# A CNDO/2 STUDY OF REACTIVITY OF METHYLENE GROUP IN 1-METHYL-1,4-DIHYDRONICOTINAMIDE*

Jiří KRECHL and Josef KUTHAN

*Department of Organic Chemistry,*
*Prague Institute of Chemical Technology, 166 28 Prague 6*

An attempt has been made to use the CNDO/2 method for prediction of the reaction profile and electronic mechanism of elimination of 4-hydrogen atom of 1-methyl-1,4-dihydronicotinamide (*I*).

According to available knowledge biochemical reductions with NADH coenzyme proceed in such way that one of the 4-hydrogen atoms of the nicotinamide part of the coenzyme is transferred to the substrate molecule[1-3]. Although electronic mechanism of this reduction step is not fully understood yet, a number of authors presume that it involves a hydride transfer[4]. Our previous communication dealt with mechanism of this process with the use of the EHT method. By this method it was found that nature of the particle eliminated from the 4-position of 1-methyl-1,4-dihydronicotinamide (*I*) approaches that of hydride anion. With respect to strongly approximative character of the EHT method we decided to study this process in more detail by the CNDO/2 method respecting the electron repulsion.

### CALCULATIONS

All the calculations were carried out with an ICL-4-72 computer using the standard CNDO/2 program. The used parameters were the same as those used in ref.[6]. The starting geometry of *I* was either that used in ref.[5] or that obtained by gradient optimization on the basis of the CNDO/2 wave functions[7].

### RESULTS AND DISCUSSION

The above-mentioned abstraction of hydrogen atom from 4 position was modelled in the following way (Fig. 1): the hydrogen atom H(4′) was carried away from its original position in the direction of original bond C(4)—H(4′) according to the *a* parameter, and at the same time the C(4) carbon centre was rehybridized, which

---

was modelled by tilting the H(4″) atom towards the plane of the heterocycle according to the $\varphi$ parameter. The value $\varphi = 54.7°$ corresponds to location of the H(4″) atom in the heterocycle plane. In the previous study[5] the EHT method was used for testing the $a$ and $\varphi$ parameters and selecting those which corresponded to the optimum energy course. There arises a problem whether the EHT energy hypersurfaces will not show detailed differences from those obtained by the CNDO/2 method in the region investigated. Therefore, we carried out a complete CNDO/2 calculation of the dependence of total energies $E_{\text{CNDO}/2}$ on the geometry parameters $a$ and $\varphi$ for the molecule $I$

TABLE I

Dependence of CNDO/2 energy on combination of $a$ and $\varphi$ geometry parameters for abstraction of H(4′) centre from the original (non-optimized) geometry of the molecule $I$

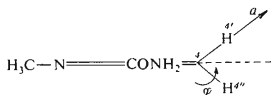| $\varphi$, ° | $a$, pm | Relative energy kJ mol$^{-1}$ |
|---|---|---|
| 0.0 | 0 | 0.0 |
| 13.7 | 25 | 110.4 |
| 13.7 | 50 | 366.5 |
| 27.4 | 75 | 627.7 |
| 27.4 | 100 | 822.7 |
| 41.1 | 125 | 966.7 |
| 41.1 | 150 | 1 058.4 |
| 54.7 | 175 | 1 123.0 |
| 54.7 | 200 | 1 164.5 |
| 54.7 | 250 | 1 216.6 |
| 54.7 | 300 | 1 246.5 |
| 54.7 | 350 | 1 265.8 |
| 54.7 | 400 | 1 280.3 |
| 54.7 | 450 | 1 290.9 |
| 54.7 | 500 | 1 297.6 |



$$H_3C—N\!\!=\!\!=\!\!=\!\!=CONH_2$$

FIG. 1

Schematic representation of abstraction of H(4′) hydrogen centre and simultaneous rehybridization of C(4) carbon centre in molecule $I$

(Fig. 2) and its cation radical $I^{+ \cdot}$ (Fig. 3). For investigation of the studied section of the hypersurface we used the geometry according to ref.[7]. From Figs 2 and 3 it follows that the optimum energy course is connected with the same combination of the $a$ and $\varphi$ parameters as that in the case of the EHT study[5]. Table I summarizes the energy dependence on the $a$ and $\varphi$ parameters for the optimum reaction coordinate. From the table it is obvious that, in contrast to the EHT course[5], the energy increases with increasing parameter $a$, no energy barrier similar to the EHT results being observed. Tables II and III summarize the charges and electron densities at some atoms at individual points of the reaction pathway. From Table II it is obvious that increasing distance of the H(4') atom from the heterocycle is connected with increasing charge at this atom up to a maximum at the arrangement described by the values $a = 250$ pm, $\varphi = 54.7°$, when the hydrogen carries a charge $-0.41$; further increase of the distance causes a slight decrease of the charge. The H(4″) atom does not markedly change its character. It is interesting that the C(4) centre acquires a somewhat negative character during the abstraction, whereas the adjacent carbon atoms C(3) and C(5) show
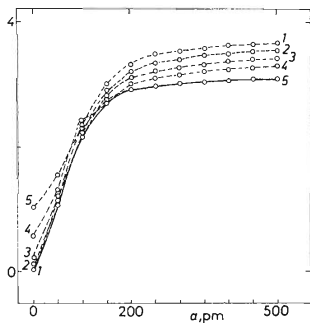


Fig. 2

Dependence of change of total CNDO/2 energy of the molecule $I$ on geometry parameters $a$ and $\varphi$. The curves 1, 2, 3, 4, and 5 correspond to the values $\varphi = 0°$, 13.7°, 27.4°, 41.1°, and 54.7°, respectively. Heavy line corresponds to the CNDO/2 approximation of reaction profile. Ax y: $\Delta E$, $10^4 \cdot$ kJ mol$^{-1}$
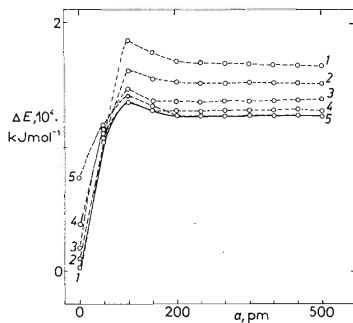
Fig. 3

Dependence of change of total CNDO/2 energy of radical cation $I^{+ \cdot}$ on geometry parameters $a$ and $\varphi$. The curves 1, 2, 3, 4, and 5 correspond to the values $\varphi = 0°$, 13.7°, 27.4°, 41.1°, and 54.7°, respectively. Heavy line corresponds to the CNDO/2 approximation of the reaction profile

a slight decrease of negative charge. The electron densities given in Table III indicate a weakening of $\sigma$ character of the H(4')—C(4) bond and (on the contrary) strenghtening of $\pi$ interaction between the centre being abstracted and the heterocycle, which can be seen from the interaction of the respective atomic orbitals representing the C(4)—H(4') bond for the heterocycle localized in the $xy$ plane. Table IV gives the expansion coefficients of the frontier orbitals HOMO and LUMO. It is obvious that, in the course of the abstraction of the H(4') atom, both localization of the HOMO and contribution of the LUMO are markedly increased at this atom. Similarly the LUMO is more and more markedly localized at the C(4) atom. This finding can be interpreted by the character of the H(4') centre approaching to a radical during abstraction, $i.e.$ to a system having simultaneously electron-donor and -acceptor character. A similar calculation using a larger iteration cycle of the $a$ and $\varphi$ parameters was also carried out for the compound $I$ with the gradient-optimized geometry[7]. Comparison of the energy course with the original non-optimized geometry is given in Fig. 4. Obviously the energy profile remains qualitatively roughly unchanged, being only shifted by 144 kJ mol$^{-1}$ towards the region of lower energies. Thus the optimization[7] has obviously no effect on qualitative characteristics of the system.

TABLE II

Distribution of CNDO/2 charges at selected centres of the original (non-optimized) molecule $I$ for certain combinations of $a$ and $\varphi$ geometry parameters

| Arrangement | | | Charges . $10^4$ | | | |
|---|---|---|---|---|---|---|
| $\varphi$, ° | $a$, pm | 4' | 4'' | 3 | 4 | 5 |
| 0·0 | 0 | −181 | −181 | −1 240 | 489 | −538 |
| 13·7 | 25 | −739 | −169 | −1 227 | 722 | −538 |
| 13.7 | 50 | −1 260 | −105 | −1 195 | 821 | −522 |
| 27·4 | 75 | −2 081 | 73 | −1 090 | 813 | −443 |
| 27·4 | 100 | −2 644 | 161 | −996 | 735 | −374 |
| 41·1 | 125 | −3 362 | 412 | −851 | 544 | −258 |
| 41·1 | 150 | −3 671 | 442 | −769 | 427 | −191 |
| 54·7 | 175 | −4 009 | 610 | −677 | 231 | −125 |
| 54·7 | 200 | −4 008 | 580 | −635 | 160 | −94 |
| 54·7 | 250 | −4 099 | 529 | −582 | 42 | −55 |
| 54·7 | 300 | −4 039 | 489 | −555 | −43 | −34 |
| 54·7 | 350 | −3 964 | 460 | −539 | −103 | −23 |
| 54·7 | 400 | −3 896 | 439 | −531 | −146 | −16 |
| 54·7 | 450 | −3 835 | 421 | −525 | −178 | −11 |
| 54·7 | 500 | −3 781 | 409 | −520 | −207 | −7 |

Also the course of changes of charges and electron densities given in Tables V and VI, respectively, resembles very much the previous situation, the strengthening of $\pi$ interaction of H(4′)—C(4) centres only being not so distinct during the abstraction course.



*I*
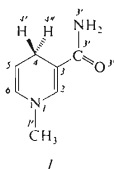
The optimized geometry[7] of the molecule *I* was used for further calculation in which the geometry parameters *a* and $\varphi$ were varied in the same way as in the previous cases, however, the whole system *I* was formulated as a radical cation $I^{+\bullet}$. From

TABLE III

Changes of electron densities in the course of abstraction of H(4′) centre from the original (non--optimized) molecule *I* for certain combinations of *a* and $\varphi$ geometry parameters

| Arrangement | | Density . $10^4$ | | | |
|---|---|---|---|---|---|
| $\varphi$, ° | *a*, pm | H(4′)—C(4)S | H(4′)—C(4)PX | H(4′)—C(4)PY | H(4′)—C(4)PZ |
| 0·0 | 0 | 4 811 | −39 | 8 448 | −261 |
| 13·7 | 25 | 3 975 | −36 | 8 621 | 542 |
| 13·7 | 50 | 3 546 | −36 | 8 479 | 655 |
| 27·4 | 75 | 2 588 | −29 | 8 110 | 1 717 |
| 27·4 | 100 | 2 251 | −27 | 7 673 | 1 832 |
| 41·1 | 125 | 1 223 | −18 | 6 916 | 2 894 |
| 41·1 | 150 | 1 048 | −16 | 6 533 | 2 912 |
| 54·7 | 175 | 36 | −4 | 5 683 | 3 805 |
| 54·7 | 200 | 0 | −2 | 5 497 | 3 768 |
| 54·7 | 250 | −18 | −1 | 5 293 | 3 709 |
| 54·7 | 300 | −13 | −1 | 5 205 | 3 673 |
| 54·7 | 350 | −7 | 0 | 5 166 | 3 652 |
| 54·7 | 400 | −4 | 0 | 5 147 | 3 640 |
| 54·7 | 450 | −2 | 0 | 5 137 | 3 633 |
| 54·7 | 500 | −1 | 0 | 5 131 | 3 628 |

TABLE IV

Expansion coefficients $|c_i| \geqq 0.1$ of the frontier orbitals HOMO and LUMO for various combinations of the $a$ and $\varphi$ geometry parameters for the original (non-optimized) molecule $I$

| AO | Arrangement[a] | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | A | B | C | D | E | F | G | H | I |
| **HOMO** | | | | | | | | | |
| H(4′) | −0·24 | −0·36 | −0·47 | −0·64 | −0·73 | −0·79 | −0·81 | −0·83 | −0·83 |
| H(4″) | 0·24 | 0·22 | 0·21 | 0·17 | 0·14 | — | — | — | — |
| N(1)PY | −0·47 | −0·45 | −0·42 | −0·35 | −0·29 | −0·25 | −0·22 | −0·21 | −0·20 |
| N(1)PZ | −0·34 | −0·32 | −0·30 | −0·25 | −0·21 | −0·18 | −0·16 | −0·15 | −0·14 |
| C(2)PY | 0·18 | 0·17 | 0·16 | 0·14 | 0·14 | 0·14 | 0·14 | 0·15 | 0·15 |
| C(2)PZ | 0·12 | 0·13 | 0·13 | 0·13 | 0·12 | 0·11 | 0·11 | 0·10 | 0·10 |
| C(3)PY | 0·35 | 0·35 | 0·33 | 0·27 | 0·22 | 0·17 | 0·14 | 0·11 | 0·10 |
| C(3)PZ | 0·25 | 0·23 | 0·21 | 0·16 | 0·13 | 0·10 | — | — | — |
| C(4)PY | −0·12 | −0·15 | −0·18 | −0·25 | −0·29 | −0·30 | −0·31 | −0·28 | −0·28 |
| C(4)PZ | — | — | — | −0·12 | −0·12 | −0·17 | −0·17 | −0·22 | −0·22 |
| C(5)PY | 0·27 | 0·27 | 0·26 | 0·22 | 0·18 | 0·13 | 0·11 | — | — |
| C(5)PZ | 0·19 | 0·18 | 0·16 | 0·13 | — | — | — | — | — |
| C(6)PY | 0·15 | 0·14 | 0·14 | 0·15 | 0·15 | 0·16 | 0·15 | 0·16 | 0·16 |
| C(6)PZ | 0·10 | 0·11 | 0·12 | 0·13 | 0·13 | 0·13 | 0·12 | 0·12 | 0·11 |
| O(3′)PY | −0·25 | −0·23 | −0·20 | −0·15 | −0·11 | — | — | — | — |
| O(3′)PZ | −0·17 | −0·17 | −0·16 | −0·12 | — | — | — | — | — |
| **LUMO** | | | | | | | | | |
| H(4′) | — | 0·18 | 0·56 | 0·59 | 0·57 | 0·56 | 0·54 | 0·54 | 0·54 |
| N(1)PY | −0·15 | −0·18 | −0·22 | −0·22 | −0·23 | −0·25 | −0·27 | −0·28 | −0·29 |
| N(1)PZ | −0·10 | −0·13 | −0·15 | −0·15 | −0·16 | −0·18 | −0·19 | −0·20 | −0·21 |
| C(2)PY | 0·51 | 0·53 | 0·35 | 0·26 | 0·24 | 0·25 | 0·25 | 0·26 | 0·26 |
| C(2)PZ | 0·36 | 0·38 | 0·28 | 0·22 | 0·20 | 0·20 | 0·19 | 0·19 | 0·18 |
| C(3)PY | −0·32 | −0·32 | −0·13 | — | — | — | — | — | — |
| C(3)PZ | −0·23 | −0·22 | −0·11 | — | — | — | — | — | — |
| C(4)PY | — | −0·11 | −0·46 | −0·53 | −0·55 | −0·53 | −0·52 | −0·48 | −0·48 |
| C(4)PZ | — | — | — | −0·17 | −0·17 | −0·25 | −0·25 | −0·32 | −0·32 |
| C(6)PY | −0·13 | — | 0·22 | 0·25 | 0·25 | 0·26 | 0·26 | 0·27 | 0·27 |
| C(6)PZ | — | — | 0·18 | 0·20 | 0·20 | 0·20 | 0·20 | 0·20 | 0·20 |
| C(3′)PY | −0·34 | −0·31 | — | — | — | — | — | — | — |
| C(3′)PZ | −0·23 | −0·22 | — | — | — | — | — | — | — |
| O(3′)PY | 0·29 | 0·27 | — | — | — | — | — | — | — |
| O(3′)PZ | 0·20 | 0·19 | — | — | — | — | — | — | — |
| N(3′)PY | 0·16 | 0·15 | — | — | — | — | — | — | — |
| N(3′)PZ | 0·11 | 0·11 | — | — | — | — | — | — | — |

[a] A corresponds to the arrangement $a = 0$ pm, $\varphi = 0.0°$, similarly B(13·7/25), C(13·7/50), D(27·4/75), E(27·4/100), F(41·1/125), G(41·1/150), H(54·7/175), I(54·7/200).

TABLE V
Distribution of CNDO/2 charges at selected centres of the optimized molecule *I* for certain combinations of $a$ and $\varphi$ geometry parameters

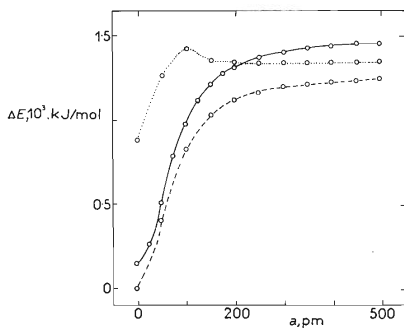| Arrangement | | Charges . $10^4$ | | | | |
|---|---|---|---|---|---|---|
| $\varphi$, ° | $a$, pm | 4′ | 4″ | 3 | 4 | 5 |
| 0·0 | 0 | −341 | −341 | −1 137 | 786 | −523 |
| 13·7 | 50 | −1 568 | −194 | −1 048 | 1 034 | −492 |
| 27·4 | 100 | −3 052 | 166 | −792 | 827 | −302 |
| 41·1 | 150 | −4 032 | 482 | −553 | 472 | −109 |
| 54·7 | 200 | −4 343 | 567 | −436 | 233 | −16 |
| 54·7 | 250 | −4 321 | 500 | −390 | 133 | 22 |
| 54·7 | 300 | −4 240 | 451 | −367 | 60 | 43 |
| 54·7 | 350 | −4 155 | 416 | −356 | 10 | 54 |
| 54·7 | 400 | −4 076 | 390 | −350 | −28 | 61 |
| 54·7 | 450 | −4 013 | 369 | −345 | −56 | 66 |
| 54·7 | 500 | −3 956 | 354 | −342 | −79 | 70 |



FIG. 4
Energy profile of abstraction of H(4′) hydrogen centre with simultaneous rehybridization of C(4) carbon centre in the molecule *I*. Full line denotes the dependence for the original geometry of *I* (ref.[5]), dashed line for the optimized geometry of *I* (ref.[7]), dotted line for radical cation $I^{+\cdot}$.

TABLE VI

Changes of electron densities in the course of abstraction of H(4') centre from the molecule *I* for certain combinations of the *a* and $\varphi$ geometry parameters (optimized geometry)

| Arrangement | | Density . $10^4$ | | | |
|---|---|---|---|---|---|
| $\varphi$, ° | $a$ pm | H(4')—C(4)S | H(4')—C(4)PX | H(4')—C(4)PY | H(4')—C(4)PZ |
| 0·0 | 0 | 4 559 | 53 | 5 289 | 6 626 |
| 13·7 | 50 | 3 262 | 45 | 4 348 | 7 106 |
| 27·4 | 100 | 1 929 | 28 | 2 713 | 7 000 |
| 41·1 | 150 | 713 | 9 | 1 079 | 6 588 |
| 54·7 | 200 | −52 | −3 | 57 | 6 192 |
| 54·7 | 250 | −40 | −2 | 8 | 6 007 |
| 54·7 | 300 | −23 | −1 | −2 | 5 923 |
| 54·7 | 350 | −11 | 0 | −3 | 5 886 |
| 54·7 | 400 | −5 | 0 | −2 | 5 867 |
| 54·7 | 450 | −2 | 0 | −1 | 5 856 |
| 54·7 | 500 | −1 | 0 | 0 | 5 849 |

TABLE VII

Distribution CNDO/2 charges at selected centres of compound *I* for certain combinations of the *a* and $\varphi$ geometry parameters (optimized geometry, radical cation $I^{+\cdot}$)

| Arrangement | | Charges . $10^4$ | | | | |
|---|---|---|---|---|---|---|
| $\varphi$, ° | $a$, pm | 4' | 4″ | 3 | 4 | 5 |
| 0·0 | 0 | 797 | 797 | 147 | 199 | 403 |
| 13·7 | 50 | 743 | 726 | −31 | 554 | 213 |
| 27·4 | 100 | 463 | 714 | −263 | 996 | −47 |
| 41·1 | 150 | 97 | 736 | −305 | 1 172 | −118 |
| 54·7 | 200 | 12 | 734 | −307 | 1 199 | −127 |
| 54·7 | 250 | 2 | 732 | −307 | 1 204 | −129 |
| 54·7 | 300 | 1 | 731 | −307 | 1 204 | −129 |
| 54·7 | 350 | 0 | 731 | −307 | 1 204 | −129 |
| 54·7 | 400 | 0 | 731 | −307 | 1 204 | −129 |
| 54·7 | 450 | 0 | 731 | −307 | 1 204 | −129 |
| 54·7 | 500 | 0 | 731 | −307 | 1 204 | −129 |

Fig. 4 it follows that the energy changes connected with changes of the geometry parameters $a$ and $\varphi$ show a not very distinct barrier for $a = 100$ pm, $\varphi = 27\cdot4°$ which could partially stabilize the dissociated system. The distribution of atomic char-

TABLE VIII

Changes of electron densities in the course of abstraction of H(4′) centre from the molecule $I$ for certain combinations of the $a$ and $\varphi$ geometry parameters (optimized geometry, radical cation $I^{+\cdot}$)

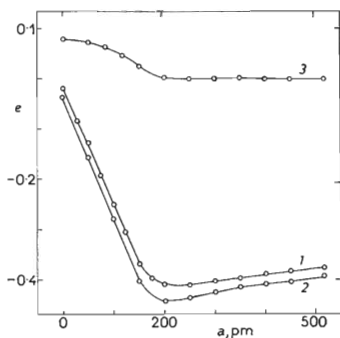| Arrangement | | Density . $10^4$ | | | |
|---|---|---|---|---|---|
| $\varphi, °$ | $a$, pm | H(4′)—C(4)S | H(4′)—C(4)PX | H(4′)—C(4)PY | H(4′)—C(4)PZ |
| 0·0 | 0 | 4 590 | 53 | 5 262 | 6 181 |
| 13·7 | 50 | 3 136 | 43 | 4 135 | 6 003 |
| 27·4 | 100 | 1 406 | 19 | 1 976 | 3 766 |
| 41·1 | 150 | 404 | 4 | 636 | 1 608 |
| 54·7 | 200 | 84 | 0 | 188 | 613 |
| 54·7 | 250 | 24 | 0 | 67 | 240 |
| 54·7 | 300 | 6 | 0 | 23 | 91 |
| 54·7 | 350 | 1 | 0 | 8 | 37 |
| 54·7 | 400 | 0 | 0 | 2 | 13 |
| 54·7 | 450 | 0 | 9 | 1 | 4 |
| 54·7 | 500 | 0 | 0 | 0 | 2 |



FIG. 5

Course of charge changes at the H(4′) atomic centre during its abstraction. The curve 1 for the original geometry of $I$ (ref.[5]), curve 2 for the optimized geometry of $I$ (ref.[7]), curve 3 for radical cation $I^{+\cdot}$.

ges given in Table VII shows that the $H(4')$ atom being abstracted leaves as a neutral particle, which would indicate that it exists in radical form for $a > 350$ pm. According to Table VIII the electron densities at the $H(4')$—$C(4)$ bond indicate that increasing distance between the $H(4')$ atom and the heterocycle is accompanied by complete cleavage of the bond to the $C(4)$ centre.

From comparison of charges at the $H(4')$ centre being abstracted (Fig. 5) in the three above-mentioned calculation series it can be concluded that, in case of the neutral molecule $I$, the leaving $H(4')$ centre takes a considerable negative charge with it. Distinct $\pi$ interaction of this centre with the $C(4)$ atom (Tables III and VI) obviously causes that the former centre does not acquire exclusively the anion character, the expansion coefficients of the frontier orbitals (Table IV) admitting the radical character, too. If the original molecule was rid of one electron in some preceding process and exists in the form of the radical cation $I^{+\cdot}$, then the $H(4')$ centre being abstracted acquires an exclusively radical character, and from Table VIII it follows that the bond to the heterocycle is entirely cleaved. Hence it seems likely that the electronic mechanism of abstraction of the $H(4')$ hydrogen centre depends on whether or not the molecule $I$ (as a model of the NADH coenzyme) has given away one of its electrons in a preceding process. From the results given it follows that the energy profiles obtained by the EHT and CNDO/2 methods for identical trajectories differ in that the latter calculation method gives no energy barrier for the $C(4)$—$H(4')$ bond splitting in compound $I$ and gives a somewhat lower extent of negative charge transfer at the leaving atomic centre $H(4')$. The latter finding is probably connected with the known tendency of the simple EHT procedure to overestimate of localization of electronic charges at atomic centres. Nevertheless, both the EHT and the CNDO/2 approaches indicate a possibility of the $C(4)$—$H(4')$ bond heterolysis producing hydride ion, however, the CNDO/2 calculation does not exclude the one-electron splitting mechanism *via* the radical cation $I^{+\cdot}$, too, the study of which gave physically unreal results of the EHT procedure[5] due to neglection of electronic repulsion. However, relative advantages of the two CNDO/2 coordinates for the mono- and bielectronic course (Fig. 4) cannot be unambiguously judged within the framework of the used approximation of the isolated $I$ molecule, because influences of other reaction partners can modify these energy profiles in various ways. Disposition of molecule $I$ to the above-mentioned $C(4)$—$H(4')$ bond splittings will be investigated in further studies at a non-empirical level taking into account the role of correlation energy.

**REFERENCES**

1. Fischer H. F., Conn E. E., Vennesland B., Westheimer F. H.: J. Biol. Chem. *202*, 687 (1953).
2. Pullman M. E., San Pietro A., Colowick S. P.: J. Biol. Chem. *206*, 129 (1954).
3. Akhtar M., Jones C.: Tetrahedron *34*, 813 (1978).

4. Bruice T. C., Benkovic S. in the book: *Bioorganic Mechanisms*, Vol. II. Benjamin, New York 1966.
5. Krechl J., Kuthan J.: This Journal *45*, 2425 (1980).
6. Krechl J., Kuthan J.: This Journal *46*, 740 (1981).
7. Böhm S., Kuthan J.: This Journal, in press.

Translated by J. Panchartek.