2-methyl-(2,6-dichlorobenzyl)-dihydronicotinamide, which reacted too fast at the highest temperature.

The reaction was run "in batch", i.e. the reaction was not followed continuously, but samples were taken from separate reaction vessels. In this way a fresh, unirradiated solution was measured so that decomposion or side reactions due to u v-irradiation could be ignored. Each time a blank vessel (containing only I) and a sample vessel (containing I and TFAP) were prepared and followed to determine the dissapearance rate of I. The solutions were kept in the dark (dihydropyridines undergo decomposition upon irradiation). At all times a nitrogen blanket was kept over the solutions in order to prevent oxidation by air oxygen (which occurs even at room temperature).

Kinetic Calculations : The decomposition of the dihydropyridines (blanks) as well as the combination of decomposition and reaction with trifluoroacetophenone (samples) are pseudo first-order in dihydropyridine (Fig. 4), since all reagents are in excess. The pseudo first-order rate constants for the reaction with TFAP can be found by substracting the rate constant for decomposition from the rate constant of the combined reaction (eq. 1). Pseudo first-order dependence was verified for each dihydropyridine by measurements at different total trifluoroacetophenone concentrations (excesses from 100 times to the 600 times the dihydropyridine

concentration). The second order rate constants can be calculated according to eq. 2.

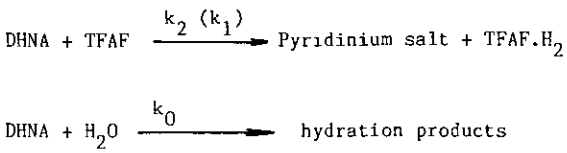


Fig. 4 : Reactions considered in the calculations.

In aqueous solutions the balance between trifluoroacetophenone and its hydrated form is shifted towards the hydrate[19,20]. The choice of the medium maximises the rate of equilibration between these two forms. The free ketone concentration is effectively buffered and the rate of its formation does not compete with the reduction itself[21,22]. The concentration of free ketone can be calculated according to Stuart[20,21] via thermodynamic parameters.
The free activation enthalpy was calculated from the second order reaction constants according to Eyring[6] (eq. 3).

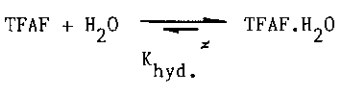


Fig. 5 : Keto-hydrate equilibrium for (TFAP)

$$k_1' = k_1 + k_o \qquad (1)$$

$$k_2 = k_1 / \mid TFAF \mid \qquad (2)$$

$$k_2 = \frac{k \cdot T}{h} \cdot e^{\frac{-\Delta G^{\neq}}{R \cdot T}} \qquad (3)$$

Thermodynamic relations

A free activation enthalpy-absolute temperature plot proved to be linear in all cases (Fig. 6). Therefore it was assumed that the activation enthalpy $\Delta H^{\neq}$ and activation entropy $\Delta S^{\neq}$ were constant in the considered temperature interval. The activation parameters were then calculated by linear regression on the basis of equation 4. The results and estimates of their reproducibility are

compiled in Table I.

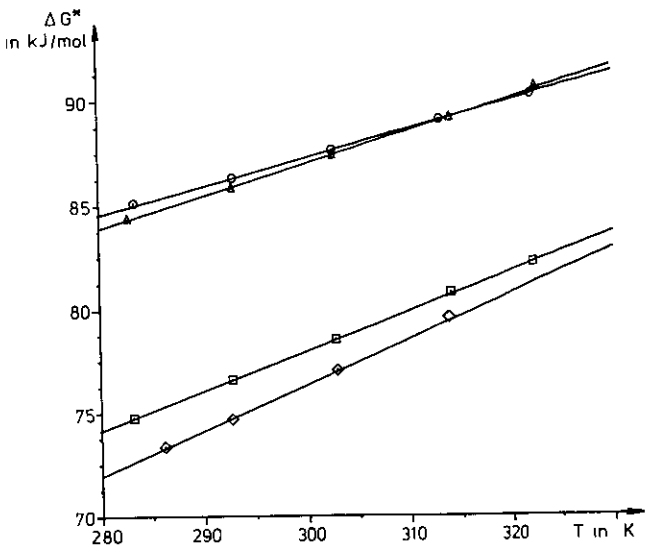


Fig. 6 : ($\Delta G^{\neq}$, T)-plot

$$\Delta G^{\neq} = \Delta H^{\neq} - T \cdot \Delta S^{\neq} \qquad (4)$$

Methyl-substitution	Activation Enthalpy in J/mol	Activation Entropy in J/mol K
none	39700 ± 1100	-158 ± 4
2-pos.	10600 ± 1300	-219 ± 4
5-pos.	46500 ± 500	-135.0 ± 1.7
6-pos.	20600 ± 900	-191 ± 3

Table I : Activation parameters as a function of methyl-substitution.

Although the results in Table I and a "classical" ($\Delta H^{\neq}$,$\Delta S^{\neq}$)-plot according to Leffler[14] (Fig. 7) suggest an isokinetic relationship, no clear isokinetic point can be discerned in an extrapolated ($\Delta G^{\neq}$,T)-plot. This supports the vieuw of Exner and others[9,17] that the ($\Delta H^{\neq}$,$\Delta S^{\neq}$)-plot is in principle unfit to substantiate a claim of an isokinetic relationship. A plot of

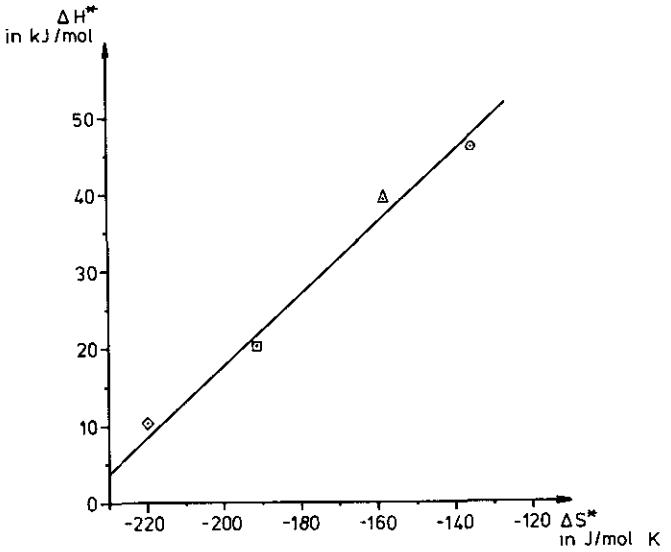


Fig. 7 : ($\Delta H^{\neq}$,$\Delta S^{\neq}$)-plot according to Leffler

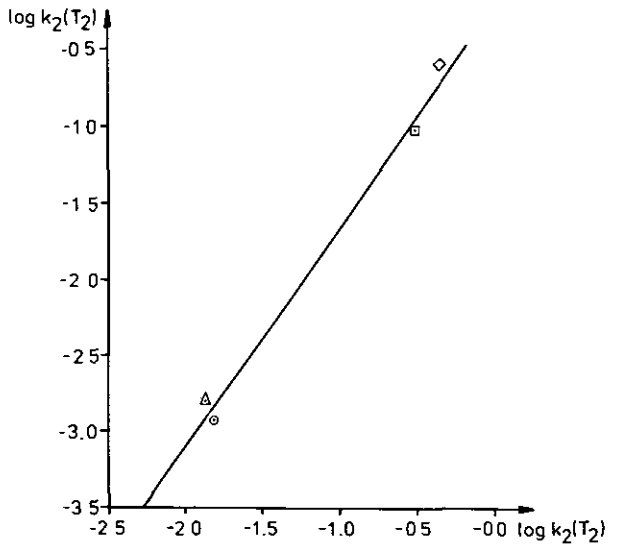


Fig. 8 : Exner-plot of log (k_2) at 2 temperatures

$(\log(k_2(T_1)),\log(k_2(T_2)))$ according to Exner[9] (Fig. 8) shows a possible isokinetic relationship with a correlation coefficient of 0.997 . It should be noted however that the points are not evenly distributed. This result should therefore be handled with caution.

It can safely be said, however, that the reactivities of Ia and Ic are comparable, whereas Ib and Ic are two orders of magnitude more reactive towards reduction of TFAP. It does not seem sensible to propose a different reaction mechanism for the Ia,Ic-couple on one hand and the Ib,Id-couple on the other hand. The eventual absence of an isokinetic relationship might well be the result of steric interactions[14], since the last two compounds are severely sterically hindered with respect to the N-DCB-rotations.

An analogous behaviour was first observed by Dommisse[7] et al. in a series of Hantzsch ester homologues. A sensible hypothesis at the time seemed to be that the methyl groups on the 2- and 6-positions tilted the ethoxycarbonyl moieties out of the dihydropyridine plane. Subsequent loss of mesomeric stabilisation would leave a higher electron density on the dihydropyridine ring, promoting a formal hydride transfer. This hypothesis was supported by the fact that 3,5-dicyano-2,6-dimethyl-1,4-dihydropyridine was also unreactive towards chloranil.

The relatively high reactivity of the 6-methyl compound (Id) makes this hypothesis implausible. Moreover, it was shown that the Hantzsch ester is plane in the solid[10,15]. This indicates that in neither case the "methyl-effect" resides in the loss of mesomeric coupling between the dihydropyridine and carbonyl moieties.

Differences in solvation can also be discarded as the source of the discrepancies, since the effect persists in totally different media (the reaction with the Hantzsch esters were carried out in anhydrous solutions).

This leaves the source of the difference in reactivity with the methyl groups themselves. However, it is not clear how the effect of methyl groups on the ground state of I could lead to the observed behaviour since C^{13}-NMR and preliminary STO-3G results indicate the normal predictable influences.

In conclusion, an explanation for the observed "methyl-effect" is not trivial. Its source might well lie in electronic effects upon the transition state or sterical effects upon the changing geometry (bond angles), while the dihydropyridine ring is changing to a pyridinium ring. A pure phenomological approach is clearly unsuitable and a more refined study is being done using quantum-chemical methods.

EXPERIMENTAL

The synthesis of the dihydronicotinamide compounds is discussed in a following article[4].

The 1,1,1-trifluoroacetophenone (Aldrich 10 784-0) was used without purification : a G.L.C.-analysis proved that there were no interfering impurities. The reaction medium was chosen in

analogy of Stuart[21,22]), i.e. a 21.7 : 79.3 mixture of sulfolane (Uvasol Merck 7991) and borate buffer at pH = 8.32.

The transformation of the dihydronicotinamides was followed on a HITACHI 181 single beam spectrophotometer at λ_{max} for each compound. These reaction vessels were kept in thermostate baths (Julabo Paratherm II) with a stability of ±.2°C.

The pseudo first-order constants were calculated by weighted linear regression[1] of the evolution of the extinction of the dihydropyridines during 25% of $T_{1/2}$ of the reaction. In this way eventual influence of side reactions was minimised. The extinction was corrected for absorption by the solvent and by trifluoroacetophenone. The calculations were carried out on a HP-41C.

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