HETEROCYCLES, Vol. 29, No. 2, 1989

AB INITIO QUANTUM-CHEMICAL STUDY OF THE INFLUENCE OF METHYL SUBSTITUTION ON THE REDOX BEHAVIOUR OF 1,4-DIHYDRONICOTINAMIDES.

PART 2 : THE SUPERMOLECULE APPROACH[1].

Jan D. Bossaerts and Frank C. Alderweireldt

Laboratory for Organic Chemistry, University of Antwerp (R.U.C.A.),
Groenenborgerlaan 171, B-2020 Antwerp, Belgium.

Paul Geerlings *

Eenheid Algemene Chemie (ALGC), Fakulteit Wetenschappen, Vrije
Universiteit Brussel, Pleinlaan 2, B-1050 Brussel, Belgium.

Abstract — Ab initio minimal basis set quantum-chemical calculation on the interaction between methylated N-alkyl-1,4-dihydronicotinamides and the simplest keto derivative (formaldehyde) are reported. The supermolecule approach provides a distinctive improvement in the interpretation of the experimentally determined reactivity of the dihydronicotinamides in their reaction with keto compounds, as compared to previously used models (e.g. Krechl's elongation model[1,2]).

INTRODUCTION

The study of the redox properties of 1,4-dihydronicotinamide is of general interest in view of its role as reactive centre in NADH, a coenzyme which is present in all living creatures[3]. Various theoretical models have been proposed to describe these redox properties. Without confrontation with experimental data, the value of conclusions from such theoretical models is limited. In principle, experimental kinetic data are most suitable for such confrontations, since they could yield information about the reaction mechanism and transition state. However, due to the scarcity of suitable experimental data, such confrontations are nearly absent in the literature.

---

[1] Part 1 : see reference 12.

With a subsequent quantum-chemical study in mind, a series of methylated N-alkyl-1,4-dihydronicotinamides has been synthesised[4,5] (Figure 1) and kinetic studies were undertaken in order to determine the activation parameters of their redox reaction with trifluoroacetophenone[4,6] (Figure 2). Minimal basis set (STO-3G[7]) ab initio calculations were performed on these compounds and nmr spectroscopic properties were correlated with the calculated charge distributions.

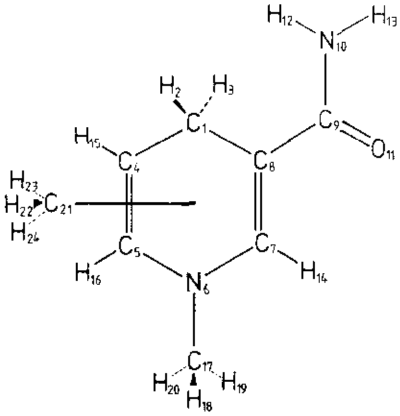

Figure 1 : Nomenclature conventions and atom numbering for the methyl substituted N-methyl-1,4-dihydronicotinamides.

0M = 1-methyl-1,4-dihydronicotinamide

2M = 1,2-dimethyl-1.4-dihydronicotinamide

5M = 1,5-dimethyl-1,4-dihydronicotinamide

6M = 1,6-dimethyl-1,4-dihydronicotinamide

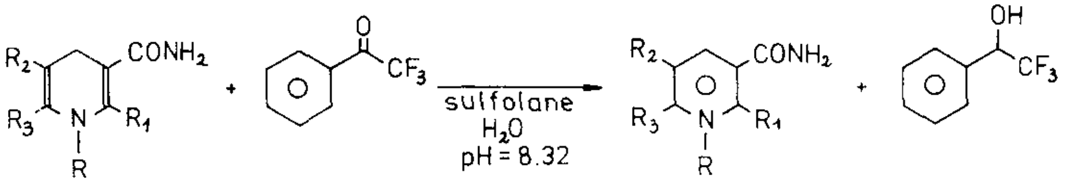

Figure 2 : The reaction between the dihydronicotinamides and trifluoroacetophenone.

In principle, the most valuable information on the mechanism of the reduction reaction by dihydronicotinamides, to be revealed in the nature of the transition state, may be obtained by accurate quantum chemical calculations (e.g. beyond the Hartree-Fock level) of possible reaction pathways. However, the vast number of degrees of freedom involved necessitates drastic simplifications, both in the computational method (e.g. neglect of electron correlation, eventually the use of a semi- empirical method ; see for example refs. 8, 9 and 10) and in the molecules studied, with the use of simplified model systems.

Another, less demanding approach is the one in which deformations, "perturbations", of the initial state of the reaction partners towards a possible transition state are studied. Klopman's "non-crossing hypothesis"[11] was formulated for similar reactants involved in the same reaction. It states that the ratio of the energies necessary to reach any particular but common point along the respective reaction paths for each of the reactants is proportional to the activation energies. Starting from this hypothesis, comparative studies on the perturbation energies of the deformed initial states in related compounds may be used to gain information about the transition state and the various factors influencing it (e.g. methyl substitution). In a later stage this information can be used to narrow the search for the structure of the transition state and to limit the number of parameters that are to be optimised.

This approach was followed in an earlier paper[12] where we correlated the activation parameters from the kinetic study with various ab initio minimal basis set properties of the analogues using Krechl's elongation model[1,2]. The promising results prompted us to investigate the application of more refined methods, which are all based on a supermolecule approach and on which we wish to report here.

Comparison of results with semi-empirical methods[8] and the ab-initio STO-3G method[9] on 1-methyl-1,4-dihydronicotinamide obtained by Kuthan showed that semi-empirical methods are not reliable for these molecules. Consequently, we no longer considered the approach involving these methods and opted for the ab-initio approach, the basis set being kept minimal (STO-3G) in view of the size of the systems.

In the following section the results of the elongation model (in which the reaction partner is not considered explicitly) are summarised. Afterwards, the influence of the reaction partner is gradually taken into account in various degrees of sophistication. As a result of the use of single determinantal wave functions, homolytic bond fission cannot be adequately described[10]. However, in view of experimental data (vide infra), the homolytic mechanism is not expected to lie on the reaction path. Charge redistribution effects upon heterolytic bond fission can, certainly in a comparative study as the present one, be expected to be reliable when calculated with the methods used.

RESULTS AND DISCUSSION**

a) Elongation model : In this model, one of the methylene hydrogen atoms (H_2) is elongated from its equilibrium position along its internuclear axis with the methylene carbon atom (C_1). This process constitutes a first perturbation of the initial state of the dihydronicotinamide molecules towards their transition state in the reaction with ketones.

Upon elongation, a negative charge develops on the migrating hydrogen. Initially, it is provided by the remainder of the methylene group. For larger elongations, it is provided by the whole of the remaining molecule. The net atomic charge in the initial geometry of the molecules, as well as the developing negative charge during elongation (perturbed state), correlate well with the experimentally obtained activation enthalpies for the methyl substituted analogues. A more negative charge on the migrating methylene atom is accompanied by a lower activation enthalpy. Moreover, the energy rise upon elongation (elongation energy) also provides a good correlation with these activation enthalpies.

These results led to the conclusion that the reaction proceeds through a hydride ion mechanism or, since experimental observations render this hypothesis highly unlikely, a mechanism in which considerable charge is transferred via the migrating hydrogen atom. A hydride ion mechanism is indeed highly unlikely in view of the instability of the ion in protic media, while the reduction with NADH model compounds can indeed take place in protic media. On the other hand, a 2-step radical mechanism as proposed by van Eikeren[13] can be rejected as (1) radical captors do not influence the reaction rate[14], (2) formation of the radical intermediate is slower than the overall-rate of the reaction[15] and (3) no radicals were detected with esr[16].

The correlations improved considerably upon neglect of the 5M-derivative. Theory indicates this derivative to be more reactive than experiment. In the kinetic study, it was also the 5M compound which disrupted a possible isokinetic relationship. According to Leffler[17], such a disruption can be the result of, for instance, steric interactions. Observations on molecular models showed that substitution of a hydrogen by a methyl group on the 5-position of the dihydronicotinamide could very well lead to steric hindrance between substrate and reagent.

**Throughout this section the atom numbering in Figure 2 will be used.

b) The Approach model : Krechl studied the approach of acetaldehyde via different paths towards 1-methyl-1,4-dihydronicotinamide on an EHT[18] and CNDO/2[19,20] level. The optimal path was the one shown in Figure 3, i.e. via the internuclear axis through the methylene hydrogen and carbon atom, and with the sp^2 plane of the carbonyl group perpendicular to this axis. Calculations by Verhoeven[21,22,23] and by Buck[24,25,26] also showed a preference for such a linear approach model.

Very recently, when the present work was already terminated, Wu and Houk[27] reported ab initio calculations on the transition state for the reaction between dihydropyridines and the methyleneimine cation. They obtained a non-linear transition state (deviation from linearity : 7°). Such a non-linear transition state can be rationalised in terms of a Coulomb interaction as a consequence of the charge separation. In aqueous media, solvation will diminish this effect. Since the non-linearity is relatively small, it will not be considered in the present discussion, in which we are moreover interested in relative activation energies.

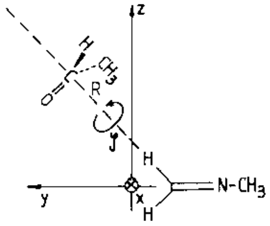

Figure 3 : Geometrical parameters describing the approach of acetaldehyde towards the dihydronicotinamides.

Notice that the use of a minimal basis set introduces a basis set superposition error[10]. However in view of our main interest in relative effects (the influence of methyl substitution) no attempt was made to correct for this deficiency.

It was decided to repeat the calculations of Krechl in part on a STO-3G level and to study the influence of methyl substitution on the approach of a formaldehyde molecule.

The energy rise due to the approach of the formaldehyde molecule (both molecules retaining their equilibrium geometry) is shown in Figure 4. In contrast to the CNDO/2 results of Krechl, there is no energy minimum discernable. There is a very slight variation in the optimal angle phi during the approach. This is due to hydrogen bond formation between the carbonyl oxygen atom of the formaldehyde molecule and the H_{12}-hydrogen atom of the carbamoyl group. In reality there are various hydrogen bonds possible between the carbonyl oxygen atom and the solvent molecules. This (small) effect was therefore not considered.

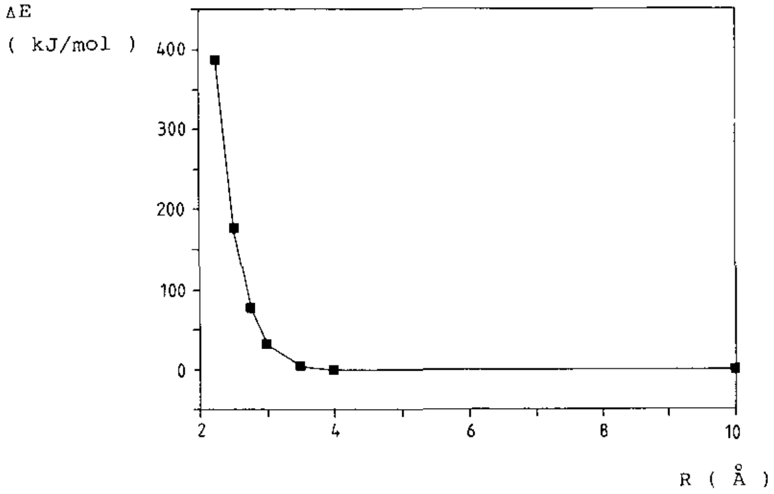

Figure 4 : Influence of the approach of the formaldehyde molecule on the energy of the supermolecule, relative to the isolated molecules (ΔE).

Figure 5 shows that during the approach, first a polarization of the methylene moiety takes place : an electron excess is transferred from the C_1 atom to the H_2 atom. From an approach of 3.5 Å on, there is a net electron transfer from the dihydropyridine ring towards the formaldehyde molecule. As shown in Figure 6, the gain in electron density mainly resides on the O_{15} atom of the formaldehyde molecule.

The hypothesis of extra steric hindrance for the 5M analogue is supported by the results in Figure 7. It can be clearly observed that the approach of a formaldehyde molecule upon the 5M compound results in an extra energy rise relative to the 0M compound.

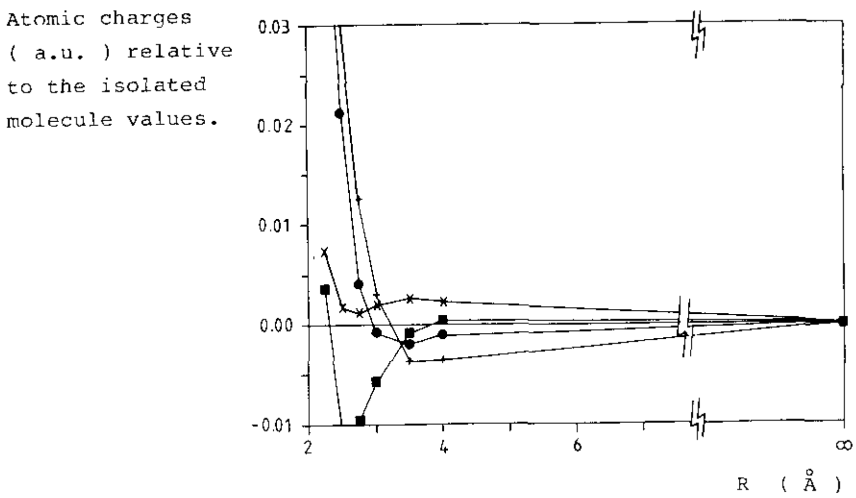

Figure 5 : Influence of the intermolecular approach on the atomic charge of the methylene group relative to the values for the isolated molecules. (+) = H_2, (×) = H_3, (■) = C_1 and (●) = total for the CH_2 group.

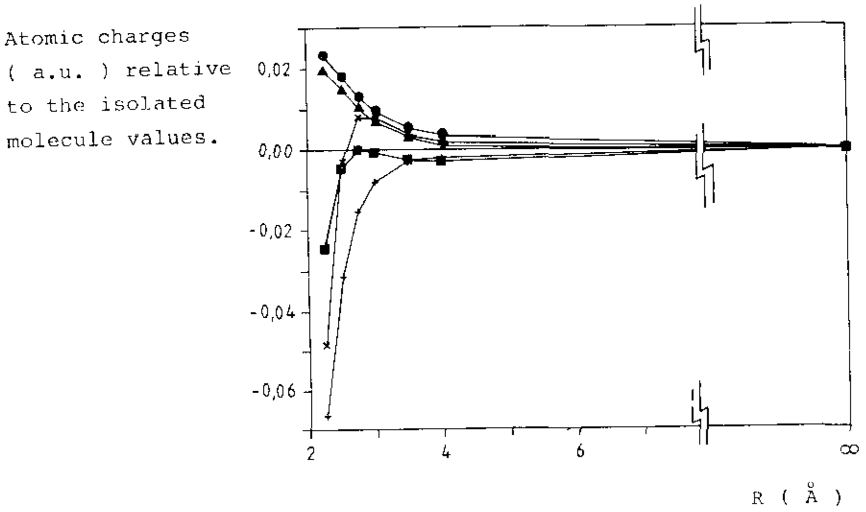

Figure 6 : Influence of the intermolecular approach on the atomic charge of the formaldehyde molecule relative to the values for the isolated molecules. (■) = C_{25}, (+) = O_{26}, (●) = H_{27}, (▲) = H_{28}, (×) = total for the CH_2O molecule.

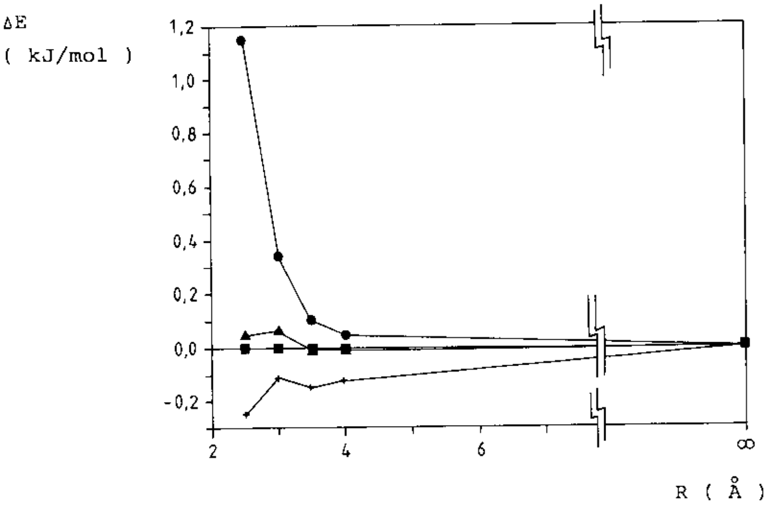

Figure 7 : Influence of methyl substitution on the energy gain due to the approach of the formaldehyde molecule, relative to Meth-0M-DHN (Δ E). (■) = 0M, (+) = 2M, (●) = 5M and (▲) = 6M.

If elongation and approach were to be combined, the possibility could exist that the electron excess on the H_2 methylene hydrogen atom would be transferred towards the formaldehyde molecule, without there being a hydride ion formed. To study the influence of the approach quantitatively (in other words, its role in the reaction coordinate) it was decided to combine elongation and approach. Also the interaction between these two deformations could then be studied.

c) The combined elongation and approach model : The influence of the choice of parameters with which the reaction coordinate will be described is shown in Figure 8a. It shows the "classic" energy hypersurface of a S_N2 mechanism such as a hydride attack on a hydrogen molecule[28] A transformation of coordinates to elongation and approach leads to the picture in Figure 8b.

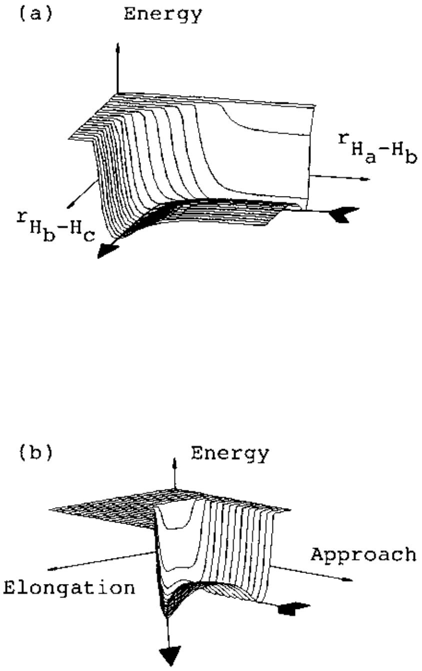

Figure 8a and b. : Energy hypersurface for a collinear attack of a hydride ion H_a^- on a hydrogen molecule H_b-H_c (a) using the H_aH_b and H_bH_c distances as variables and (b) using variables describing elongation ($r_{H_a-H_b}-r_{H_a-H_b,0}$) and approach ($r_{H_a-H_c}$).

The influence of approach on the elongation energies is shown in Figure 9. A different part of the energy hypersurface is shown in Figure 10 which shows the influence of elongation on the approach energies. It can be clearly seen that in none of the cases a crossing of the energy curves occurs. This means that, apparently, there is no approach for which elongations leads to a diminishing of the energy of the supermolecule. In other words, the elongation model would seem preferable. However, this conclusion would lead to the less acceptable hydride ion mechanism, we suspected that this result was due to the extensive approximations made in this model (nor the dihydropyridine ring nor the formaldehyde molecule evolve towards their end-structures). Nonetheless, this model shows a few interesting characteristics.

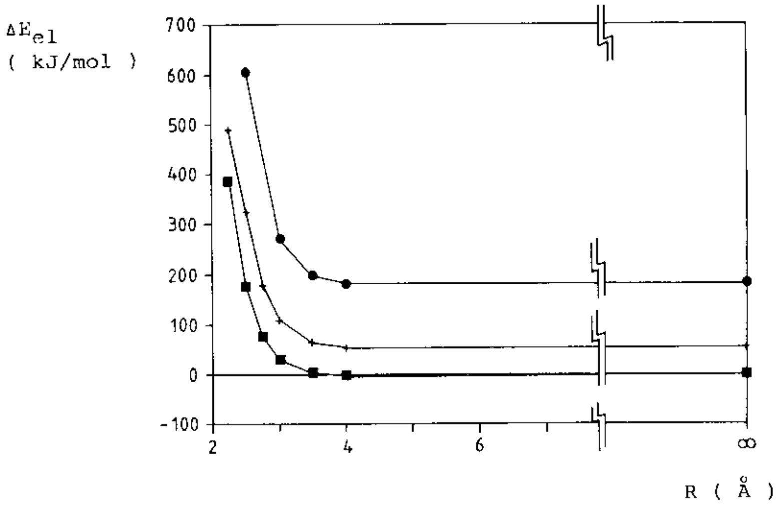

Figure 9 : Influence of the intermolecular approach on the elongation energy ΔE_{el} for elongation values of 0 Å (■), 0.2 Å (+) and 0.4 Å (●). The elongation energy ΔE_{el} is defined as the energy difference between a geometry with a dihydronicotinamide molecule which has an elongated CH bond and a geometry with its equilibrium geometry.

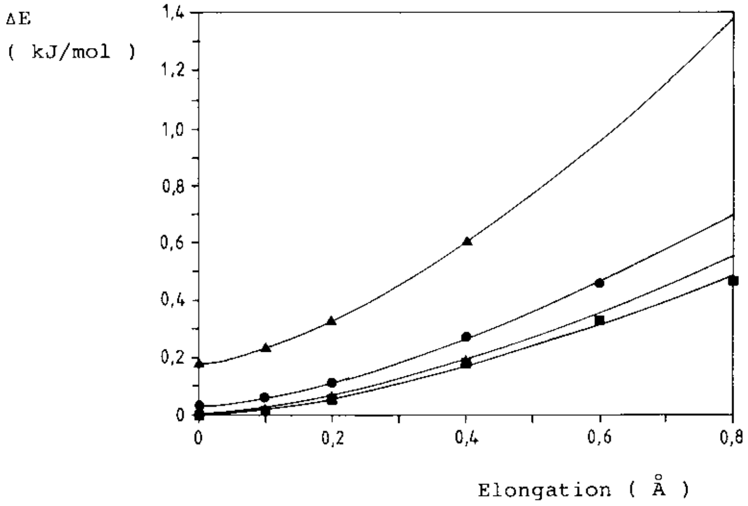

Figure 10 : Influence of elongation on approach energy ΔE (cfr. Figure 4). (■) : R = , (+) : R = 3.5 Å, (●) : R = 3.0 Å and (▲) : R = 2.5 Å.

If one observes the influence of elongation upon the atomic charge on the H_2 methylene hydrogen atom at different approaches (Figure 11), it can be clearly seen that for large intermolecular distances and small elongations there is still a gain in electron excess. An increase in both perturbations results in a decrease in the distance between the H_2 methylene hydrogen atom and the carbonyl carbon atom. This leads to an electron loss towards the formaldehyde molecule. The electron arrangements upon reaction do not reveal a hydride ion mechanism as in the case of the elongation model.

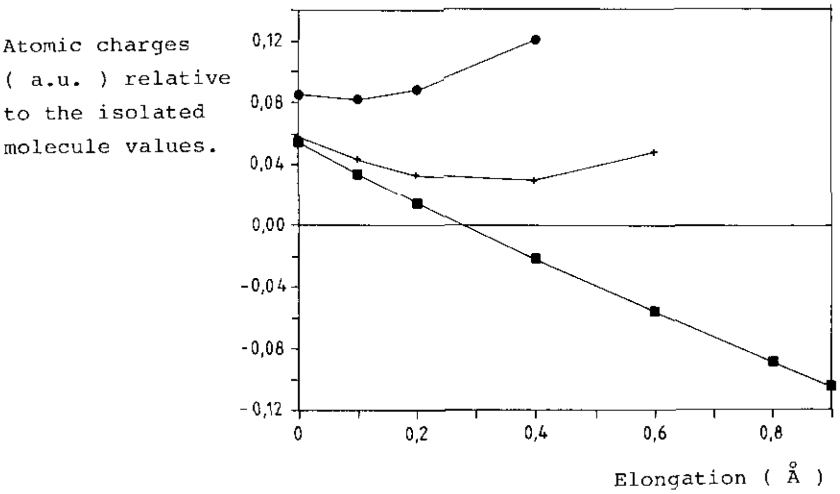

Figure 11 : Evolution of the net atomic charge for the H_2 atom upon elongation for various intermolecular distances. (■) : R = ∞, (+) : R = 3.0 Å and (●) : R = 2.5 Å.

In order to determine which combinations of values for the perturbations lie on the reaction path, the relationship between perturbation energies and activation enthalpies was studied. The best fit between elongation energies and activation enthalpies for the different analogues occurred at an approach of ca. 3.5 Å. This seems a realistic value, since it leads to a H_2-C_{25} distance of 1.5 Å (Figure 12). Comparison with the fit for the elongation model there is a clearly discernable improvement.

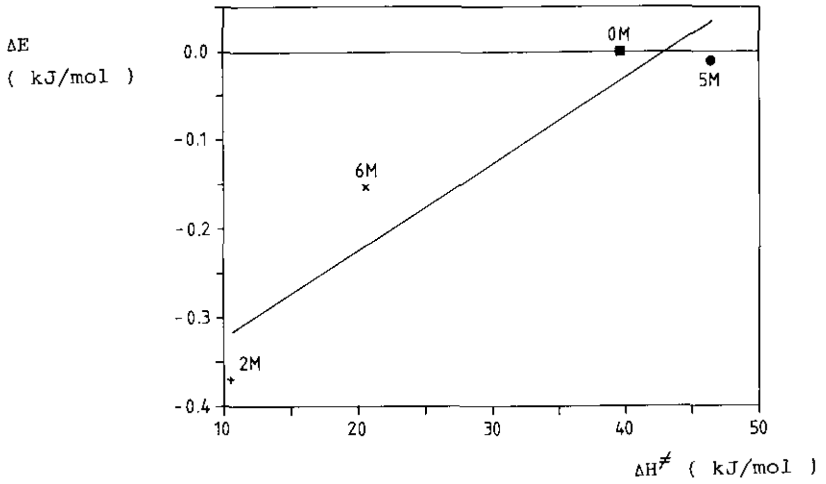

Figure 12 : Correlation of the elongation energy ΔE_{el} and activation enthalpy $\Delta H^{\neq}$ for an intermolecular distance R of 3.5 Å for the methyl substituted analogues.

So, although the combined model still shows a severe internal inconsistency viz. the non-existence of a crossing of the perturbation energies, this model is not only more realistic –there is no occurrence of a hydride ion– but it also lies more closely to the reaction path –it shows a better fit– than the elongation model. Nonetheless it seemed advisable to take the complete evolution of the starting geometries towards end geometries (pyridinium and alcoholate ion) into account.

d. The rehybridisation model : In this model all structural parameters of the individual molecules vary simultaneously from the initial towards the end geometry upon approach of the reaction partners. The coupled parameters are varied with a "hybridization factor" λ . A value of $\lambda = 0$ signifies the initial geometry, a value of $\lambda = 1$ designates the end geometry. Figure 13 shows a typical S_N2 energy contour after this transformation into a suited system of coordinates.
In our earlier work[5] we noted a convergence problem for the positively charged pyridinium ions. For λ-values larger than 0.4 no convergence could be obtained with the present model. Note that the calculations show a continuous energy decrease, related to the fact that the reaction products are stabilised by an intermolecular Coulomb interaction (caused by charge separation). Nevertheless

the limited energy hypersurface shows an important improvement when compared with the combined elongation-approach model. The energy as a function of approach for different λ-values shows a crossing (Figure 14) : i.e. the supermolecule 1,4-dihydronicotinamide/formaldehyde can undergo, during approach, a decrease in energy if it evolves towards the end-geometry.

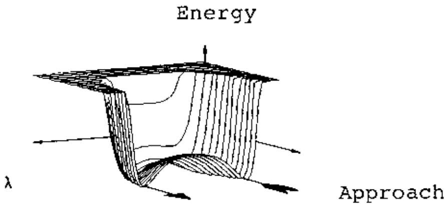

Figure 13 : Energy hypersurface for a S_N2 type reaction such as the collinear attack of a hydride ion H_a^- on a hydrogen molecule H_b-H_c in terms of approach Ap and rehybridisation factor λ (see text).

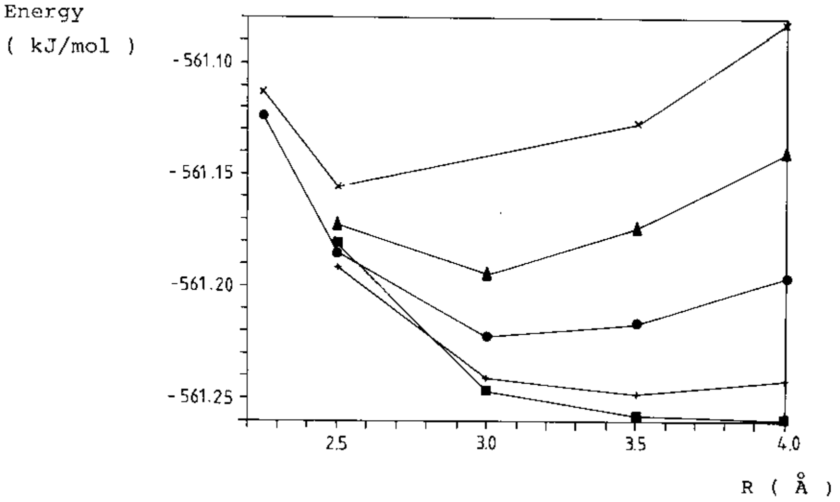

Figure 14 : Sections through the energy hypersurface for the Meth-OM-DHN/CH_2O supermolecule. Rehybridisation factors : 0.0 (■), 0.1 (+), 0.2 (●), 0.3 (▲) and 0.4 (×).

Conversely, also the energy as a function of rehybridisation (λ) for different approaches shows a crossing. This means that the supermolecule can be more easily converted towards its end structure if the reaction partners approach each other. This model is therefore internally consistent with a concerted evolution of the parameters where an approach between the reaction partners facilitates conversion towards the end structures.

In agreement with experimental data, a detailed analysis of the atomic charges[5] on the dihydropyridine ring shows that the methyl group exerts a polarization of the π-system. As a result the methyl group causes an electron deficiency on the sp^2 carbon atom to which it is connected and an electron excess on the neighboring atoms of this carbon atom. This alternation of charges leads to an electron excess on the methylene hydrogen atoms for the 2M and 6M compounds where the inductive effect of the N-atom is reinforced, whereas for the 5M compound these two effects are working in opposite sense, leading to a negligible methyl effect in the latter case. This conclusion is consistent with Pople's work[29].

CONCLUSIONS

The experimental kinetic results show a good correlation with a theoretical model in which electron and proton transfer occur in a concerted fashion.

Further research in which solvent effects and protonation of the attacking formaldehyde is taken into account (in order to avoid the charge separation between anion and cation into the reaction products) could lead to more detailed conclusions.

APPENDIX : COMPUTATIONAL DETAILS

The cartesian atomic coordinates are calculated from local polar coordinates in which the position of each atom is defined relative to three reference atoms.

The elongation is defined by equation A.1 in analogy to Krechl's work.

$$El = |\underline{r}|_{C_1-H_2} - |\underline{r}|_o \qquad (A.1)$$

$\underline{r}_{C_1-H_2}$ designates the vector joining atom C_1 and atom H_2. The value of this vector in the initial geometry is designated by $|\underline{r}|_o$.

The approach vector is defined by equation A.2 also in analogy to work of Krechl.

$$\underline{Ap} = \underline{r}_{H_2-C_{25}} - \underline{r}_{C_1-H_2} \qquad (A.2)$$

The local polar coordinates were varied from initial geometries towards the end geometries using the rehybridisation factor λ as shown in equation A.3.

$$\begin{aligned} \underline{r}_1 &= (1-\lambda)\ \underline{r}_{1,b} + \lambda\,\underline{r}_{1,e} \\ \underline{r}_2 &= (1-\lambda)\ \underline{r}_{2,b} + \lambda\,\underline{r}_{2,e} \\ &\vdots \qquad\qquad\qquad \vdots \\ \underline{r}_n &= (1-\lambda)\ \underline{r}_{n,b} + \lambda\,\underline{r}_{n,e} \end{aligned} \qquad (A.3)$$

where $\underline{r}_{i,b}$ and $\underline{r}_{i,e}$ are the position vectors associated to an atom i in the starting and final geometry, respectively (i = 1,2,...N, where N is the total number of atoms in the supermolecule).

The geometries for the starting compounds were taken from Karle[30] for the dihydronicotinamide (as described in our previous work[5]) and from electron diffraction results by Kato[31] for the formaldehyde. The geometry for the pyridinium ion was taken from Voet[32] whereas for the alcoholate ion geometrical parameters were taken from Kimura[33].

The STO-3G calculations were performed with the MONSTERGAUSS- program[34].

REFERENCES

1. J. Krechl and J. Kuthan, J. Coll. Czech. Chem. Comm., 1980, **45**, 2425.
2. J. Krechl and J. Kuthan, J. Coll. Czech. Chem. Comm., 1986, **47**, 621.
3. J. Kuthan and A. Kurfürst, Ind. Eng. Chem. Prod. Res. Dev., 1982, **21**, 191.
4. J. Bossaerts, R.A. Dommisse, and F.C. Alderweireldt, Tetrahedron. Lett., 1984, 2235.
5. J. Bossaerts, R.A. Dommisse, F.C. Alderweireldt, and P. Geerlings, J. Chem. Res., (S) 1987, 284 and (M), 1987, 2360.
6. J. Bossaerts, R.A. Dommisse, and F.C. Alderweireldt, Heterocycles, 1986, **24**, 115.
7. W.J. Hehre, R.F. Stewart, and J.A. Pople, J. Chem. Phys., 1969, **51**, 2637.
8. J. Kuthan, L. Musil, and V. Jehlicka, Coll. Czech. Chem. Comm., 1977, **42**, 283.
9. S. Böhm and J. Kuthan, Coll. Czech. Chem. Comm., 1983, **48**, 1842.

10. See for example P. Carsky and M. Urban, Ab initio Calculations in 'Lecture Notes in Chemistry', Vol. 16, Springer Verlag, Berlin, 1980, Chapter 4.

11. G. Klopman, 'Chemical Reactivity and Reaction Paths', G. Klopman Editor, Wiley, New York, 1973, 9.

12. J. Bossaerts, R.A. Dommisse, F.C. Alderweireldt, and P. Geerlings, *Heterocycles*, 1986, **24**, 2519.

13. P. van Eikeren and D.L. Grier, *J. Am. Chem. Soc.*, 1979, **101**, 7406.

14. see for instance : R.A. Hood, R.H. Prince, and K.A. Rubinson, *J. Chem. Soc. Chem. Comm.*, 1978, 300.

15. see for instance : W. Tagaki, H. Sakai, Y. Yano, K. Ozeki, and Y. Shimzu, *Tetrahedron Lett.*, 1976, 2542.

16. F.M. Martens, J.W. Verhoeven, U.K. Pandit, and Th. De Boer, *Tetrahedron*, 1978, **34**, 443

17. J.E. Leffler, *J. Org. Chem.*, 1955, **20**, 1202.

18. J. Krechl and J. Kuthan, *Coll. Czech. Chem. Comm.*, 1980, **45**, 2187.

19. J. Krechl and J. Kuthan, *Coll. Czech. Chem. Comm.*, 1981, **46**, 740.

20. J. Krechl and J. Kuthan, *Coll. Czech. Chem. Comm.*, 1983, **48**, 484.

21. S.M. van der Kerk, W. van Gerresheim, and J.W. Verhoeven, *Recl. Trav. Chem. Pays-Bas*, 1984, **103**, 143.

22. W. van Gerresheim and J.W. Verhoeven, *Recl. Trav. Chim. Pays Bas*, 1983, **102**, 975.

23. J.W. Verhoeven, W. van Gerresheim, F.M. Martens, and S.M. van der Kerk, *Tetrahedron*, 1986, **42**, 975.

24. R.H.A.M. Brounts and H.M. Buck, *J. Am. Chem. Soc.*, 1983, **105**, 1284.

25. P.M.T. de Kok, M.C.A. Donkersloot, P.M. van Lier, G.H.W. Meulendijcks, L.A.M. Bastiaansen, H.J.G. van Hooff, J.A. Kanters, and H.M. Buck, *Tetrahedron*, 1986, **42**, 941.

26. M.C.A. Donkersloot and H.M. Buck, *J. Am. Chem. Soc.*, 1981, **103**, 6549.

27. Y. Wu and K.N. Hook, *J. Am. Chem. Soc.*, 1987, **109**, 2226.

28. C.D. Ritchie and H.F. King, *J. Am. Chem. Soc.*, 1968, **90**, 825.

29. J.A. Pople and D.L. Beveridge, 'Approximate Molecular Orbital Theory', Mc-Graw-Hill, New York, 1970.

30. I.C. Karle, *Acta Cryst.*, 1961, **14**, 497.

31. C. Kato, C. Kouck, I.T. Ijima, and M. Kimura, *Bull. Soc. Chem. Jpn.*, 1969, **42**, 2148.

32. D. Voet, J. Am. Chem. Soc., 1973, **95**, 3763.

33. K. Kimura and M. Kubo, J. Chem. Phys., 1959, **30**, 1512.

34. M.R. Peterson and R.A. Poirier, Program 'MONSTERGAUSS', University of Toronto, Toronto, Canada, 1980.

Received, 21st July, 1988