EHT STUDY OF INTERACTION OF 1-METHYL-3-CARBAMOYLPYRIDINIUM WITH CYANIDE*

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The local extremes of EHT energy curves of 1-methyl-3-carbamoylpyridinium cyanide (*I*) corresponding to approach of CN^- towards plane of the heterocycle have been shown to predict the energetically most favourable attack at he positions 4 > 2 > 6. The subsequent rehybridization of 4-carbon atom from trigonal to tetrahedral configuration results in a further decrease of overall EHT energy in accord with the known formation of 1-substituted 3-carbamoyl-4-cyano-1,4-dihydropyridines during reaction of alkali cyanides with quarternary salts of nicotineamide and NAD.** The EHT energy map is interpreted for motion of CN^- at a distance of 200 pm above plane of the heterocyclic ring.

Interaction of anions with 1-alkyl-3-carbamoylpyridinium cations RNA^+ (general formula *I*) is interesting for better understanding of chemical details of biological oxidation processes based on NAD^+. So far from this viewpoint quantum chemistry has provided interpretation of reactivity of RNA^+ cation in approximation of isolated molecule with[1-4] or without[4] neglect of individuality of nucleophilic reagent. The latter approach[4] shows that various nucleophiles can preferably attack 2, 4, or 6 position of heterocyclic ring of RNA^+ cation in the kinetically fastest step according to their "softness" or "hardness" in the sense of the general concepts[5,6]. This approach, of course, does not sufficiently respect (with regard to approximation of isolated molecule) further possible factors, especially the problem of mutual orientation of the substrate and reagent. In order to understand better the operation of these effects and investigate further the possibilities of EHT method in this area[7], we decided to study in more detail the "supermolecule" of $MeNA^+$ cation and CN^- anion in several selected configurations. We started from the experience that EHT procedure gives qualitatively correct interpretation[8-10] of interactions of extremely weak nucleophiles F^-, Cl^- and BF_4^- with pyridinoid cations. The aim of this work is

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** The used abbreviations: $MeNA^+$ 1-methyl-3-carbamoylpyridinium cation, RNA^+ 1-alkyl-3-carbamoylpyridinium cation, NAD^+ nicotineamide adenine dinucleotide, CN-NADH 4-cyano-1,4-dihydronicotineamide adenine dinucleotide.

a study of influence of geometry of the ion-pair *I* on its EHT electronic energy E_{tot} of valence electrons.

Calculations

The EHT calculations were carried out with the standard program using the IBM 370/145 computer. Diagonal elements of **H**-matrix were ionisation potentials of the respective valence states[11]. For calculation of non-diagonal elements we used the Wolfsberg–Helmholtz approximation[12] with the empirical constant $K = 1{\cdot}75$. Values of the individual parameters are given in Table I. Location of the EHT model of the ion-pair *I* is represented in Fig. 1 wherefrom we also can see the way of orientation of CN^- anion with respect to the $MeNA^+$ cation ring and meaning of the distance parameter *r*. Conformation of the amide group was fixed in the plane of the heterocycle (formula *I*) on the basis of studies[4,13] of isolated $MeNA^+$ cation and experimentally supported bond lengths and angles used in ref.[13]. In the course of the E_{tot} values the orientation of amide group was not further optimized.

RESULTS AND DISCUSSION

The energy $E_{tot}(I)$ of the ion-pair *I* behaves in similar way as that in the cases of the pyridinium salts studied to far[8–10], especially it is

$$E_{tot}(I) \geqq E_{tot}(MeNA^+) + E_{tot}(CN^-)\,, \qquad (1)$$

where the terms on the right-hand side mean EHT energies of the isolated ion partners. In accord with general discussion[8] of this feature of EHT method in similar systems, the $E_{tot}(I)$ quantity does not show any overall minimum for lower distances between $MeNA^+$ and CN^- ions, and it converges to the value given by the right-hand side of relation (*1*) for distances above 400 pm regardless of direction. Therefore, we tried to interpret the local energy anomalies. For the approach of CN^- particle to plane

TABLE I

The Parameters Used in EHT Calculations

IP(*s*) Ionisation potential of *s* orbital, *IP*(*p*) ionisation potential of *p*-orbital, *S.E.* the Slater exponent.

Atom	*IP*(*s*), eV	*IP*(*p*), eV	*S.E.*
H	−13·6	—	1·300
C	−21·4	−11·4	1·625
N	−26·0	−13·4	1·950
O	−32·3	−14·8	2·275

of the heterocycle of $MeNA^+$ cation in the way shown in Fig. 1 it was found that the curves $E_{tot}(I) = f(r)$ exhibit pure repulsive character in most cases, *i.e.* simple increase of the $E_{tot}(I)$ energy with decreasing distance parameter r. Only the approach perpendicular to positions 2, 4, and 6 results in formation of shoulders at $r = 170$ pm, the effect being most marked for 4 position (Fig. 2). This phenomenon is interpreted as being probably the consequence of the fact that configuration of the CN^- anion directly above the given carbon atom centre lies out of the correct reaction coordinate. Nevertheless the existence of shoulder in the mentioned cases can be considered indication of such section through the energy hypersuperface of the ion-pair I in which the configuration of the both partners CN^- and $MeNA^+$ is not too far from the corresponding local energy minimum. The deviation of the most favourable configuration can be supposed to be due to not only non-respecting the best way of the anion CN^- to the respective reaction centre, but also to neglect of "response" of this atomic centre consisting in additional configuration change in its valence sphere, *i.e.* in rehybridization effect of the approaching ionic particle.

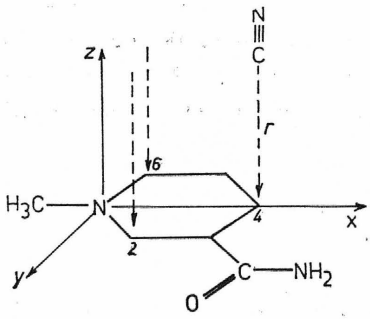


FIG. 1

Location of Ion-Pair I in Coordinate System and Meaning of Distance Parameter r

Interrupted arrows denote direction of approach of CN^- particle to reactive centres.

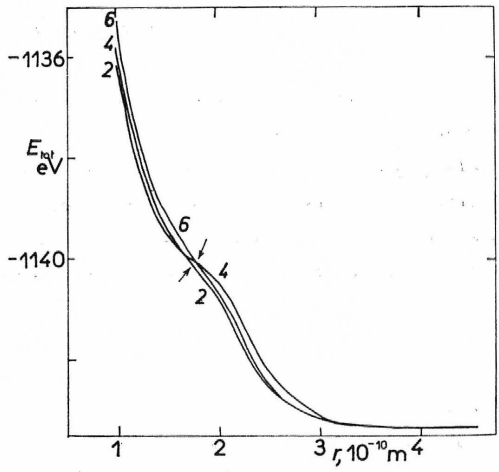


FIG. 2

Dependence of EHT Electron Energy of Ion-Pair I on Distance between Cyanide Ion above some Carbon Atomic Centres of 1-Methyl-3-carbamoylpyridinium Cation (Fig. 1)

The numbers correspond to the individual positions. The arrows point at shoulders on the energy curves.

To verify this presumption, we investigated the behaviour of $E_{tot}(I)$ during additional variation of the valence angles α and β and parameter r (Fig. 3). The obtained results are graphically represented in Fig. 4 wherefrom it follows that the mentioned rehybridization effect on the reaction centre results really in a further decrease of the $E_{tot}(I)$ energy until the moment when this centre becomes tetrahedral ($\alpha \approx \beta = 45$ to 55°). These energetically minimalized configurations of the ion-pair *I* correspond then to initial formation of covalent σ-complexes *Ia*–*c* between the starting partners $MeNA^+$ and CN^- and to final formation of dihydropyridine derivatives *II* to *IV*.* From available experimental findings[14,15] it follows that reactions of alkali cyanides with quaternary salts containing the RNA^+ cation give exclusively the respective 1,4-dihydropyridinium derivative *III*. Similar course was determined in analogous reaction of NAD^+ giving 4-CN-NADH as biochemical product. In this context it is noteworthy that for EHT energies of σ-complexes *Ia*–*c* it is $E_{tot}(Ic) > E_{tot}(Ia) \gg E_{tot}(Ib)$ (−1 140·96, −1 141·02, −1 141·36 eV), which mean that the 1,4-dihydro derivative *III* should be thermodynamically the most stable product. It is remarkable that reversibility of the attack of RNA^+ cations by CN^- anions is supported by con-

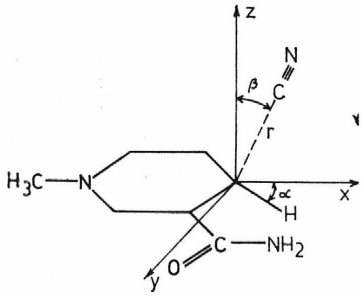


FIG. 3

Variable Geometric Degrees of Freedom of Ion-Pair *I* during Rehybridization of the Atomic Centre Attacked by Cyanide Anion

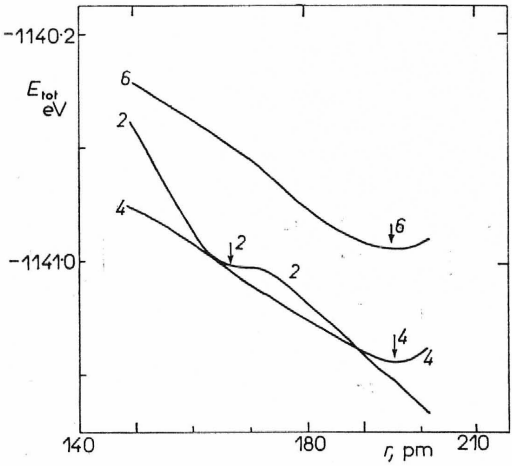
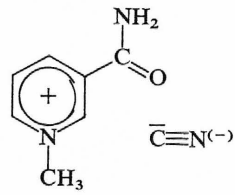


FIG. 4

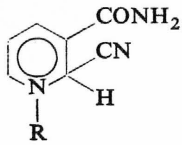
Dependence of EHT Electronic Energy of Ion-Pair *I* on Geometric Degrees of Freedom during Rehybridization of Atomic Centres at 2, 4 and 6 Positions of the Heterocyclic Cation (Fig. 3)

* The final geometry change corresponding to location of multiple bonds in the processes *Ia* → *II*, *Ib* → *III*, and *Ic* → *IV* was not further investigated.

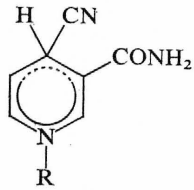
vincing experimental arguments[14,15]. It is, of course, problematic whether the predominant product type *III* results from a rapid antecedent attack preferring *e.g.* 2 and 6 positions (kinetic control) and subsequent isomerization of the primary intermediates *II* and *IV* to 1,4-dihydro derivative *III* (thermodynamic control), which is given[16] for a substrate slightly different from RNA^+ cations. On the basis of the above-discussed EHT energy characteristics this problem can hardly be solved unambiguously, since the values $E_{tot}(Ia)$ and $E_{tot}(Ib)$ differ only little, and their relation could be incorrectly affected by approximative character of the used theoretical procedure. Nevertheless the more marked difference between these quantities and the $E_{tot}(Ic)$ value makes that explanation the most probable in which the primary attack by CN^- anion should take place either exclusively at 4 position or simultaneously at 2 and 4 positions. Only in the latter case the factor of thermodynamic control could shift the equilibrium $II \rightleftarrows III$ to the right.



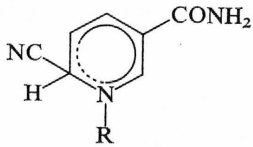
I



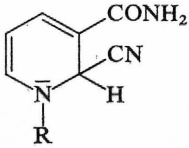
Ia



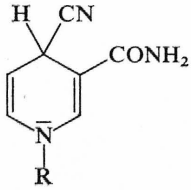
Ib



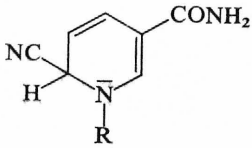
Ic



II



III



IV

The given results interpret quite correctly the fact that interaction between $MeNA^+$ and CN^- ions is distinctly different in nature from those involving F^- and BF_4^-

anions[10]. For overall characterization of these differences within EHT formalism we decided to investigate the energy map of the ion-pair *I* which could be comparable with the analogous map investigated[10] in the case of interaction of $MeNA^+$ and F^-. For this purpose we chose, as a typical situation, motion of CN^- anion situated perpendicularly to plane of $MeNA^+$ heterocycle (Fig. 1), the carbon atom of CN^- being in a parallel plane at a distance 200 pm. This distance *r* was chosen on the basis of preliminary EHT calculations so that the quantity $E_{tot}(I)$ might be sufficiently sensitive to variations of CN^- position keeping constant the distance of both ionic partners which is physically justified from the viewpoint of effective radii of the atomic centres. The obtained EHT energy map of the ion-pair *I* given in Fig. 5 is not inconsistent with the above-given way of interpretation of approach of the particles $MeNA^+$ and CN^-. The whole map exhibits only one local minimum, *viz.* above carbon centre of amide group: its existence could represent a possibility of formation of labile π-complex of the perpendicularly oriented CN^- anion above the carbon atomic centre of the amide group, the formation being followed by σ-interactions at 2, 4 or 6 positions. Approach of CN^- to these positions corresponds to energy "valleys" cutting into the energy "mountains" inside the heterocyclic ring, the cutting being the deepest just at the position 4. The fact that there is no local minimum above 2,4,6 positions can be easily understood on the basis of the above-mentioned presumption that the optimum way for approach of CN^- particle is not perpendicular to the plane of the heterocycle and necessitates, in addition to it, rehybridization of the given atomic centre, which was not respected in construction of the map. The most marked difference between the map of the ion-pair *I* and that of analogous interaction with fluoride anion[10] consists in that the former lacks the local minimum above the centre of the heterocycle which is characteristic of ionic bond in EHT

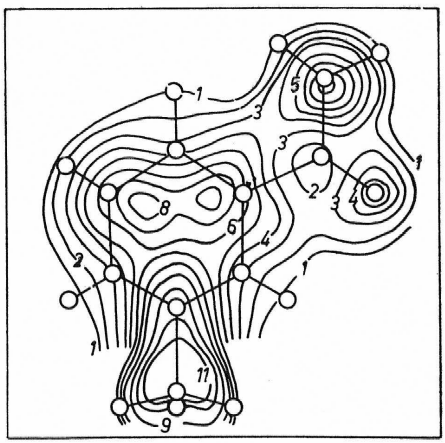


FIG. 5

EHT Energy Map of Ion-Pair *I* for Motion of Perpendicular Cyanide Ion (see Fig. 1) with Carbon Atom Moving in Parallel Plane to Heterocyclic Cation ($r = 200$ pm)

The level 0 corresponds to $-1142{\cdot}0$ eV; the level distances 0·4 eV.

models of pyridinium salts[8-10]. Hence ionic structure of quaternary cyanide *I* is not likely on the basis of these interpretation considerations, which is in accord with experimental findings[14-17] concerning addition of CN^- anion to RNA^+ and NAD^+ cations. Another interesting difference following from the EHT maps consists in that CN^- has a greater affinity to carbon atom of the amide group, whereas F^- has greater affinity to nitrogen atom[10]. Thus it can be stated that the method of local extremes of the EHT energy characteristics[8] is chemically and physically justified in the case of the ion-pair *I*, too. More studies, however, need to be done for evaluation of its more general applications to structurally more attractive systems.

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