

STUDY OF THE ELECTROCHEMICALLY INITIATED CYANO-METHYLATION OF AZOMETHINES BY MEANS OF THE MNDO AND AM1 SEMIEMPIRICAL METHODS

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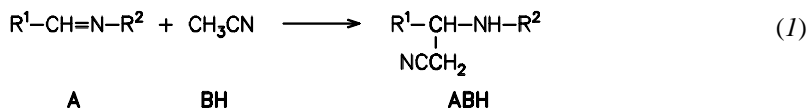
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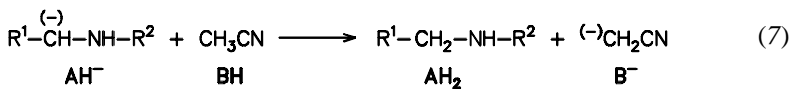
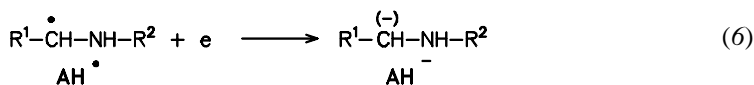
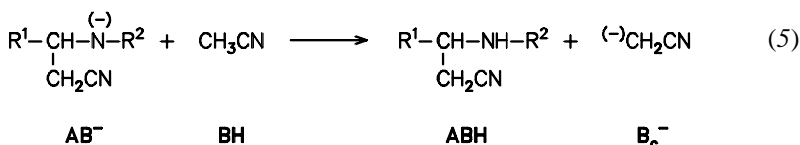
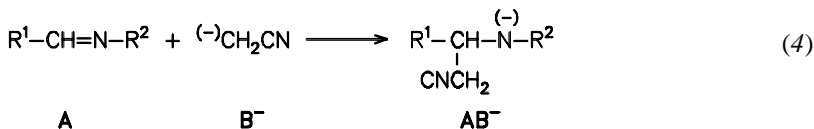
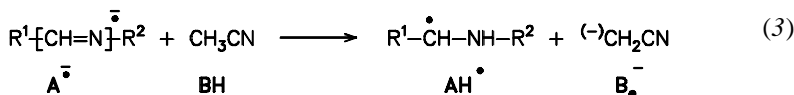
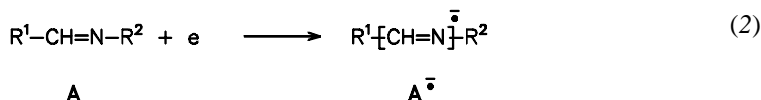
The semiempirical methods (MNDO and AM1) have been used in the quantum chemical study of electrochemically initiated cyanomethylation of azomethines. Reaction steps leading to the main product of the studied reaction, β -aminonitrile, have been described. The stationary points on the reaction path have been found and the activation enthalpies of reaction steps have been determined. Three possible mechanisms for the abstraction of a proton from acetonitrile have been described (by azomethine radical anion, by β -aminonitrile anion, and by hydrogenated azomethine anion). At the MNDO level, the abstraction of a proton by azomethine radical anion has the highest activation enthalpy ($\Delta H = 197 \text{ kJ mol}^{-1}$) and the abstraction of a proton by hydrogenated azomethine anion has the lowest activation enthalpy ($\Delta H = 146 \text{ kJ mol}^{-1}$). The activation enthalpy of the next reaction step (the reaction of acetonitrile anion with azomethine) is low compared to the activation enthalpies of the previous reaction steps ($\Delta H = 12 \text{ kJ mol}^{-1}$).

The cyanomethylation^{1,2} of azomethines (Eq. (1)) leads to the formation of β -aminonitriles which are important in pharmaceutical industry.



The reaction mechanism has been shown³ in Eqs (2)–(7) where R^1 is the aryl with the heteroatom and R^2 is the aryl.

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According to this mechanism, in the first step azomethine is reduced to its radical anion A^{\ominus} , which reacts with acetonitrile BH forming acetonitrile anion (reaction (3) where acetonitrile anion is denoted B_e^{\ominus} since it was formed via electrochemical process). This anion then acts as a nucleophile and reacts with azomethine forming cyanomethyl anion AB^{\ominus} (Eq. (4)). AB^{\ominus} abstracts a proton from acetonitrile producing a β -aminonitrile ABH and acetonitrile anion B^{\ominus} (which is denoted B_e^{\ominus} since it is formed via chemical process, Eq. (5)). The AH^{\bullet} radical, which is present in the system, is farther reduced to form anion AH^{\ominus} (Eq. (6)). This anion reacts with acetonitrile again, forming B^{\ominus} and AH_2 (reaction (7)). In this paper, we present the calculations of the most important reaction steps (acetonitrile anion formation including its regeneration and subsequent formation of β -aminonitrile) by means of MNDO (refs^{4,5}) and AM1 (refs^{6,7}) methods. As a typical example we have chosen a system with R^1 being pyridine and R^2 being phenyl.

EXPERIMENTAL

The preparative electrolysis of azomethines (in amount of 1.0 g) was carried out potentiostatically on the mercury cathode with the 10 cm² surface at the potentials of their voltammetric peaks; 70 ml of electrolyte (0.1 M tetraethylammonium bromide in dry acetonitrile) was used. The anode and reference electrode were graphite and silver bromide, respectively. The cathode space was separated from the anode space by fritted glass of density G4. The sample was electrolyzed at 20 °C in the nitrogen atmosphere while stirring with the magnetic stirring bar. The current decreased from the starting 150–170 mA to 10–30 mA after 5–10 min. This value remained constant through out the duration of electrolysis (2–3 h). The color of the solution in the cathode space turned from colorless to orange-brown and brown. The electrolytic course was controlled by DC measurement. After electrolysis, the solvent was evaporated from the solution in vacuum, the rest was extracted with 100 ml of ether and 100 ml of water, and the water phase was again extracted with ether. The combined ether extracts were evaporated and the product was purified using chromatography on silica gel and analyzed by IR and MS spectroscopy and ¹H NMR. The detailed description of experiment and of each of the derivatives have been presented elsewhere^{3,8}.

The overall current consumption was in the range of 0.1–0.3 F per mole of reacted azomethine. The low current consumption needed for the formation of β-aminonitriles from starting azomethines suggests that the process is catalyzed on the electrodes, and it is based on the reactions and regeneration of acetonitrile anion generated via the electrochemical way.

CALCULATIONS

In order to find the stationary points on the reaction paths and to determine the activation enthalpies of reaction steps, the quantum chemical semiempirical MNDO and AM1 methods of the AMPAC program package have been used. The geometries of the reactants, products, and reaction intermediates were fully optimized. In order to find the transition state structures, the approximate geometries were found first^{9,10} and these geometries were farther optimized. Subsequently, the Hessian for each transition state structure was calculated in order to verify that there is just one negative eigenvalue.

The UHF method was used in the studies of the abstraction of proton from acetonitrile by azomethine radical anion. The RHF method was used in all other studies.

RESULTS AND DISCUSSION

The Abstraction of a Proton from Acetonitrile by Azomethine Radical Anion

The MNDO results. The energy profile of the reaction (3) is summarized in Table I. This table gives the enthalpies of formation (ΔH_f) for the species with the geometries corresponding to the stationary points on the reaction coordinate. As the reactants come closer, the ΔH_f decreases, with the minimum found at the distance N(2)–H(3) = 0.347 nm (numbering is given in Fig. 1). This complex between azomethine anion and neutral molecule (BH...A⁻) is in fact ion–dipole complex. The geometries of the reactants are almost unchanged at this stage. The distribution of the electron density is slightly

changed, especially in the molecule of acetonitrile, due to the interaction with N(2) atom. The higher electron density on this atom causes the larger polarization of the H(3)–C(4) bond.

In order to find an approximate geometry of the transition state, the probable reaction centers of both molecules were faced to each other (see Fig. 1) and the distance between them was gradually decreased. At a given distance, the other parameters were optimized, and the enthalpies of formation at a given N(2)–H(3) distance were calculated. The geometry of the system with the maximum enthalpy was taken as the geometry of the transition state. This procedure is in the farther text referred as the method of reaction coordinate. The transition state (Fig. 1) is characterized mainly by the N(2)–H(3) (0.108 nm) and H(3)–C(4) (0.179 nm) distances. As one can see from these parameters, the transition state is formed at relatively short N(2)–H(3) distance which corresponds

TABLE I

The enthalpies of formation for species at the geometries corresponding to the stationary points on the reaction coordinate and activation enthalpy for the reaction (3) (TS stands for transition structure)

System	ΔH_f , kJ mol ⁻¹	
	MNDO	AM1
BH + A ^{•+}	291	268
BH...A ^{•+}	211	245
TS	409	–
B ⁻ ...HA [•]	399	–
B ⁻ + HA [•]	426	–
Eq. (3), ΔH^\ddagger	198	–

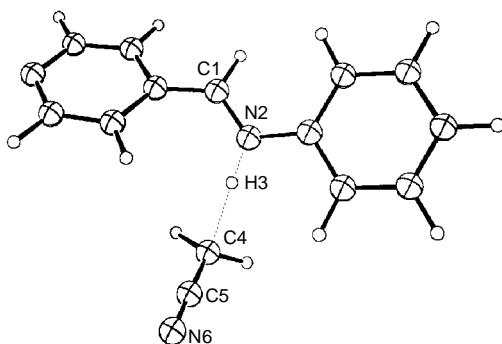


FIG. 1

MNDO geometry of the transition structure in Eq. (3). The C(4)–H(3) bond lengths in reactants and TS are 0.111 and 0.179 nm, respectively, and the N(2)–H(3) bond lengths in TS and product are 0.108 and 0.100 nm, respectively

to relatively high activation enthalpy of the reaction (197 kJ mol^{-1}). Another stationary point on this reaction path is the ion-dipole complex $B^{\dots}HA$, characterized by the enthalpy of formation only slightly lower than the energy of the transition state. The $H(3)-C(4)$ distance in this complex is 0.296 nm and the other geometrical parameters are almost the same as in isolated species AH^{\bullet} and B^{-} . The complex and the products differ only in the distribution of electron density; the electron density on $H(3)$ atom is lower due to the interaction with $C(4)$ atom. As the $H(3)-C(4)$ distance increases, ΔH_f of the system increases and becomes comparable to the sum of ΔH_f of the isolated product molecules.

The AM1 results. The enthalpies of formation of the stationary points on the reaction path are given in Table I. As it was found at the MNDO level, ΔH_f decreases as the distance between A^{\bullet} and BH decreases, with the minimum of the $N(2)-H(3)$ distance 0.273 nm . The ΔH_f increases when this distance farther decreases.

Unlike at the MNDO level, the minimum corresponding to the products was not found on the PES of the studied system at the AM1 level. The calculations using the MNDO method predict such a minimum, but this is very shallow compared to the activation enthalpy of the reaction ($\Delta H^{\ddagger} = 197 \text{ kJ mol}^{-1}$). It can be concluded that the equilibrium is significantly shifted towards the reactants.

The Abstraction of a Proton from Acetonitrile by β -Aminonitrile Anion

The MNDO results. The enthalpies of formation of the stationary points representing the energy profile of the reaction (5) are given in Table II. Also in this process, the complex is formed first. This complex is characterized by the $N(2)-H(3)$ distance 0.351 nm .

The approximate geometry of the TS was found by means of the reaction coordinate method. The $N(2)-H(3)$ distance was used as a reaction coordinate (numbering is given in Fig. 2). In this TS (Fig. 2), the $N(2)-H(3)$ and $H(3)-C(4)$ distances are 0.111 nm and 0.168 nm , respectively. As in previous cases, the $N(2)-H(3)$ distance is significantly

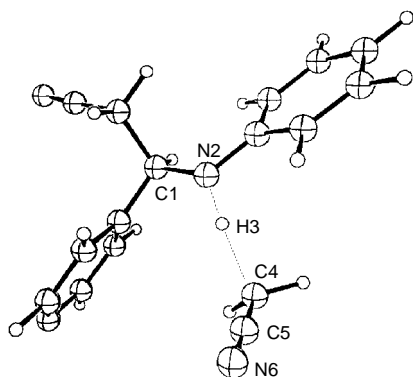


FIG. 2
MNDO geometry of the transition structure in Eq. (5). The $C(4)-H(3)$ bond lengths in reactants and TS are 0.111 and 0.168 nm , respectively, and the $N(2)-H(3)$ bond lengths in TS and product are 0.111 and 0.101 nm , respectively

shorter than the H(3)–C(4) distance, although, the difference is not as large as in the case of the abstraction of a proton by azomethine radical anion. Consequently, the activation enthalpy of the reaction is smaller ($\Delta H^\ddagger = 177 \text{ kJ mol}^{-1}$), probably due to the lower electron density on N(2) atom in $A^{\bullet-}$ molecule than in AB^- molecule. The lower electron density results from the presence of unpaired electron in the former molecule.

The N(2)–H(3) distance in $ABH\dots B^-$ complex is 0.277 nm. The energy minimum of this complex is again rather shallow (as in the previous complex) compared to the activation enthalpy of the reaction.

The AM1 results. As in the case of reaction (3), the results obtained with the AM1 method differ from those obtained with the MNDO method. The complex between the neutral molecule and anion is predicted at the N(2)–H(3) distance 0.282 nm. As the N(2)–H(3) distance decreases, the ΔH_f of the system increases, and even though the gradient of ΔH_f decreases at small N(2)–H(3) distances (when the N(2)–H(3) distance farther decreases the gradient again increases), the minimum on the PES corresponding to the products was not found.

Results of calculations including sparkle. Both MNDO and AM1 results indicate the small probability of reaction (5). The fact that the reaction proceeds at the given experimental conditions is probably due to the effect of environment. The preparative electrolysis was carried out in the liquid acetonitrile with the main electrolyte tetrabutylammonium bromide (with the concentration 10 times larger compared to the concentration of azomethines). The influence of this environment probably caused the larger stabilization of acetonitrile anion and, consequently, enables the abstraction of a proton from acetonitrile. This effect was simulated by including so called sparkle (Sp) particle into the calculations¹¹. The sparkle is a special particle which can simulate a presence

TABLE II

The enthalpies of formation for species at the geometries corresponding to the stationary points on the reaction coordinate and activation enthalpy for the reaction (5) (TS stands for transition structure)

System	$\Delta H_f, \text{ kJ mol}^{-1}$	
	MNDO	AM1
BH + AB^-	363	382
BH... AB^-	349	356
TS	526	–
B^- ...ABH	517	–
B^- + ABH	536	–
Eq. (5), ΔH^\ddagger	177	–

of a positively charged particle. At the beginning of calculations, the sparkle was located at the vicinity of N(6) atom (N(6)–Sp distance was 0.30 nm, and C(5)–N(6)–Sp angle was 180°). This starting position of Sp was chosen in order to respect a significant increase of the electron density on the N(6) atom during the acetonitrile anion formation. During the localization of the stationary points on the reaction paths and calculations of their structures, the position of Sp was always optimized (results of calculations with Sp are given in Tables III and V).

The values of ΔH_f of the stationary points on the reaction path of the reaction (5) calculated with Sp are given in Table III. The results obtained with the MNDO method

TABLE III

The enthalpies of formation for species at the geometries corresponding to the stationary points on the reaction coordinate and activation enthalpy for the reaction (5) calculated with the sparkle particle present in the model (TS stands for transition structure)

System	ΔH_f , kJ mol ⁻¹	
	MNDO	AM1
BH...AB ⁻	95	57
TS	219	118
B ⁻ ...ABH	151	94
Eq. (5), ΔH^\ddagger	124	61

TABLE IV

The enthalpies of formation for species at the geometries corresponding to the stationary points on the reaction coordinate and activation enthalpy for the reaction (7) (TS stands for transition structure)

System	ΔH_f , kJ mol ⁻¹	
	MNDO	AM1
BH + AH ⁻	258	267
BH...AH ⁻	245	234
TS	391	–
B ⁻ ...AH ₂	368	–
B ⁻ + AH ₂	395	–
Eq. (7), ΔH^\ddagger	146	–

are in the qualitative agreement with the results obtained without Sp. In the first step, the complex between the neutral molecule and the anion is formed. In the transition state, the N(2)–H(3) and H(3)–C(4) distances are 0.121 nm and 0.147 nm, respectively. Thus, the proton transfer is not as much advanced as it was in the TS optimized without the sparkle.

The results obtained with the AM1 method with Sp included qualitatively agree with those obtained with the MNDO method. The former method predicts the N(2)–H(3) distance 0.124 nm and H(3)–C(4) distance 0.143 nm in the transition state. The activation enthalpy of this reaction is 61 kJ mol⁻¹ at AM1 level.

The Abstraction of a Proton from Acetonitrile by AH⁻ Anion

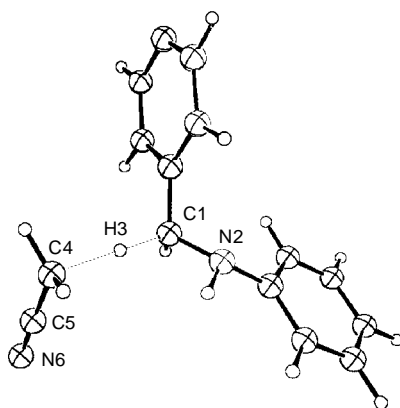
The MNDO results. Similarly as for the other proton abstractions from acetonitrile described above, ΔH_f of the system decreases as the molecules of the reactants ap-

TABLE V

The enthalpies of formation for species at the geometries corresponding to the stationary points on the reaction coordinate and activation enthalpy for the reaction (7) calculated with the sparkle particle present in the model (TS stands for transition structure)

System	ΔH_f , kJ mol ⁻¹	
	MNDO	AM1
BH...AH ⁻	-56	-65
TS	80	9
B ⁻ ...AH ₂	6	-8
Eq. (7), ΔH^\ddagger	136	74

FIG. 3
MNDO geometry of the transition structure in Eq. (7). The C(4)–H(3) bond lengths in reactants and TS are 0.111 and 0.159 nm, respectively, and the C(2)–H(3) bond lengths in TS and product are 0.124 and 0.121 nm, respectively



proach (Table IV). The minimum was found at the C(1)–H(3) distance 0.378 nm (numbering is given in Fig. 3).

The approximate geometry of the transition state was found using the reaction coordinate method, with the C(1)–H(3) distance chosen as the reaction coordinate. In the TS (Fig. 3), the C(1)–H(3) and H(3)–C(4) distances are 0.124 nm and 0.159 nm, respectively. The proton transfer is not as advanced as it was found in the systems described above. Also, the activation enthalpy of the reaction is somewhat lower ($\Delta H^\ddagger = 146 \text{ kJ mol}^{-1}$).

The AM1 results. Based on the results obtained at the AM1 level, the complex between the neutral molecule and anion (B...AH⁻) is formed at the C(1)–H(3) distance 0.301 nm. As the distance between reactants is farther decreased, the ΔH_f increases only, and there is no minimum found on the PES which corresponds to presence of the products in the system.

The results of calculations including sparkle. As in the case of the reaction (5), the influence of the sparkle on the energetical profile of the reaction was studied. The results are summarized in Table V. At the MNDO level, the activation enthalpy of the reverse reaction is significantly larger. The results are qualitatively the same as they were found in calculations without the sparkle. In this TS, the C(1)–H(3) and H(3)–C(4) distances are 0.136 nm and 0.142 nm, respectively. Thus, the former distance is larger than predicted in calculations without Sp.

At the AM1 level, the results obtained with Sp included in the system are qualitatively different from those obtained without Sp. On the other hand, these results are qualitatively the same as the results obtained at the MNDO level. There is a minimum found on the PES corresponding to the presence of the products in the system. The activation enthalpy of the reaction is 74 kJ mol^{-1} . The C(1)–H(3) and H(3)–C(4) distances are 0.131 and 0.151 nm, respectively.

The Reaction of Azomethine with Acetonitrile Anion

The MNDO results. The acetonitrile anion, the formation of which was described in the previous paragraphs, farther reacts as a nucleophile with azomethine. The enthalpy of the formation of the stationary points on the reaction path of reaction (4) is summarized in Table VI. Even in this process, the complex between the neutral molecule and anion (B⁻...A) is formed first, with the C(1)–C(4) distance being 0.391 nm (numbering is defined in Fig. 4).

The approximate geometry of the TS was found using the reaction coordinate method, with the C(1)–C(4) distance chosen as a reaction coordinate. This distance is relatively large in the TS (0.258 nm). Consequently, the C(1)–N(2) distance (0.132 nm) only slightly differs from that in AB⁻ molecule. The activation enthalpy for this process is very small ($\Delta H^\ddagger = 12 \text{ kJ mol}^{-1}$).

The AM1 results. At the AM1 level, this reaction does not require any activation enthalpy, therefore, the reaction enthalpy is decreasing along the reaction path. From the results obtained with the AM1 and MNDO methods, it can be concluded that this reaction step proceeds without significant energetical requirements.

CONCLUSIONS

In this paper, the reaction steps leading to the formation of the main product of the studied reaction, β -acetonitrile, have been described, in particular, the formation and regeneration of acetonitrile anion. Three different mechanisms of a proton abstraction from acetonitrile have been studied. The results of calculations on the isolated molecules have shown that in the given reaction step, the equilibrium is either shifted towards the reactants (MNDO results) or the reaction should not proceed at all (AM1 results). The results obtained at the MNDO level have shown that the abstraction of a proton from acetonitrile by azomethine radical anion requires a higher activation enthalpy than the abstraction of a proton by β -aminonitrile anion. This is probably due to

TABLE VI

The enthalpies of formation for species at the geometries corresponding to the stationary points on the reaction coordinate and activation enthalpy for the reaction (4) (TS stands for transition structure)

System	ΔH_f , kJ mol ⁻¹	
	MNDO	AM1
B ⁻ + A	461	485
B ⁻ ...A	444	—
TS	455	—
AB ⁻	279	304
Eq. (4), ΔH^\ddagger	11	—

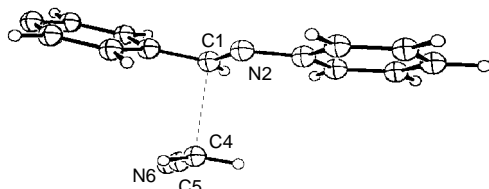


FIG. 4

MNDO geometry of the transition structure in Eq. (4). The C(1)–N(2) bond lengths in reactants, TS, and product are 0.129, 0.132, and 144 nm, respectively, and the C(1)–C(4) bond lengths in TS and product are 0.258 and 0.157 nm, respectively

the lower electron density on N(2) atom in azomethine radical anion than in β -aminonitrile anion resulting from the presence of an unpaired electron in the former anion. The abstraction of a proton by AH^- species where the reaction center (carbon atom) has the formal negative charge requires the lowest activation enthalpy.

The calculations with the sparkle suggest that the environment can influence individual reaction steps, mainly it can stabilize the acetonitrile anion. The AM1 and MNDO results with Sp included are comparable. The AM1 method predicts the energetical barriers of the studied reaction lower than the MNDO method. Comparison of the activation enthalpies of the abstraction of a proton from acetonitrile by AB^- and AH^- anions can be misleading since the position of Sp was optimized. Therefore, the presence of the sparkle influenced not only the stability of acetonitrile anion but also the stability of AB^- , and possibly AH^- anions.

The other reaction step studied in this paper (the reaction of azomethine with acetonitrile anion) requires very low or no activation enthalpy at the AM1 and MNDO levels, respectively. Thus, we can expect that the equilibrium will be significantly shifted towards the products. We conclude that the rate limiting step in the formation of β -aminonitrile is the abstraction of a proton from acetonitrile. The product of this reaction (acetonitrile anion) is very reactive species and, thus, the reaction of this product with azomethine will proceed without significant energetical barrier.

The results of this study help us to understand very low current consumption during the electrochemical cyanomethylation of azomethines: only the initiation of the reaction process takes place on the electrode; during the reaction, the active agent (acetonitrile anion) is regenerated.

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