that marked departure from linearity in the hydrogen bond produces a significant change in efg parameters, particularly at deuterium. In a subsequent paper we will present experimental results that relate to strongly bent intramolecular hydrogen bonds.[61]

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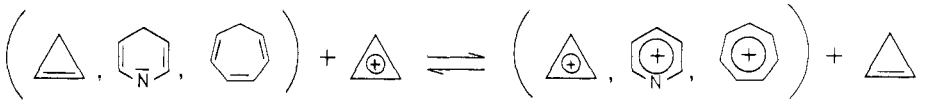
The Hydride-Donation Reaction of Reduced Nicotinamide Adenine Dinucleotide. 1. MINDO/3 and STO-3G Calculations on Analogue Reactions with Cyclopropene, Tropilidene, and 1,4-Dihydropyridine as Hydride Donors and the Cyclopropenium Cation as Acceptor

M. C. A. Donkersloot* and H. M. Buck

Contribution from the Department of Organic Chemistry, Eindhoven University of Technology, Eindhoven, The Netherlands. *Received December 2, 1980*

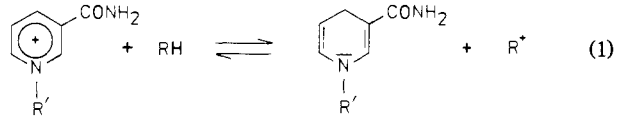
Abstract: On the basis of MO arguments it is made plausible that the hydride-transfer reactions are valid and useful analogues



of the $NAD^+/NADH$ hydride-transfer reaction. By means of MINDO/3-enthalpy contour maps a suitable reaction coordinate is found for each reaction. For the simplest system cyclopropene/cyclopropenium cation, the enthalpy profile along the reaction coordinate is compared with ab initio (STO-3G) results. It is demonstrated that both methods produce very similar results with regard to the overall course of the reaction (the reaction pathway), but that MINDO/3 yields a much lower activation enthalpy than STO-3G. The results indicate that the studied hydride-transfer reactions can all be conveniently described with reference to a supermolecule of C_s symmetry, containing a linear C···H···C fragment. The reaction consists of a concerted and gradual breaking of one, and forming of the other one of the C–H bonds in this fragment. Simultaneously transfer of negative charge takes place, the overall result being the migration of a hydride ion.

Introduction

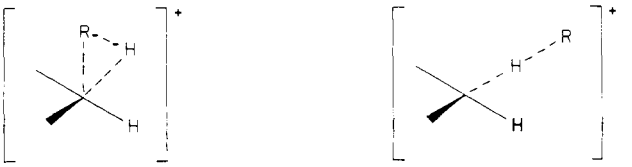
During recent years the coenzyme nicotinamide adenine dinucleotide (NAD^+) has received widespread attention. This coenzyme plays an important role in a large number of enzyme-catalyzed oxidation–reduction reactions.[1] The characteristic event in these reactions is always the reversible transfer of a hydride ion from the substrate to the 4 position of the nicotinamide moiety of NAD^+ or vice versa:



(1)

where RH = a suitable hydride donor

Much work has been done to elucidate the reaction mechanism of this process. In particular, kinetic studies on $NAD^+/NADH$ as well as on a variety of model compounds—with or without enzymatic catalysis—contributed to our understanding of the hydride-transfer reaction. However, up to now it has not been possible to combine all results in one simple overall scheme. We refer, for instance, to two recent studies on nonenzymatic hydride-transfer model reactions, leading to quite different conclusions. Van Eikeren et al.[2] studied the hydride transfer between *N*-benzyl-3-carbamoyl-1,4-dihydropyridine and the *N*-benzyl-3-carbamoylpyridinium cation. On the basis of their results they proposed a mechanism involving an intermediate radical–cation-radical pair, formed by the initial transfer of an electron. On the other hand, Kurz and Frieden[3] studied the reductive desulfonation of 4-cyano-2,6-dinitrobenzenesulfonates with dihydronicotinamide and reached the conclusion that this reaction occurs by direct hydride-ion transfer with the transfer of negative charge and of the hydrogen nucleus taking place in a single kinetic event. In addition to this ambiguity with respect to the identity of the migrating moiety there is also an uncertainty as regards the structure of the transition state. A triangular arrangement was proposed by Lewis and Symons,[4] whereas Swain et al.[5] advocated a linear transition state:



Finally, a very typical and as yet not fully understood feature of the $NAD^+/NADH$ hydride-transfer reaction is its stereospecificity under enzymatic conditions, demonstrated by Vennesland and Westheimer.[6] In this and the subsequent paper we endeavor to elucidate the nature of the $NAD^+/NADH$ hydride-transfer re-

(1) Sund, H. "Pyridine Nucleotide-Dependent Dehydrogenases"; W. de Gruyter & Co.: Berlin, West Germany.
(2) Van Eikeren, P.; Kenney, P.; Tokmakian, R. *J. Am. Chem. Soc.* **1979**, *101*, 7402–7406.
(3) Kurz, L. C.; Frieden, C. *J. Am. Chem. Soc.* **1980**, *102*, 4198–4203.
(4) Lewis, E. S.; Symons, M. C. R. *Q. Rev. Chem. Soc.* **1958**, *12*, 230–249.
(5) Swain, C. G.; Wiles, R. A.; Bader, R. F. W. *J. Am. Chem. Soc.* **1961**, *83*, 1945–1950.
(6) Vennesland, B.; Westheimer, F. H. In "The Mechanism of Enzyme Action"; McElroy, W. D.; Glass, B., Eds.; John Hopkins Press: Baltimore, 1954.

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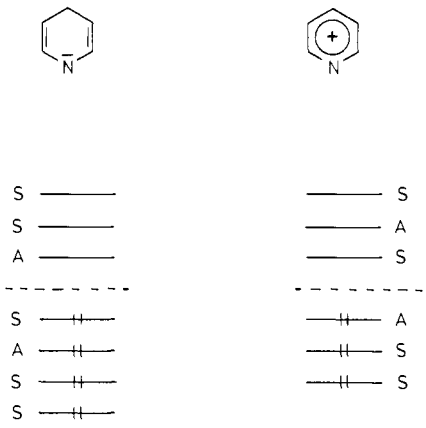
Scheme I. π MO Energy Level Schemes for 1,4-Dihydropyridine and the Pyridinium Cations[a]

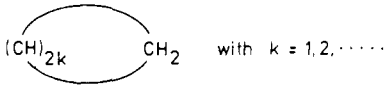


[a] S and A denote the symmetry and antisymmetry of the MOs with respect to σ_v perpendicular to the plane of the heterocyclic ring.

action with recourse to MINDO/3 and STO-3G calculations for a series of model reactions.

Choice of the Model Reactions

Qualitatively, the ability of the NADH/NAD$^+$ system to act as a depository for hydride ions can be understood in terms of those MOs which are antisymmetric with respect to the (dihydro)pyridine ring. The effect of hydride donation on these π-type MOs can be illustrated with the help of Hückel MO theory, supplemented with perturbation theory.[7] This technique leads to π MO energy schemes for 1,4-dihydropyridine (derived from the five π MOs of divinylamine interacting with the π and π^* MOs of the CH_2 group) and the pyridinium cation as given in Scheme I. It can be seen that, whereas 1,4-dihydropyridine can accommodate eight electrons in the bonding orbitals of its π orbital system, the cation can accommodate only six, the remaining two electrons necessarily being donated to the leaving proton. Moreover, it appears that these electrons are given by the HOMO of the 1,4-dihydropyridine, which is symmetric with respect to the plane of the CH_2 group. In the course of the reaction this MO transforms into the LUMO of the pyridinium cation. This circumstance neatly accounts for the reversible nature of the hydride-transfer reaction. The same reasoning, applied to the series of homoconjugated monocyclic polyenes,



leads to the following well-known classification: members with odd values of k are hydride donors (e.g., cyclopropene, tropilidene), whereas members with even values of k are proton donors (e.g., cyclopentadiene, cyclononatetraene). Because of the similarity of the π MO energy schemes, we have studied the hydride-donation reactions of cyclopropene and tropilidene along with that of 1,4-dihydropyridine. In particular, this last compound is identical with the reactive fragment of NADH but for the absence of the $CONH_2$ group attached to C(3). It can be shown[8] that the π electron system of this substituent is cross-conjugated with that of the pyridine ring; that is to say, the bond between C(3) and the $CONH_2$ group is essentially single and there is no first-order effect on the π electron density of the pyridine ring. Consequently, we expect the $CONH_2$ group to be quite inactive with respect to the mechanism of the hydride-transfer reaction, and, for the moment, we ignore its presence in NADH. We should like to mention, however, that the $CONH_2$ group is essential for the discussion of the stereospecificity of the NAD$^+$/NADH hydride-transfer reaction because it provides the reaction with a possibility to differentiate between the two hydrogen atoms available for transfer. We will return to this interesting role of the $CONH_2$ group in the subsequent paper.

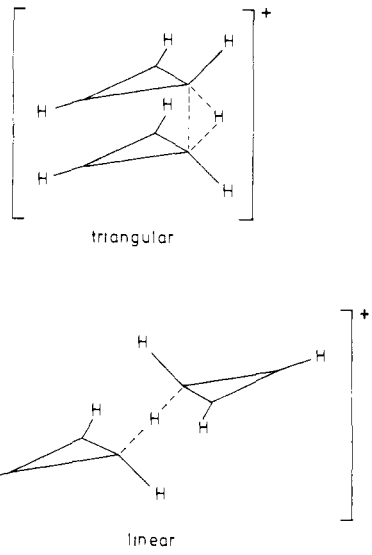


Figure 1. Triangular and linear intermediate structures for the reaction $C_3H_4 + C_3H_3^+ \rightleftharpoons H_3C_3\cdots H\cdots C_3H_3^+ \rightleftharpoons C_3H_3^+ + C_3H_4$.

For the sake of simplicity the cyclopropenium cation has been chosen as a hydride acceptor. As the MINDO/3 program[9] is the main tool in this study, the inclusion of the hydride-transfer reaction between cyclopropene and the cyclopropenium cation is especially suitable as it provides us with the opportunity to compare MINDO/3 results pertaining to the studied class of compounds with results from ab initio STO-3G calculations, performed on the same structures with the Gaussian 70 program.[10] This is very valuable in view of the suggestion[11,12] that MINDO/3 is unreliable for calculations on hydrogen-bonded systems.

Results

a. Intermolecular Hydride Transfer from Cyclopropene to the Cyclopropenium Cation and Vice Versa. This reaction is the simplest one in our series, and it could therefore be studied in considerable detail. In the first instance the system was searched with MINDO/3 for a triangular intermediate structure (Figure 1) of relatively low enthalpy. Such a structure could, however, not be found; efforts to bring the two moieties close enough together to provoke a reaction resulted in a complete rearrangement of the constituting atoms. As regards a linear intermediate structure (Figure 1), it was found that a formation-enthalpy surface could be conveniently described using as parameters the two distances r_1 and r_2 measured from the migrating hydrogen atom to the donating and accepting carbon atoms. Figure 2 gives the relevant region of the formation-enthalpy surface with the calculated MINDO/3 enthalpy values mapped as a function of r_1 and r_2. All other structural parameters were optimized with respect to the total enthalpy. It can be seen that the reaction proceeds very easily along a shallow valley, with the distance r_1 continuously increasing, and r_2 decreasing in length (or vice versa). In going from the reactants to the products, two slight barriers, located in the plotted region of the enthalpy surface, have to be passed.

Figure 3 shows the enthalpy along the minimum-gradient reaction path (MGRP) together with the results of STO-3G calculations performed for the MINDO/3-optimized structures.

(7) Hoffmann, R. *Acc. Chem. Res.* **1971**, *4*, 1–9.
(8) Dewar, M. J. S.; Dougherty, R. C. "The PMO Theory of Organic Chemsitry"; Plenum Press: New York, 1975; p 179.
(9) Dewar, M. J. S.; Metlu, H.; Student, P. J.; Brown, A.; Bingham, R. C.; Lo, D. H.; Ramsden, C. A.; Kollmar, H.; Weiner, P. *QCPE* **1975**, *11*, 279.
(10) Hehre, W. J.; Lathan, W. A.; Ditchfield, R.; Newton, M. D.; Pople, J. A. *QCPE* **1973**, *11*, 236.
(11) Zielinski, T. J.; Breen, D. L.; Rein, R. *J. Am. Chem. Soc.* **1978**, *100*, 6266–6267.
(12) Klopman, G.; Andreozzi, P.; Hopfinger, A. J.; Kikuchi, O.; Dewar, M. J. S. *J. Am. Chem. Soc.* **1978**, *100*, 6267–6268.

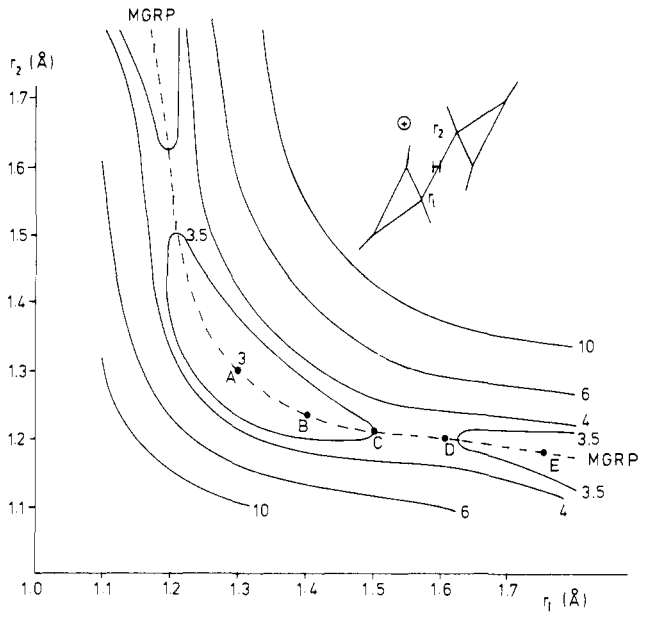


Figure 2. Enthalpy-contour map for the reaction of C_3H_4 with $C_3H_3^+$. Enthalpy values are given in kcal mol^{-1} and relative to the reaction-product state. The contours are constructed by interpolation of enthalpies calculated for points (r_1, r_2) with intervals of 0.1 Å.

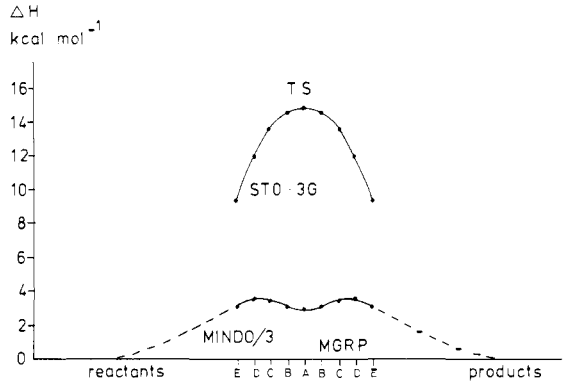


Figure 3. Enthalpy values relative to the reaction-product state for intermediate structures along the MGRP for the reaction of C_3H_4 with $C_3H_3^+$. Both MINDO/3 and STO-3G results are calculated for MINDO/3-optimized structures.

These structures can be characterized as having C_s symmetry anywhere on the plotted region of the enthalpy surface. The two C_3H_2 fragments remain planar and the C···H···C bridge remains linear. The nonreacting α hydrogen atoms perform a gradual bending motion into or out of the plane of the C_3H_2 fragments they below to,[13] depending on whether the hydride ion is being donated or accepted. Concerning the true location of the transition state the MINDO/3 enthalpy curve is ambiguous. On the one hand, one can easily recognize two maxima separated by a local minimum corresponding to a stable intermediate of C_{2h} symmetry; on the other hand, the depth of the minimum is less than 1 kcal mol^{-1} and therefore of little real significance. The STO-3G curve shows a single and much higher maximum enthalpy value for a transition state with C_{2h} symmetry. This encourages us to disregard the local depression in the MINDO/3 curve. We have reoptimized the MINDO/3 structures of the reactants and the C_{2h} transition state at the STO-3G level of accuracy. This results in a further increase of the activation enthalpy with 0.4 kcal mol^{-1} (see Table I). The structure of the transition state alters only slightly; e.g., complete MINDO/3 optimization with $r_1 = r_2$ as constraint results in $r_1 = r_2 = 1.300$ Å, whereas a similar STO-3G optimization results in the value 1.290 Å for this distance. As hydride transfer is associated with a transfer of charge, it is of interest to study not only the geometrical and energy aspects of the reaction but also the behavior of the charge distribution along the reaction coordinate. In Table II we have collected the values of the total charges localized on atoms as calculated for reactants and intermediate states. It can be seen that the MINDO/3 charges and those calculated with STO-3G show very little resemblance. A much better agreement is found if one compares the total charges on groups of atoms, as is shown in Table II for C(2) + H(2). Apparently MINDO/3 and STO-3G differ considerably in their treatment of the C–H bond, all C atoms being more positive and all H atoms being more negative calculated with MINDO/3 as compared with STO-3G.

This prevents us from even guessing the real charge on the migrating hydrogen although both theoretical models agree on the negative sign. Also we note that neither model suggests that at any particular instant a complete hydride ion is donated by one and accepted by the other reactant. The real process is rather the simultaneous transfer of negative charge and the loosening and building up of C–H bonds. In Figure 4 we have plotted the total net charge q_1 on a cyclopropyl (C_3H_3) fragment and the net

(13) In the context of this paper we feel justified in describing only those features of the reacting molecules and the intermediate structures which change significantly along the reaction path.

Table I. Enthalpies Calculated for the Equilibrium $C_3H_4 + C_3H_3^+ \leftrightharpoons TS \leftrightharpoons C_3H_3^+ + C_3H_4$

	MINDO/3[a]	STO-3G[a]	STO-3G[b]
C_3H_4 (C_{2v})	59.29[c]	−114.39603[d]	−114.40116[d]
$C_3H_3^+$ (D_{3h})	240.42[c]	−113.61978[d]	−113.62032[d]
TS (C_{2h})	302.61[c]	−227.99240[d]	−227.99739[d]
ΔH_{act}	2.90[c]	14.69[c]	15.11[c]

[a] MINDO/3-optimized structures. [b] STO-3G-optimized structures. [c] In kcal mol^{-1}. [d] In atomic energy units.

Table II. Net Atomic Charges[a] Calculated for the Species C_3H_4, $C_3H_3^+$, $H_3C_3\cdots H\cdots C_3H_3^+$

	MINDO/3[b]	STO-3G[b]	STO-3G[c]
C_3H_4: C(1)	0.092	−0.098	−0.110
H(1)	−0.055	0.036	0.046
C(2)	−0.037	−0.079	−0.082
H(2)	0.046	0.092	0.091
$C_3H_3^+$: C(1)	0.175	0.102	0.101
H(1)	0.158	0.231	0.232
$C_6H_7^+$: C(1)	0.186	0.009	0.009
H(1)	0.046	0.141	0.145
C(2)	0.051	0.008	0.005
H(2)	0.117	0.169	0.170
$H_{hydride}$	−0.133	−0.009	−0.006
C_3H_4: C(2) + H(2)	0.009	0.013	0.009
$C_6H_7^+$: C(2) + H(2)	0.168	0.177	0.175

[a] In atomic units of charge. [b] MINDO/3-optimized structures. [c] STO-3G-optimized structures.

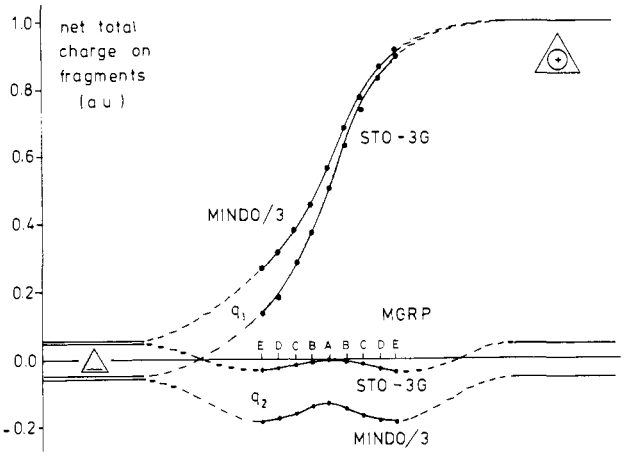


Figure 4. Variation of total charges q_1 and q_2 along the MGRP, calculated with MINDO/3 and STO-3G for MINDO/3-optimized structures $H_3C_3\cdots H\cdots C_3H_3^+$.

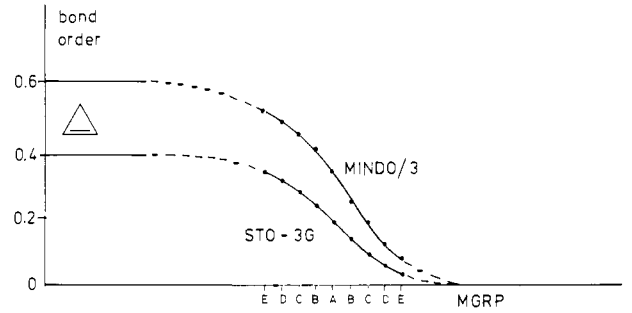


Figure 5. Variation of C···H···C bond orders along the MGRP, calculated both with MINDO/3 and STO-3G for MINDO/3-optimized structures H_3C_3···H···$C_3H_3^+$. Note that the MINDO/3 and Gaussian 70 programs use slightly different definitions of bond order.

Table III. Standard Formation Enthalpies Calculated with MINDO/3

species[a]	ΔH_f°[b]
1,4-dihydropyridine	20.05
pyridinium cation	167.11
tropilidene	33.56
tropilium cation	195.56

[a] Geometries fully optimized at MINDO/3 level. This leads to planar structures for all species listed. [b] In kcal mol^{-1}.

charge q_2 on the migrating hydrogen atom as they change along the MGRP, beginning with cyclopropene and going toward the corresponding cation with the hydrogen atom now being bound to the hydride acceptor. The behavior of q_2 along the MGRP closely parallels the behavior of the total enthalpy as calculated with MINDO/3. This similarity might be used in the following way to explain the depression in the MINDO/3 enthalpy curve noted earlier. As the cyclopropene molecule is approached by the cyclopropenium cation, electrostatic polarization takes place, causing the charge on the migrating hydrogen to become more negative. This effect lowers the total enthalpy and appears to be much more pronounced with MINDO/3 than with STO-3G. However, both procedures are known to be quite inadequate to study small effects of this type in a quantitative way, and we feel therefore justified in our disregard of the small enthalpy variations in the MINDO/3 results. Of much more interest is the qualitative agreement of our MINDO/3 and STO-3G results, visible in the progress of both q_1 and q_2 along the MGRP. Qualitative agreement can also be found in Figure 5, where the decrease in bond order of the C–H bond along the MGRP is plotted. Comparison of Figures 4 and 5 shows that both processes, charge transfer and bond breaking, are quite synchronous and of a gradual nature. In addition it can be concluded that the reaction is a fast one, our results indicating an activation enthalpy of 4 (MINDO/3) to 15 (STO-3G) kcal mol^{-1}. Finally we note that MINDO/3 and STO-3G lead to very similar conclusions as regards the reaction path. This means that, although MINDO/3 enthalpies of intermediate structures containing a hydrogen bridge may be inaccurate, the general appearance of the total-enthalpy surface and the structures along the MGRP appear to be substantially correct. In other words, MINDO/3 seems capable of predicting a realistic reaction mechanism for the hydride-transfer reactions studied in this paper.

b. Intermolecular Hydride Transfer from 1,4-Dihydropyridine and Tropilidene to the Cyclopropenium and Vice Versa. In Table III the standard formation enthalpies are given for the hydride donors and the corresponding acceptors introduced here. The main distinction between these hydride-transfer reactions and the one of cyclopropene with the cyclopropenium cation is that now reactants and reaction products are no longer the same. In consequence the enthalpy contours no longer show symmetry with respect to r_1 and r_2. This can clearly be seen in Figure 6, which is the result of MINDO/3 enthalpy optimizations with fixed values of r_1 and r_2 for the combination 1,4-dihydropyridine and the cyclopropenium cation. The total enthalpy along the MGRP is

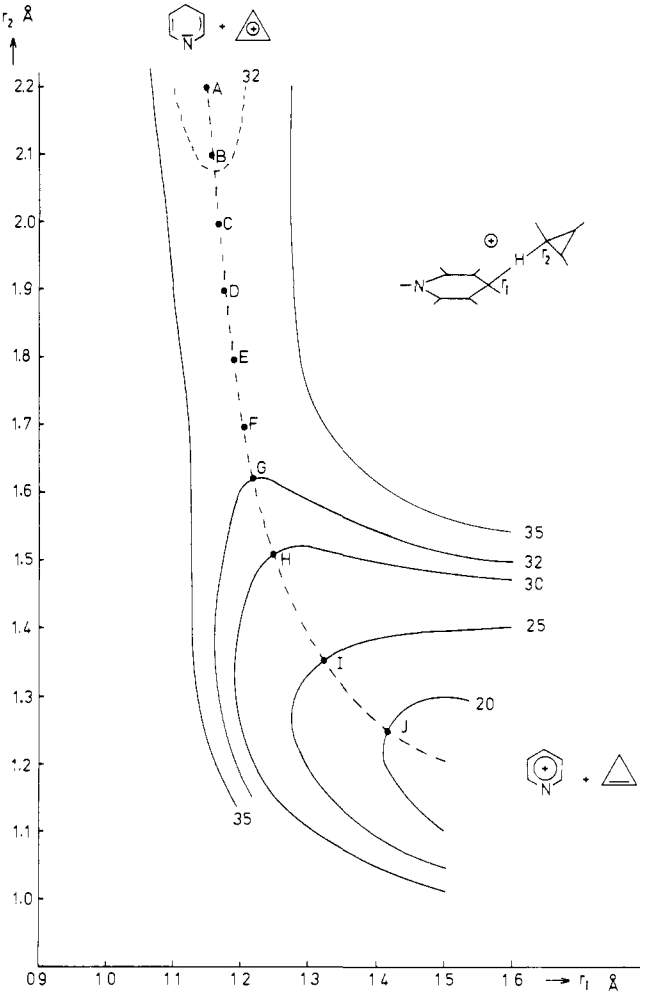


Figure 6. The enthalpy-contour map for the reaction of 1,4-dihydropyridine with $C_3H_3^+$. Enthalpies are given in kcal mol^{-1} with reference to the reaction-product state.

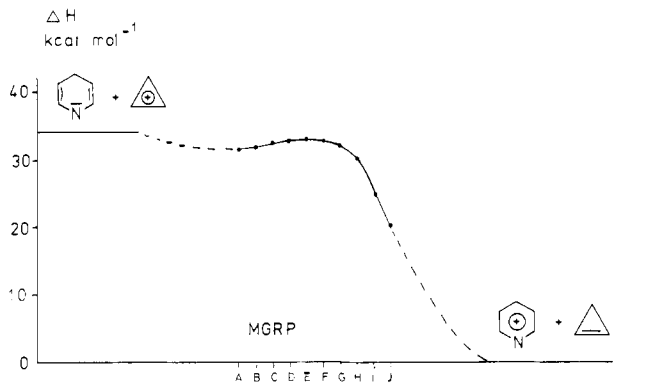


Figure 7. Enthalpy values relative to the reaction-product state for intermediate structures along the MGRP for the reaction of 1,4-dihydropyridine and $C_3H_3^+$.

given in Figure 7. It appears, as was the case with cyclopropene as hydride donor, that the MINDO/3 enthalpy values do not give a clear indication as to the location of a transition state. A local maximum in enthalpy can be found but this enthalpy is less than the total enthalpy of the isolated reactants. From the experience with cyclopropene it can be suspected that intermediate-state enthalpies are underestimated and that a real transition state must be situated not far from the local MINDO/3 enthalpy maximum. Figures 8 and 9 show how the net charges on the composing fragments and the bond orders of the C···H···C chain change along the MGRP. In addition we mention that all fully optimized intermediates have a structure of C_s symmetry with a linear

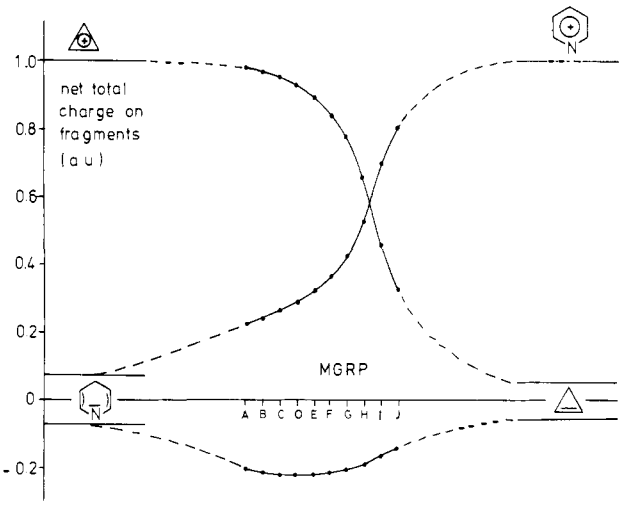


Figure 8. Variation of the net fragmental charges along the MGRP for the reaction of 1,4-dihydropyridine with $C_3H_3^+$.

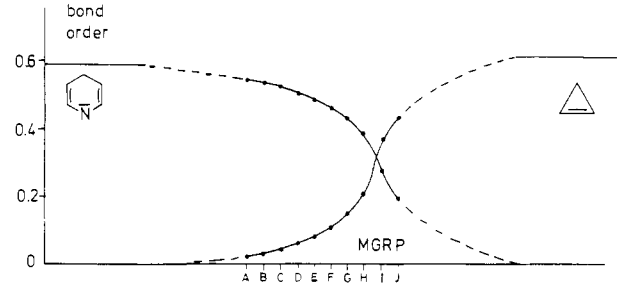


Figure 9. Variation of C···H···C bond orders along the MGRP for the reaction of 1,4-dihydropyridine with $C_3H_3^+$.

C···H···C chain. The pyridinium frame, originally planar, reacts to the approach of the cyclopropenium cation with a slight displacement of C(4) out of the N(1), C(2), C(3), C(5), C(6) plane toward the cation whereas the hydrogen atoms H(1), H(2), H(3), H(5), and H(6) leave the plane by bending away from it. The actual distances from the plane, as calculated with MINDO/3, remain very small: less than 0.1 Å for C(4) and less than 0.05 Å for the hydrogen atoms.

In summary, it can be concluded that the hydride-donation reaction of 1,4-dihydropyridine resembles that of cyclopropene in that both reactions proceed along a course of simultaneous charge transfer and bond breaking and forming. Both reactions probably are relatively fast with an activation enthalpy of roughly the same magnitude. A difference is that now the transition state is early, that is to say, reactant-like, and also that during the reaction the pyridine ring slightly loses its planarity.

The same conclusions can be reported for the reaction between tropilidene and the cyclopropenium cation. Although this system was not investigated in much detail, it can be seen from Figures 10–13 that very similar features are exhibited. The intermediate structures too resemble those derived from 1,4-dihydropyridine in that the tropilidene ring, initially planar, shows a very slight bending of C(1) toward, and of H(2), H(3), H(4), H(5), and H(6) away from the cation. The essential planarity of the tropilidene ring, in contrast with experimental evidence,[14] results from the well-known tendency of MINDO/3 to underestimate ring puckering[15] and is of little importance in the present context.

Discussion

In this paper it has been attempted to provide a theoretical background for a wealth of experimental data on the hydride-donation reaction of NADH available in the literature. The model that has emerged from this study of three analogue compounds

(14) Traetteberg, M. *J. Am. Chem. Soc.* **1964**, *86*, 4265–4270.
(15) Bingham, R. C.; Dewar, M. J. S.; Lo, D. H. *J. Am. Chem. Soc.* **1975**, *97*, 1294–1301.

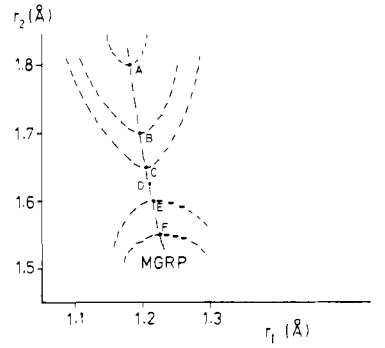


Figure 10. Schematic enthalpy-contour map for the reaction of tropilidene with $C_3H_3^+$. Enthalpies have been calculated for points A–F; quantitative results are given in Figure 11.

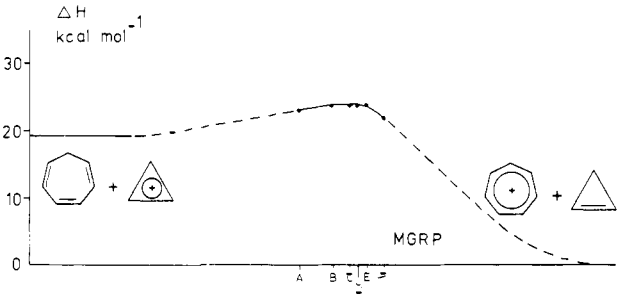


Figure 11. Enthalpy values relative to the reaction-product state for intermediate structures along the MGRP for the reaction of tropilidene with $C_3H_3^+$.

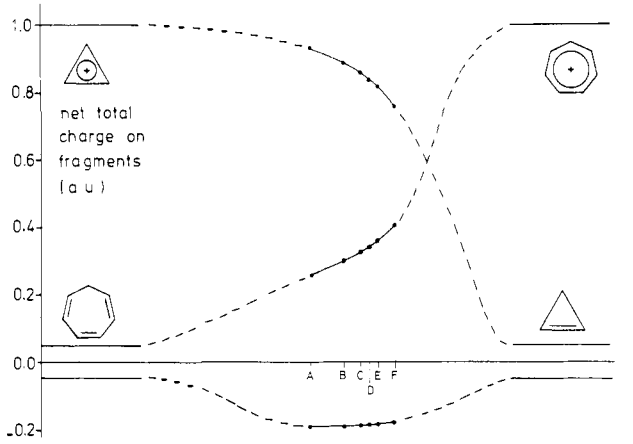


Figure 12. Variation of the net fragmental charges along the MGRP for the reaction of tropilidene with $C_3H_3^+$.

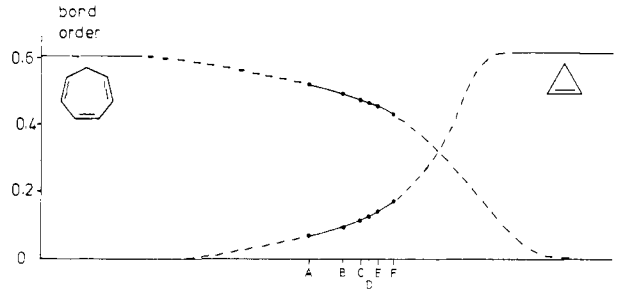
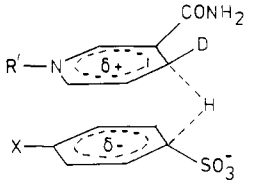


Figure 13. Variation of C···H···C bond orders along the MGRP for the reaction of tropilidene with $C_3H_3^+$.

is in many respects very similar to a model recently derived from kinetic isotope effects.[3] In particular, we refer to identical conclusions with regard to the synchronous transfer of electronic charge and the hydrogen nucleus and the fact that the transition state resembles NADH + hydride acceptor rather than NAD^+ + hydride donor. On the other hand, the kinetic study results

in a sandwich-type transition state:



which, at first sight, shows more resemblance with the triangular state we had to disclaim than with the linear one our study led us to adopt. However, in contrast with the positively charged hydride acceptor we used, the kinetic study was concerned with a neutral hydride acceptor with, in addition, a negatively charged substituent. Taking into consideration the importance of electrostatic contributions to the total energy of such compounds, the sandwich-type intermediate becomes an understandable variation of the linear structures of this study. Moreover, it should be noted that the main characteristic of the triangular transition state, the C(α)-C(α′) bond, is absent in the proposed sandwich-type structure. For the system cyclopropene/cyclopropenium cation MINDO/3 produces an activation enthalpy value which is low as compared with the STO-3G result. However, on other features of the enthalpy contour map, especially the reaction path and the structure of intermediates, MINDO/3 and STO-3G appear to be in good agreement, If, in all fairness, we remember that both MINDO/3 and STO-3G are approximative methods producing possible enthalpy inaccuracies of at least 5 to 10 kcal mol^{-1}, we must come to the conclusion that the overall agreement is satisfactory.

As stated earlier, the model compounds chosen for this study are, for reasons of symmetry, unable to demonstrate the interesting stereospecificity of the hydride-donation reaction of NADH. In the subsequent paper we will show that the 3-carbamoyl substituent, present in the NADH molecule, is capable of inducing different kinetic reactivities for the two α hydrogen atoms, provided the enzymatic environment locks the $CONH_2$ group in an orientation where it is rotated out of the plane of the (dihydro)pyridine ring. Although our calculations cannot be expected to give accurate results with regards to the thermodynamic aspects of the reaction, we expect our conclusions pertaining to the reaction mechanism to be substantially correct for the enzymatic hydride-transfer reaction of NAD^+/NADH.

Acknowledgment. We wish to thank Mr. W. Landa for many helpful discussions.

The Hydride-Donation Reaction of Reduced Nicotinamide Adenine Dinucleotide. 2. MINDO/3 and STO-3G Calculations on the Role of the $CONH_2$ Group in Enzymatic Reactions

M. C. A. Donkersloot* and H. M. Buck

Contribution from the Department of Organic Chemistry, Eindhoven University of Technology, Eindhoven, The Netherlands. *Received July 25, 1980*

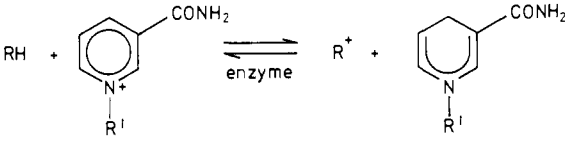
Abstract: The enzyme-catalyzed stereospecific hydride-transfer equilibrium RH + $NAD^+ \rightleftharpoons R^+$ + NADH has been studied with the help of semiempirical (MINDO/3) and ab initio (STO-3G) calculations on corresponding model compounds. It seems possible to relate the stereospecificity simply to an out-of-plane orientation of the $CONH_2$ group in the transition state of the reaction. One of the important functions of the enzyme would be to freeze the otherwise almost freely rotating $CONH_2$ group in a favorable orientation.

Introduction

During recent years the coenzyme nicotinamide adenine dinucleotide (NAD^+) has received wide-spread attention.[1] It is well known that the stereochemistry of this redox coenzyme is controlled by a number of dehydrogenation enzymes, the characteristic reaction being the transfer of a hydride ion from the substrate to the 4 position of the nicotinamide moiety of NAD^+; see Scheme I.

An, as yet, not fully understood feature of this equilibrium is the stereospecificity of the hydride transfer. This effect was demonstrated by Vennesland and Westheimer[2] for the oxidation of CH_3CD_2OH by NAD^+, catalyzed by alcohol dehydrogenase (ADH); see Scheme II. They showed that in this reaction direct transfer of $:D^-$ takes place and that this transfer is stereospecific with respect to both coenzyme and substrate. This stereospecificity

Scheme I. Prototype of the Enzymatic Reduction of NAD^+ to NADH



Scheme II. Reduction of NAD^+ by CH_3CD_2OH with Alcohol Dehydrogenase

$$CH_3CD_2OH + NAD^+ \underset{ADH}{\rightleftharpoons} CH_3CDO + NADD + H^+$$

is absent when the reaction is carried out under nonenzymatic conditions. In the preceding paper[3] we demonstrated that the hydride-transfer reactions with cyclopropene, 1,4-dihydropyridine, and tropilidene as hydride donors, and the cyclopropenium cation

(1) Sund, H. "Pyridine Nucleotide-Dependent Dehydrogenases"; W. de Gruyter: Berlin, West Germany.

(2) Vennesland, B.; Westheimer, F. H. In "The Mechanism of Enzyme Action"; McElroy, W. D.; Glass, B., Eds.; John Hopkins Press: Baltimore, 1954.

(3) Donkersloot, M. C. A.; Buck, H. M. *J. Am. Chem. Soc.*, preceding paper in this issue.

0002-7863/81/1503-6554$01.25/0