AB INITIO QUANTUM-CHEMICAL STUDY ON THE INFLUENCE OF METHYL SUBSTITUTION ON THE REDOX BEHAVIOUR OF 1,4-DIHYDRONICOTINAMIDES. PART 1 : UNPERTURBED MOLECULES AND PERTURBATIONS TOWARDS A POSSIBLE TRANSITION STATE

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Abstract - The experimental^{31} reactivity sequence of a series of methyl substituted 1-(2,6-dichlorobenzyl)-1,4-dihydronicotinamides is compared with the results of an ab-initio STO-3G quantum-chemical calculations on the corresponding 1-methyl compounds. The molecules were studied both in approximative equilibrium geometry and geometries distorted towards a possible transition state. The theoretical results are successfully confronted with the experimental data.

1. Introduction

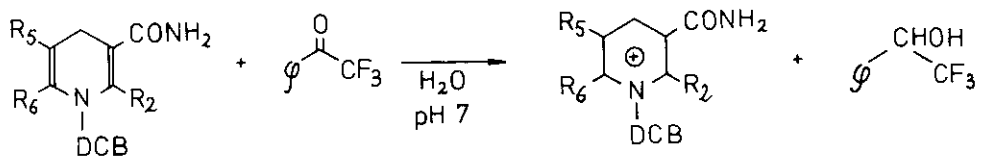
The reductive behaviour of dihydropyridines has been the subject of intensive research [1,2] in the past as well as in the present. Among these, 1,4-dihydronicotinamides (DHNA-s) received considerable interest in view of their

role as model compounds for NADH (reduced nicotinamide adenine dinucleotide). The reduction of activated ketones by DHNA's can be considered as a biomimetic reaction[3] for the enzymatic reduction of ketones, for instance by H.L.A.D. (Horse Liver Alcohol Dehydrogenase), using NAD as coenzyme. The mechanism of this reaction, in which -formally- a hydride ion is transferred from the DHNA to the carbonyl of the ketone, has been studied extensively[4-17].

Basically, three models have been proposed to describe this transfer[1]. The most obvious model is the one where the hydrogen is considered to migrate as a real hydride ion. In a second model an electron migration is proposed to occur first (creating a radical pair), followed by the migration of a hydrogen radical. Some authors consider even this migration to occur as a two step mechanism, where first a proton migrates and then an electron. Finally, models were proposed for concerted mechanisms where both transfers (of electrons and hydrogen) as well as rehydridisations (of DHNA and ketone) occur simultaneously. Such models do not exclude unequal rates for bond formation and bond cleavage.

Experiments with radical captors[5,7], E.S.R.-studies [16,7] and kinetic studies[17] on the rate of formation of the hydrogen radical showed that the radical mechanism is highly improbable, at least as far as the reduction of ketones is concerned[18]. The hydride ion itself is highly reactive with protic media. Many of the experiments with NADH or DHNA's are conducted in aqueous solutions, which implies that they are relatively stable in these media. Consequently, a direct hydride migration is not a likely mechanism. The most realistic model is therefore some form of concerted mechanism. Quantum-chemical studies are used to get a deeper insight into the precise nature of this mechanism. 1-Methyl-1,4-dihydronicotinamide has been the subject of many quantum-chemical studies. In 1959, Pullman[19] performed a L.C.A.O. M.O.-study to elucidate its electronic structure. Until quite recently a wide variety of quantum-chemical methods has been applied to study various properties of this compound : from simple all-valence semi-empirical EHT[20-22] and NDO-type [23-28] methods to more sophisticated ab initio methods (STO-3G) as used by Boehm[29,30] in 1983. The subject of these studies varies from calculations on the geometry and properties of the DHNA-s themself[19,20,22,29,30] to more elaborate calculations on possible transition states (TS)[21,22,24-28]. A problem in most of these studies, especially in the TS-studies, is the scarcity of confrontation with experimental results, because of the lack of suitable experimental material.

In an earlier paper[31], the experimental results of a kinetic study on the reduction



0M : $R_2 = R_5 = R_6 = H$

1-(2,6-dichlorobenzyl)-1,4-dihydronicotinamide

2M : $R_2 = CH_3$, $R_5 = R_6 = H$

1-(2,6-dichlorobenzyl)-2-methyl-1,4-dihydronicotinamide

5M : $R_5 = CH_3$, $R_2 = R_6 = H$

1-(2,6-dichlorobenzyl)-5-methyl-1,4-dihydronicotinamide

6M : $R_6 = CH_3$, $R_2 = R_5 = H$

1-(2,6-dichlorobenzyl)-6-methyl-1,4-dihydronicotinamide

DCB : 2,6-dichlorobenzyl

Fig. 1 : The model reaction for the reduction of ketones by NADH.

of 1,1,1-trifluoroacetophenone (TFAP) by methyl substituted DHNA-s (fig. 1) have been reported. The reactivity sequence of these compounds with TFAP in aqueous solution was 2M > 6M > 0M > 5M, the activation enthalpies being 10.6, 20.6, 39.7 and 46.5 kJ/mol, respectively. The aim of the present study is a quantum-chemical interpretation of these kinetic results. In the quantum-chemical discussion, the DHNA-s are considered as isolated molecules, i.e. in the absence of an oxidising reagent. Both the approximative equilibrium geometries (unperturbed molecules) and geometries distorted towards a possible transition state (perturbed molecules) according to Krechl's[22,25] hydrogen elongation model will be studied. The influence of methyl substitution and the conformation of the carbamoyl moiety on the enrgy as well as on the charge distribution of these isolated molecules will be investigated.Kuthan et al.[19-24,26,28,29] used various quantum-chemical methods (EHT, CNDO, STO-3G) to describe the properties of 1-methyl-1,4-dihydronicotinamide. On the basis of his work, it was decided to discard semi-empirical methods of the NDO-type due to their obvious shortcomings

and to perform all calculations at a common level of sophistication. . In spite of their size, all calculations will be performed at the minimal basis set ab initio (STO-3G) level. In the past fifteen years this simple ab initio method has proved to be an extremely usefull and reliable working tool in innumerable studies in the field of theoretical organic chemistry[32].

2. Results and discussion

I. Studies on the unperturbed molecules

I.a. Geometry :

Although the kinetic study was conducted on 1-(2,6-dichlorobenzyl)-1,4-dihydronicotinamides it was decided to perform the calculations on 1-methyl substituted compounds because of computational limitations. There are two X-ray structures available (α[33] and β[34], see Fig. 2) on which a geometry for 1-methyl-1,4-dihydronicotinamide could be based. It could be argued that the 1-alkyl substituent of structure β resembles the 1-methyl group most. However, by choosing structure α as basis, we simplify the benzyl-group to a methyl group. We will make a similar idealisation when simplifying the dichlorobenzyl-moiety to a methyl group, while comparing the kinetic results with the quantum-chemical ones. The $\hat{C_3C_4C_5}$ angle in structure β is 118°. This angle is atypical for an sp^3-hybridisation. Structure α and X-ray structures of other 1,4-dihydropyridines

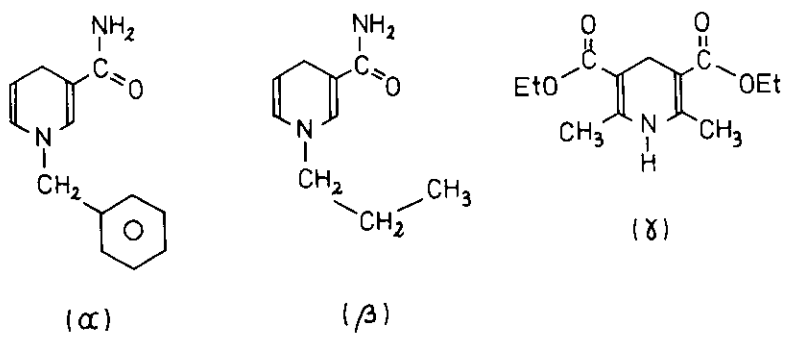


Fig. 2 : 1,4-dihydropyridines of interest in the present study for which X-ray structures are available.

(e.g. structure γ[35]) do not show such a large angle. On the basis of these arguments, structure α is preferred over β. It should be noted that structure α is almost exclusively used by other authors.

The hydrogen atom positions were calculated, assuming equal bond lengths (C-H at 1.08 Å), since they were not given in reference 33. The positions of the hydrogen atoms on sp^2 carbon atoms, as well as on the amide moiety, were assumed to be symmetrical. The $H_R\text{-}\hat{C}_4\text{-}H_S$ angle in the methylene group was calculated according to equation 1[36], where $\psi = H_R\text{-}\hat{C}_4\text{-}H_S$ and $\xi = C_3\text{-}\hat{C}_4\text{-}C_5$. An idealised geometry was used for all methyl groups (C-H = 1.08 Å, $\hat{HCH}$ = 109.5°, C-C = 1.54Å). A common orientation was used , with one hydrogen atom pointing in the positive z-axis direction (see Fig. 3). These idealisations are plausible since we are

$$\psi = 126.1° - .175\ \xi \qquad (1)$$

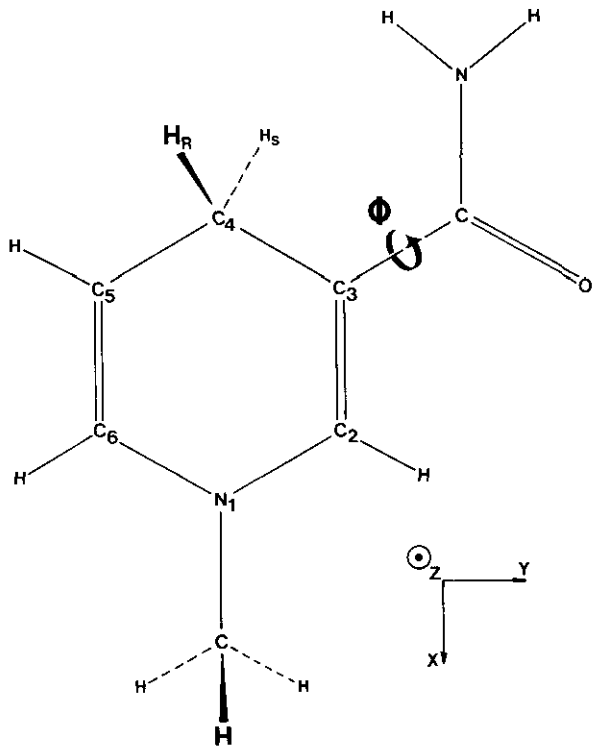


Fig. 3 : Numbering convention and orientation of substituents in 1-methyl-1,4-dihydronicotinamide. The conformation with a carbamoyl rotation angle (see text) ϕ = 0° is shown.

essentially interested in the relative behaviour of the various compounds. No further structure optimisation was performed. At an ab initio level this would lead to prohibitively large computation times, at NDO-type semi-empirical level the results might not be thrustworthy[29,30].

I.b. Influence of idealised methyl substitution

As a reference , the calculated total energies for the analogues 0M, 2M, 5M and 6M, are compiled in TABLE 1.

Analogues	Total energy in a.u.
0M	-448.905841
2M	-487.446279
5M	-487.487936
6M	-487.482815

Table 1 : Total energy of the analogous DHNA-s (0M-6M)
(1 a.u. = 1 Hartree = 627.50959 kJ/mol)

The quantities we are most interested in at this level are the valence electron populations on the atoms of the methylene moiety. These are shown in fig.4. All other atoms show some influence of methyl substitution, but lend themselves less to correlation with the kinetic data. In general it is seen that upon methyl substitution the methylene group as a whole becomes more negative, mainly because of the changes on H_R and H_S. Note that the electron populations on H_R and H_S differ slightly. Because of the orientation of the methyl group, they are not completely equivalent. The results concerning the influence of methyl substitution on the electron excesses at H_R are supported by the N.M.R.-shifts of these protons in Fig. 5 - when leaving the value for the 5-methyl analogue out of consideration. In this case, the methylene hydrogen atoms receive a large extra upfield shift due to sterical screening[37]. A very satisfying correlation between these electron excesses and chemical shift is obtained, indicating that the higher the electron population of H_R, the larger the proton upfield shift.

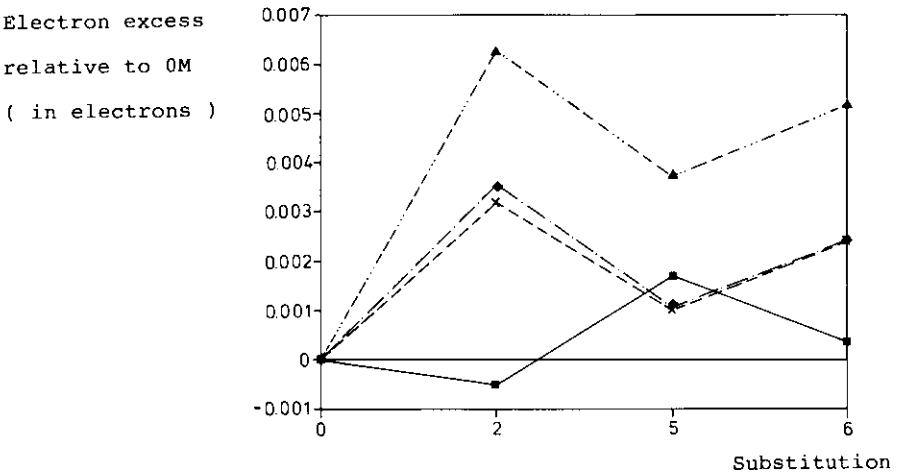


Fig. 4 : Influence of methyl substitution on the electron population of the methylene atoms (depicted as electron excess relative to 0M).
■ = C_4, ◆● = H_S, ✕ = H_R, ▲ = CH_2.

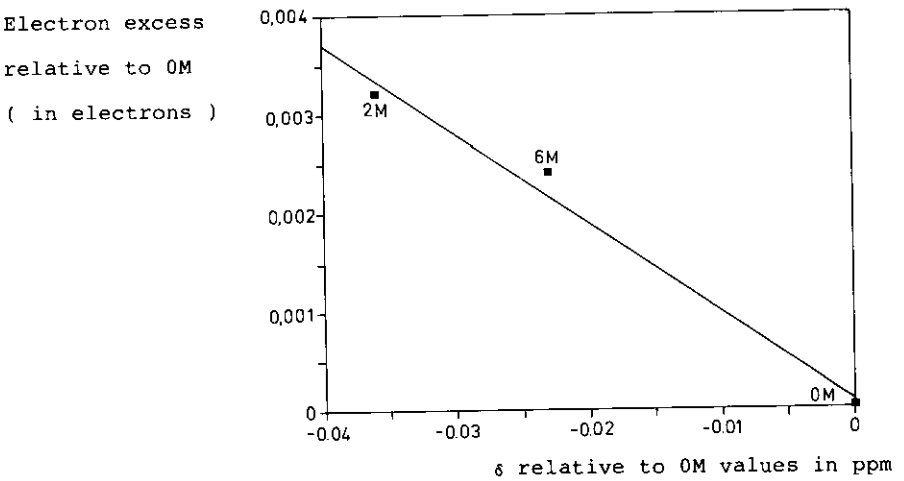


Fig. 5 : NMR-shifts of the methylene protons versus the electron populations on the H_R atoms.

The electron density on H_R is compared to the observed activation enthalpy in Fig.6. Including all compounds, a reasonable correlation is achieved. On omission of the 5M analogue (for which a rationale will be discussed later), the

correlation improves substantially.

These results are a first support for a model in which the hydrogen atom is transferred as a hydride ion or where at least a considerable amount of negative charge is transferred via the hydrogen atom.

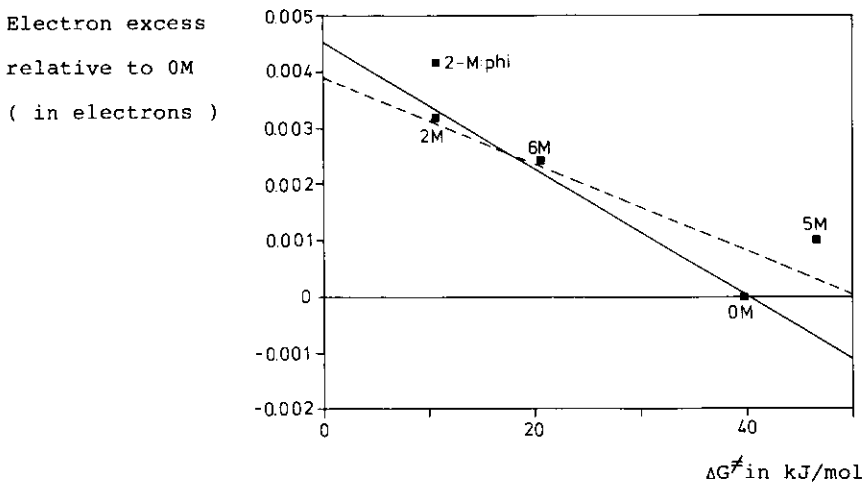


Fig. 6 : Activation enthalpy versus electron population on H_R relative to 0M. – – – : correlation including all compounds, ——— : correlation excluding 5M analogue. 2M Incl. designates the inclined 2M, vide infra.

I.c. Influence of carbamoyl rotation

The carbamoyl moiety was rotated in such a way that the amine part first approaches the H_S and is subsequently positioned "under" the dihydropyridine plane for positive angles δ (see Fig. 3). Intervals of 30° were chosen.

Various properties (e.g. energy, electron population etc.) can be expected to show a symmetry around 90° (and 270°), if the effect of rotation is mainly the loss of conjugation between the carbamoyl moiety and the unsaturated ring. At this rotation angle, the effect is minimal. If sterical or polarising effects are dominant, a symmetry around 0° and 180° would be expected.

The rotation energy (i.e. total energy relative to the conformation with $\phi = 0$) follows a profile which confirms the findings of Boehm[30] (Fig. 7). The maximum at 90° can be regarded as the result of a loss of conjugation between the carbamoyl moiety and the dihydropyridine ring. The maximum at 180° can be the result of

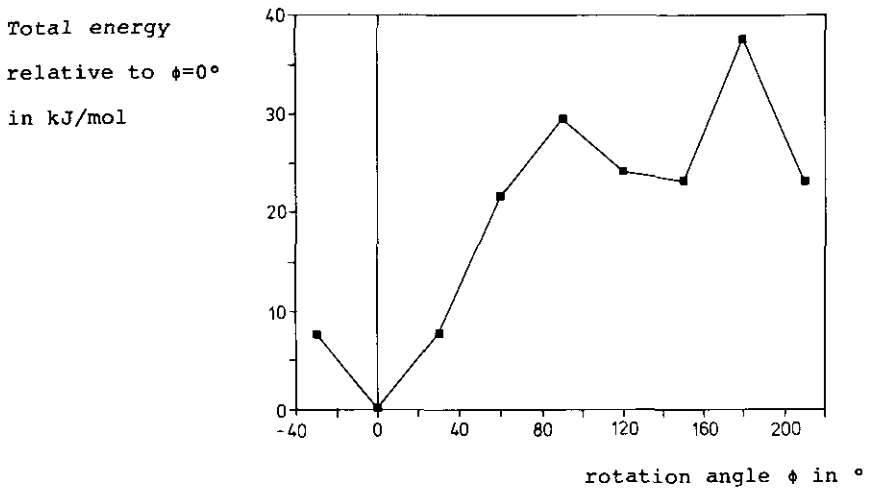


Fig. 7 : Influence of $CONH_2$-rotation on the total energy.

sterical hindrance between the NH_2 of the carbamoyl moiety and C_2-H group of the ring. The relative values of the maxima at 90 and 180° suggest that restoring the conjugation at 180° does not compensate completely for the sterical hindrance. The resulting local minimum cannot be discerned in CNDO/2. This illustrates the danger of mixing results from CNDO/2 and from ab initio while optimising (these) structures. The differences between our results and those of Boehm are due to the use of different geometries. Whereas Boehm uses partially optimised structures (with CNDO/2), we used the original X-ray diffraction structures. Because of the above mentioned deficiencies of CNDO/2, this choice seems to be more suitable.

The influence of rotation on electron populations is depicted in Fig. 8. Only those groups showing a variation larger than .01 e are discussed. As intuitively expected, these are the carbamoyl group, the methylene group and the C_2-H group. During rotation, a charge transfer from the methylene moiety to C_2-H seems to take place. The symmetry suggests that steric and polarisation effects are at the origin. The electron population of the carbamoyl moiety reaches a minimum at 90°. Its symmetry seems to indicate loss of conjugation as the cause.

I.d. Influence of idealised methyl-substitution on the carbamoyl rotation

The energy profile for all analogues is shown in Fig. 9. The 5M and 6M analogues

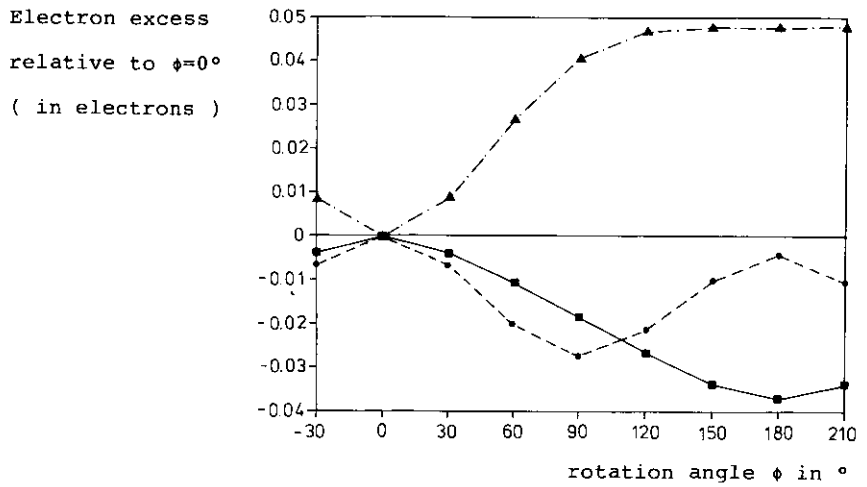


Fig. 8 : Influence of $CONH_2$-rotation on the electron populations of the CH_2- (■), $CONH_2$- (●) and C_2-H group (▲).

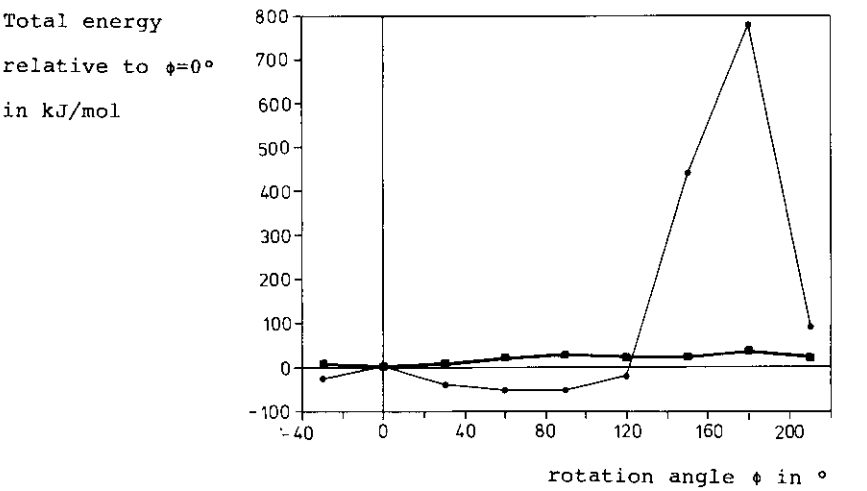


Fig. 9 : Influence of methyl substitution on the rotation energies : the 2M (●) follows a totally different profile than the other analogues, whose values overlap (■).

show an almost identical profile as the 0M analogue. This can be intuitively predicted in view of the large distance between the methyl and carbamoyl groups. The 2M analogue shows minima at 61.8° and -73.2°, i.e. close to the regions where

the others show a maximum (the minimum at -73.2° lies 1.38kJ/mol higher than the one at 61.8°). Then it starts rising strongly due to hindrance between the NH_2 and the methyl group on C_2. Here the effect of steric hindrance is more important than the loss of conjugation as the methyl group in 2M is much bulkier than the hydrogen atom in the other analogues. Even the carbonyl oxygen has an unfavourable interaction with this methyl group, which results in a maximum at 0°. For ϕ-values between 120° and 180°, this leads to structures which are extremely high in energy and which will certainly distort from the idealised geometries used.
The electron populations (not given) show an analogous behaviour for all analogues, except in those cases where steric hindrance obviously interferes with the normal profile.

Summarising, from the calculations on the structures with a planar carbamoyl group, it is seen that the methyl group directly influences the electronic distribution of the DHNA-s. The correlation illustrated in Fig. 6 advocates a hydride- like model or a concerted mechanism where the methylene hydrogen transfers considerable charge. If the indirect effect of methyl substitution is taken into account (i.e. its effect on the carbamoyl orientation in the 2M analogue), the same trend can be discerned, albeit with a lesser degree of correlation (2M Incl. in Fig. 6 designates the 2M with ϕ = -73.2°). This indicates that the differences in reactivity, at least at this level of sophistication, are mainly caused by electronic effects of methyl substitution. Sterical influences on the rotation of the carbamoyl group play a less important role.
A next step is obtaining information about the influence of methyl substitution on the TS. In a first approach, the influence of this substitution on DHNA-s which are perturbed towards the TS, will be studied.

II Perturbation of the DHNA-s towards the TS

IIa. Geometry

The model chosen is based on the work by Krechl[22,25], which was conducted at CNDO/2 level. In this model one of the methylene C-H bonds (here H_R) is elongated. It was shown by Krechl that rehybridisation of the methylene carbon atom did not influence the results significantly. Here also, no rehybridisation was introduced

upon elongation. Because of this restriction only relatively small elongations will be studied (from 0 Å to .9 Å). Therefore they can still be looked upon as perturbations of the GS towards the TS.

The SCF approach, which lies at the basis of the ab initio method, might be inadequate to describe homolytic bond fission, since it uses a single determinantal wave function[38]. Experimental evidence (vide supra) indicates that the radical mechanism is highly improbable. As far as heterolytic bond fission is concerned, the SCF procedure ca be expected to predict correctly the direction of charge separation.

IIb. Influence of the perturbation on energy and electron density

The elongation energy (rise in total energy due to elongation) versus distance curve (Fig. 10) follows a profile comparable to the CNDO/2 results by Krechl[25]. It shows the expected parabolic behaviour for relatively small elongations until it starts levelling off from .6 Å on.

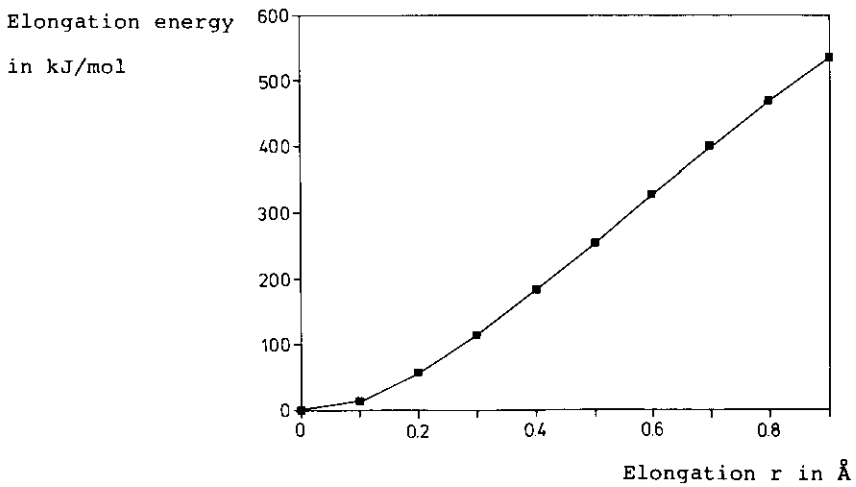


Fig. 10 : Influence of H_R-elongation on the total energy.

From Fig. 11 it can be concluded that considerable charge separation takes place between H_R and the remaining methylene atoms. For small elongations the (relative) negative charge on H_R monotoneously increases whereas the C_4-atom carries all developing positive charge. At larger elongations this positive charge

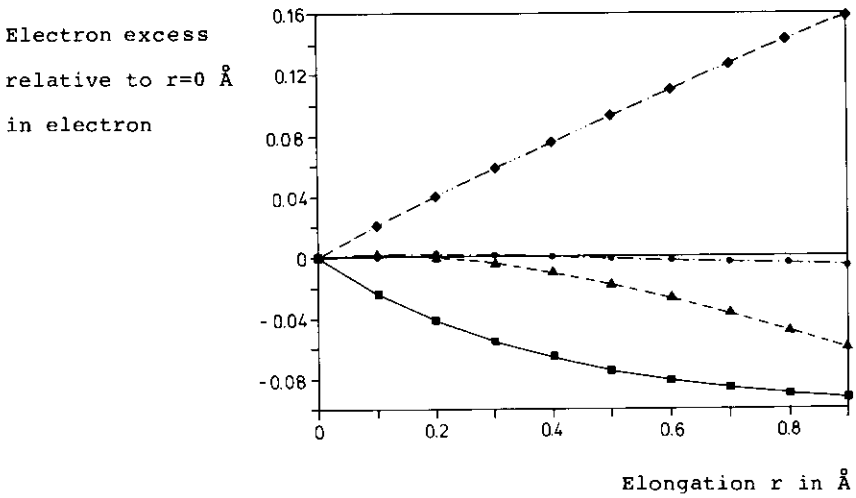


Fig. 11 : Influence of H_R-elongation on the electron populations of the atoms of the CH_2-group : C_4 (■), H_S (•), H_R (●), molecule without migrating hydrogen = ▲. The values are given relative to the unperturbed geometry.

levels off at .09 e. The excess positive charge is then distributed over the dihydropyridine system, which starts evolving - electronically - towards a pyridinium ion structure.

This result is a confirmation of the hypothesis that during the reaction, considerable negative charge is transferred via the methylene hydrogen.

II.c. Influence of idealised methyl substitution

The differences between the elongation energies are 100 times smaller than their absolute values. To stress these differences, the relative elongation energies of all compounds are plotted in Fig. 12, using the 0M-values as a reference. It is readily observed that it takes less energy to elongate the H_R from the DHNA in the sequence 2M < 6M < 5M < 0M.

The relative elongation energies at .9 Å elongation are plotted against the activation enthalpy for all analogues in Fig. 13. A reasonable fit results, showing that the smaller the relative elongation energy the smaller the activation energy. The fit ameliorates upon exclusion of the 5M analogue.

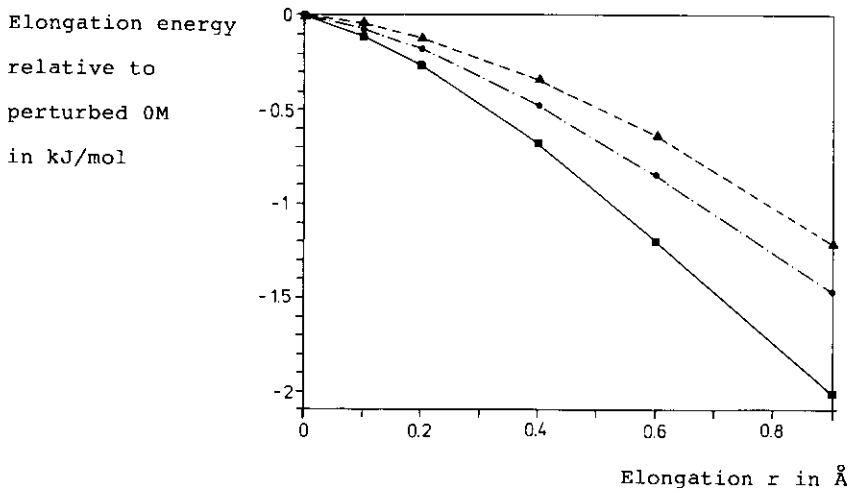


Fig. 12 : Influence of CH_3-substitution on the elongation energies relative to the corresponding perturbed state of 0M for 2M (■), 5M (▲) and 6M = (●).

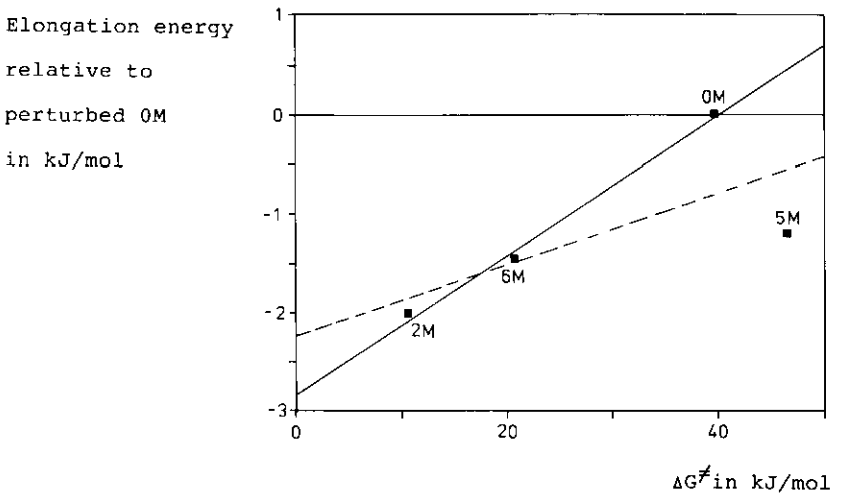


Fig. 13 : Activation enthalpy versus relative elongation energy at r = 0.9 Å. – – – : linear correlation including all compounds, ——— : linear correlation excluding 5M.

Fig. 14 shows the behaviour of the electron population on H_R during elongation for each analogue. The differences found in the unperturbed molecules are enforced

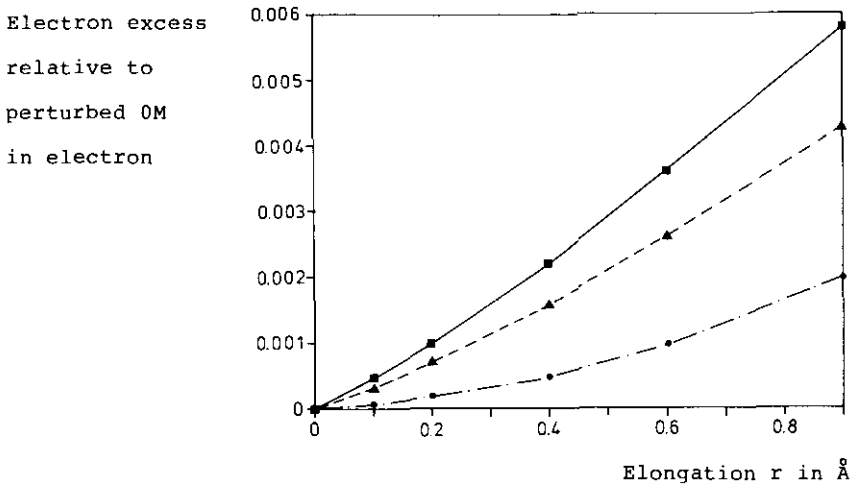


Fig. 14 : Influence of CH_3-substitution on the electron population on H_R during elongation for 2M (■), 5M (●) and 6M (▲). Values are given relative to the corresponding perturbed 0M values.

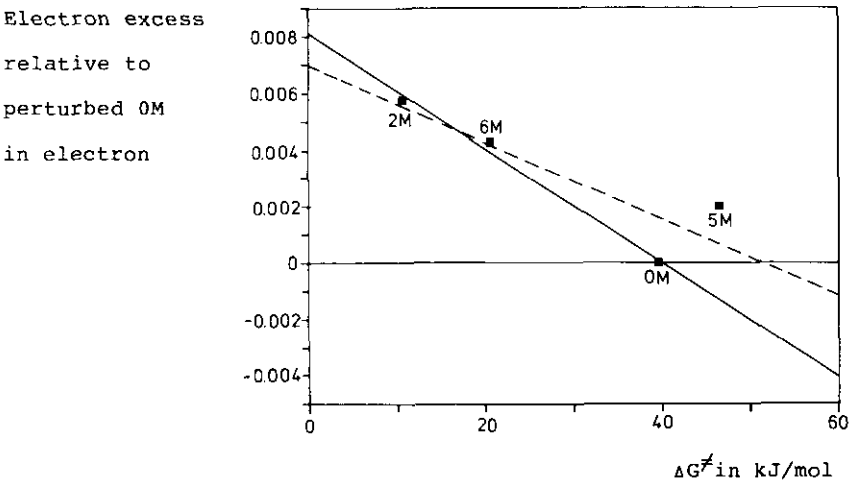


Fig. 15 : Activation enthalpy versus relative electron population on H_R at r = 0.9 Å. — — — : linear correlation including all compounds, ——— : linear correlation excluding 5M.

upon perturbation towards the TS. In Fig. 15 a plot of the relative electron density difference (perturbed minus unperturbed molecule) versus the activation

enthalpy again shows a reasonable fit for all analogues. This indicates that the higher the developing negative charge the lower the activation enthalpy. Again, the fit improves upon exclusion of the 5M analogue.

II.d. Effect of the methyl induced inclination of the carbamoyl moiety

Fig. 16 shows the relative elongation energies for 2M (as before relative to 0M) for elongation of H_R with planar and inclined carbamoyl-groups. At ϕ = -73.2°, the NH_2-group of the carbamoyl moiety lies closer to the H_R, at ϕ = 61.8° the NH_2 lies closer to H_S. The elongation energy of a H_R methylene hydrogen with a nearby NH_2-group is hardly affected, while a H_R methylene hydrogen with an opposed NH_2-group has an elongation energy which is even higher than in the 0M case. This means that the elongation of a methylene hydrogen opposed to the NH_2-group is inhibited.

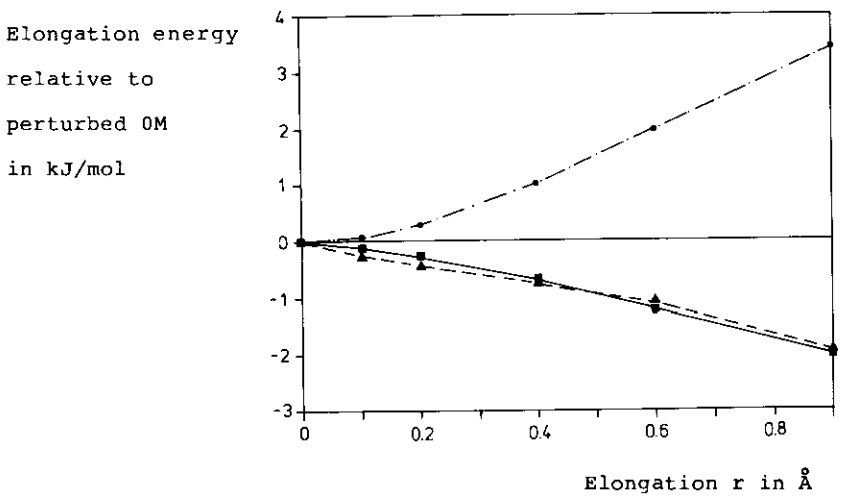


Fig. 16 : Indirect influence of methyl substitution via the $CONH_2$-conformation on the H_R-elongation energies relative to the corresponding perturbed 0M state for ϕ = -73.2° (▲), ϕ = 0° (■) and ϕ = 61.8° (●).

The relative electron excess (relative to 0M) of the migrating hydrogen atoms are plotted versus elongation in Fig. 17. The H_R at ϕ = -73.2° gains much more negative charge than the H_R with a planar carbamoyl. The H_R at ϕ = 61.8° gains even less negative charge than the H_R in the 0M case.

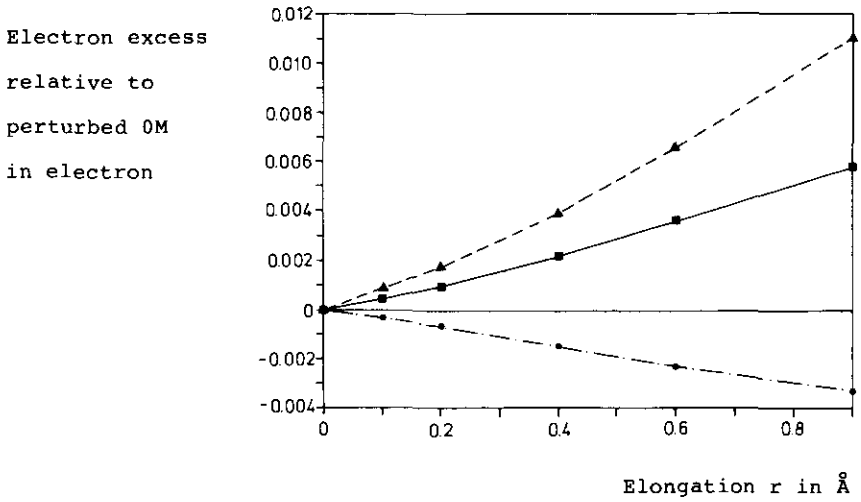


Fig. 17 : Indirect influence of CH_3-substitution via $CONH_2$-conformation on the electron population on the migrating hydrogen atom H_R relative to the corresponding perturbed 0M for ϕ = -73.2° (▲), ϕ = 0° (■) and ϕ = 61.8° (●).

The elongation model successfully describes the observed reactivity sequence, except in the case of the 5-M analogue. This implies that the hydrogen atom migrates as a hydride ion, or transfers a considerable amount of charge during a concerted process. This supports the conclusion from the calculations on the unperturbed molecules as far as the relations between the negative charge excess at H_R and the activation enthalpy are concerned.

The secondary effect of methyl substitution, namely on the orientation of the carbamoyl, complicates the issue.

3. Conclusion

The influence of methyl substitution on the reactivity in the model reaction is to facilitate the departure of both methylene hydrogen atoms as hydride ions in the sequence 2M > 6M > 5M > 0M by influencing their electronic populations. Moreover, it stabilises the developing pyridinium structure on elongation in the same sequence.

In the case of the 5-methyl analogue, theory predicts more reactivity than is observed experimentally. This particular behaviour might well be due to steric

effects. Two arguments can be invoked to support this :

- In linear transition states as advocated by Verkerk[28] and others[26] (Fig. 18), it is clear that a methyl group at 5-position adds considerable steric hindrance to the TS in comparison to the other analogues, which are expected to show a common behaviour.
- As discussed in our first paper[31], the disruption of the isokinetic relation, expected on the basis of a common mechanism in all reactions, might well be due to steric effects, as discussed by Leffler[39]. The obvious candidate for extra steric interaction is the 5-methyl analogue as can also be seen from the slope of the activation enthalpy versus temperature plot in Fig. 6 of ref.[31].

A study at the level of a supermolecule, in which the influence of these sterical effects in the TS can be quantified, is clearly needed to settle the problem of the 5-methyl analogue. Such a study will also clarify the issue of the secondary effect. These calculations are currently under way.

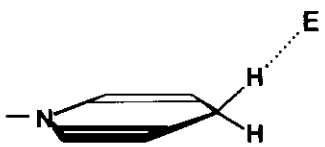


Fig. 18 : Linear transition state model : the migrating hydrogen atom follows a straight line between the methylene atom C_4 and the electrophile E to which it will bind.

EXPERIMENTAL

The STO-3G[40] minimal basisset calculations were performed with the MONSTERGAUSS program[41] in which atomic charges are evaluated by means of a Mulliken population analysis[42].

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