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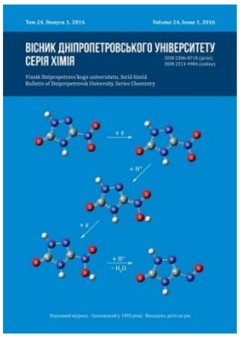

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TWO-ELECTRON REDUCTION OF NITROAROMATIC COMPOUNDS BY FLAVIN MONONUCLEOTIDE. DFT COMPUTATIONAL STUDY

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Abstract

The mechanism for reduction of nitroaromatic compounds by flavin mononucleotide (FMN) was examined at MPWB1K/tzvp level. The solvent effects were calculated using a PCM(Pauling) and SMD(Pauling) solvation models for ions and neutral molecules, respectively. Calculated thermodynamics of the reduction of nitro group to nitroso group suggests consequtive four-steps' process (electron–proton–electron–proton transfer) where the first proton comes from solution, while the second one – from FMN. Water molecule releases during fourth step of the process. Electron attachment to nitrocompound and electron lose by reduced FMN facilitate the breaking of N–O bond and proton release, respectively. Calculations show that reduction of nitro group to nitroso group in studied nitrocompounds is a thermodynamically feasible with 56–59 kcal/mol Gibbs free energy release. The most easy electron transfer proceeds for TNT (2,4,6-trinitrotoluene) and NTO (5-nitro-2,4-dihydro-3H-1,2,4-triazol-3-one). While the most energy release occurs during proton transfer in case of ANTA (5-amino-3-nitro-1H-1,2,4-triazole).

Keywords: nitroaromatics; reduction; flavin mononucleotide; DFT.

ДВОХЕЛЕКТРОННЕ ВІДНОВЛЕННЯ НІТРОАРОМАТИЧНИХ СПОЛУК ФЛАВІНМОНОНУКЛЕОТИДОМ. ТФГ РОЗРАХУНКОВЕ ДОСЛІДЖЕННЯ

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Анотація

Розглянуто механізм відновлення нітроароматичних сполук флавінмононуклеотидом (ФМН) методом MPWB1K/tzvp. Вплив розчинника враховано шляхом застосування сольватних моделей PCM(Pauling) і SMD(Pauling) відповідно для іонів і нейтральних молекул. Розрахована термодинаміка відновлення нітрогрупи в нітрозогрупу передбачає послідовний чотирьохстадійний процес (перенесення електрона–протона–електрона–протона), в якому перший протон надходить з розчину, в той час як другий – від ФМН. Молекула води виділяється під час четвертої стадії процесу. Приєднання електрона до нітросполук і віддача електрона відновленою формою ФМН відповідно полегшує розрив N–O зв'язку і відщеплення протона. Згідно розрахунку, відновлення нітрогрупи до нітрозогрупи у досліджуваних нітросполуках – це термодинамічно вигідний процес з виділенням 56–59 ккал/моль вільної енергії Гіббса. Найбільш легко перенесення електронів відбувається для TNT (2,4,6-тринітротолуєн) і NTO (5-нітро-2,4-дигідро-3H-1,2,4-триазол-3-он). У той час як найбільше вивільнення енергії відбувається під час перенесення протона у випадку ANTA (5-аміно-3-нітро-1H-1,2,4-триазол).

Ключові слова: нітроароматичні сполуки; відновлення; флавінмононуклеотид; ТФГ.

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ДВУХЭЛЕКТРОННОЕ ВОССТАНОВЛЕНИЕ НИТРОАРОМАТИЧЕСКИХ СОЕДИНЕНИЙ ФЛАВИНМОНОНУКЛЕОТИДОМ. ТФП РАСЧЕТНОЕ ИССЛЕДОВАНИЕ

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Аннотация

Рассмотрен механизм восстановления нитроароматических соединений флавинмононуклеотидом (ФМН) методом MPWB1K/tzvp. Влияние растворителя учтено путем применения сольватных моделей PCM (Pauling) и SMD (Pauling) соответственно для ионов и нейтральных молекул. Рассчитанная термодинамика восстановления нитрогруппы в нитрозогруппу предполагает последовательный четырехстадийный процесс (перенос электрона–протона–электрона–протона), в котором первый протон приходит из раствора, в то время как второй – от ФМН. Молекула воды выделяется во время четвертой стадии процесса. Присоединение электрона к нитросоединению и отдача электрона восстановленной формой ФМН облегчает соответственно разрыв N–O связи и отщепление протона. Согласно расчета, восстановление нитрогруппы до нитрозогруппы в исследуемых нитросоединений – это термодинамически выгодный процесс с выделением 56–59 ккал/моль свободной энергии Гиббса. Наиболее легко перенос электронов происходит для TNT (2,4,6-тринитротолуол) и NTO (5-нитро-2,4-дигидро-3H-1,2,4-триазол-3-он). В то время как наибольшее высвобождение энергии происходит во время переноса протона в случае ANTA (5-амино-3-нитро-1H-1,2,4-триазол).

Ключевые слова: нитроароматические соединения; восстановление; флавинмононуклеотид; ТФП.

Introduction

Nitroaromatic compounds, encountered in drugs, dyes, and explosives, represent a group of hazardous contaminants which could be dispersed in the environment during production, processing, destruction, and recycling. One of the ways to clean out the environment from these contaminants is enzymatic reduction by oxygen-insensitive nitroreductase. This enzyme contains flavin mononucleotide (**FMN**) cofactor, and uses a nicotinamide adenine dinucleotide phosphate (**NADPH**) as initial electron–proton donor [1–3]. First, **NADPH** binds to the enzyme and donates two electrons and one proton to the **FMN** cofactor, which transforms to the $FMNH^-$ form. $NADP^+$ is then released, allowing the opportunity for the substrate to bind to the active site of the reduced enzyme and thereby be reduced itself [3]. The reduction of one nitro group to the amino group requires six electrons and six protons and occurs through highly reactive nitroso and hydroxylamino intermediates. The reduction of nitro group to nitroso group proceeds via the two hydride transfers, which involve the addition of two protons and two electrons, and release of one water molecule. Traditionally, hydride transfer is considered to be the concerted transfer of one proton and two electrons from the same source; in this case, the $FMNH^-$. The addition of the proton from solution may occur either before or after this hydride transfer.

There are two points on the mechanism of nitrocompound reduction. The first one assumes sequential electron and proton transfer [4]. The second one suggests a two electrons and then two protons transfer [5]. In this study, we modeled the two-electron reduction of the nitro group to the nitroso group for such nitrocompounds as 2,4-dinitroanisole (**DNAN**), 2,4-dinitrotoluene (**DNT**), trinitrotoluene (**TNT**), 5-nitro-2,4-dihydro-3H-1,2,4-triazol-3-one (**NTO**), 5-amino-3-nitro-1H-1,2,4-triazole (**ANTA**). This will help to clarify the pathway for the reduction of these powerful energetic compounds by nitroreductase of **FMN** family.

Computational Methodology

All of the calculations were performed using the Gaussian 09 program package [6]. The geometry of neutral, radical, and ionic species were optimized using the Density Functional Theory at the MPWB1K/tzvp level [7; 8]. The present functional and basis set were chosen because of the results of the recent study where such level of theory was able to provide accuracy close to that obtained by experimental measurements [9]. Harmonic vibrational frequencies were calculated for all structures obtained, to establish that a minimum was observed. The solvent effects were assessed by calculations using a PCM(Pauling) and SMD(Pauling) solvation models for ions and neutral molecules calculations, respectively [10; 11]. In all cases, the ribityl tail of the FMN was replaced with a methyl group in order to decrease computation time.

Results and Discussion

To provide insight into the mechanism of nitrocompound reduction by **FMN** we investigated two cases of initial step for the process. The first one is an electron transfer from $FMNH^-$ to nitrocompound, the second one is a proton attaching to nitrocompound. In case of **NTO** the calculation shows that the electron transfer is 16 kcal/mol more favorable than the proton attaching (from reduced **FMN** or solution) to **NTO**. Therefore, further modeling of the reduction process used electron transfer as an initial step for reduction.

Next, we examined the sequences of electrons and protons transfer using **NTO** as an example of nitrocompound. Three models (**A**, **B**, **C**) were investigated. In models **A** and **B** reduction occurs by consecutive attaching to **NTO** the first electron, the first proton, the second electron, and the second proton. In model **A** the first proton transfer occurs from **FMN**, the second one – from aqueous solution. In model **B** the first proton transfer occurs from aqueous solution, the second one – from **FMN**. In model **C** occurs through an initial transfer two electrons and then two protons. Solvated proton (hydronium H_3O^+) was used to approximate calculated results to experimental conditions. It should be noted, that the loss of a water molecule from nitrocompound occurs simultaneously with second proton transfer (step 4). Obtained results show that the most favourable pathway is **B**, indicating that the proton from **FMN** is transferred after **NTO** obtains a proton from solution (Table 1). This model was further applied for reduction of **DNAN**, **DNT**, **TNT**, and **ANTA** (Table 2).

Table 1

Gibbs free energy of reaction steps for reduction of NTO by reduced FMN

Step	Model A	Transfer to NTO	ΔG, kcal/mol
1A	$NTO + FMNH^- \rightarrow NTO^{-\cdot} + FMNH^{\cdot}$	e^-	–8.80
2A	$NTO^{-\cdot} + FMNH^{\cdot} \rightarrow NTO\text{-}H^{\cdot} + FMN^{-\cdot}$	H^+	15.54
3A	$NTO\text{-}H^{\cdot} + FMN^{-\cdot} \rightarrow NTO\text{-}H^- + FMN$	e^-	–8.63
4A	$NTO\text{-}H^- + H_3O^+ \rightarrow NO\text{-}TO + 2H_2O$	H^+	–57.65
	Model B		
1B	$NTO + FMNH^- \rightarrow NTO^{-\cdot} + FMNH^{\cdot}$	e^-	–8.80
2B	$NTO^{-\cdot} + H_3O^+ \rightarrow NTO\text{-}H^{\cdot} + H_2O$	H^+	–16.55
3B	$NTO\text{-}H^{\cdot} + FMNH^{\cdot} \rightarrow NTO\text{-}H^- + FMNH^+$	e^-	4.92
4B	$NTO\text{-}H^- + FMNH^+ \rightarrow NO\text{-}TO + H_2O + FMN$	H^+	–39.09
	Model C		
1C	$NTO + FMNH^- \rightarrow NTO^{-\cdot} + FMNH^{\cdot}$	e^-	–8.80
2C	$NTO^{-\cdot} + FMNH^{\cdot} \rightarrow NTO^{2-} + FMNH^+$	e^-	40.56
3C	$NTO^{2-} + FMNH^+ \rightarrow NTO\text{-}H^- + FMN$	H^+	–33.64
4C	$NTO\text{-}H^- + H_3O^+ \rightarrow NO\text{-}TO + 2H_2O$	H^+	–57.65
1–4 (all models)	$NTO + FMNH^- + H_3O^+ \rightarrow NO\text{-}TO + 2H_2O + FMN$		–59.53

Table 2

Gibbs free energy of reaction steps for reduction of ANTA, DNAN, DNT, and TNT by reduced FMN

Step	Model B	Transfer to nitrocompound	ΔG, kcal/mol
1B	$ANTA + FMNH^- \rightarrow ANTA^{-\cdot} + FMNH^{\cdot}$	e^-	2.05
2B	$ANTA^{-\cdot} + H_3O^+ \rightarrow ANTA\text{–}H^{\cdot} + H_2O$	H^+	–24.42
3B	$ANTA\text{–}H^{\cdot} + FMNH^{\cdot} \rightarrow ANTA\text{–}H^- + FMNH^+$	e^-	14.79
4B	$ANTA\text{–}H^- + FMNH^+ \rightarrow NO\text{–}ATA + H_2O + FMN$	H^+	–51.40
1B–4B	$ANTA + FMNH^- + H_3O^+ \rightarrow NO\text{–}ATA + 2H_2O + FMN$		–58.98
1B	$DNAN + FMNH^- \rightarrow DNAN^{-\cdot} + FMNH^{\cdot}$	e^-	–2.74
2B	$DNAN^{-\cdot} + H_3O^+ \rightarrow DNAN\text{–}H^{\cdot} + H_2O$	H^+	–18.14
3B	$DNAN\text{–}H^{\cdot} + FMNH^{\cdot} \rightarrow DNAN\text{–}H^- + FMNH^+$	e^-	7.37
4B	$DNAN\text{–}H^- + FMNH^+ \rightarrow 2\text{-}NO\text{-}4\text{-}NO_2\text{-}AN + H_2O + FMN$	H^+	–45.62
1B–4B	$DNAN + FMNH^- + H_3O^+ \rightarrow 2\text{-}NO\text{-}4\text{-}NO_2\text{–}AN + 2H_2O + FMN$		–59.13
1B	$DNT + FMNH^- \rightarrow DNT^{-\cdot} + FMNH^{\cdot}$	e^-	–3.28
2B	$DNT^{-\cdot} + H_3O^+ \rightarrow DNT\text{–}H^{\cdot} + H_2O$	H^+	–18.30
3B	$DNT\text{–}H^{\cdot} + FMNH^{\cdot} \rightarrow DNT\text{–}H^- + FMNH^+$	e^-	10.07
4B	$DNT\text{–}H^- + FMNH^+ \rightarrow 4\text{-}NO\text{-}2\text{-}NT + H_2O + FMN$	H^+	–45.22
1B–4B	$DNT + FMNH^- + H_3O^+ \rightarrow 4\text{-}NO\text{-}2\text{-}NT + 2H_2O + FMN$		–56.74
1B	$TNT + FMNH^- \rightarrow TNT^{-\cdot} + FMNH^{\cdot}$	e^-	–10.16
2B	$TNT^{-\cdot} + H_3O^+ \rightarrow TNT\text{–}H^{\cdot} + H_2O$	H^+	–13.28
3B	$TNT\text{–}H^{\cdot} + FMNH^{\cdot} \rightarrow TNT\text{–}H^- + FMNH^+$	e^-	3.63
4B	$TNT\text{–}H^- + FMNH^+ \rightarrow 4\text{-}NO\text{-}2,6\text{-}DNT + H_2O + FMN$	H^+	–38.19
1B–4B	$TNT + FMNH^- + H_3O^+ \rightarrow 4\text{-}NO\text{-}2,6\text{-}DNT + 2H_2O + FMN$		–58.00

Calculations show that reduction of nitro group to nitroso group in **NTO**, **DNAN**, **DNT**, **TNT**, and **ANTA** is a thermodynamically feasible with 56–59 kcal/mol free energy release (Tables 1, 2). The only endothermic step is the second electron transfer. The most exothermic step is the second proton attaching with elimination of water molecule. Structure of the nitrocompounds affects on ability to attach an electron or proton. The most easy electron transfer proceeds for **TNT**, while the most hard an attaching of electron occurs for **ANTA**. While the energy release, as a results of proton attachment, is the most in case of **ANTA** among studied compounds.

Optimized structures of the reactive species on the $2e^-/2H^+$ reduction pathway of nitrocompounds and $2e^-/1H^+$ oxidation pathway of $FMNH^-$ are displayed in Figs. 1, 2, S1-S4. As can be seen from Fig. 1 electron transfer reflects on lengthening of N–O bonds by 0.08–0.11 Å that implies the activation for the N–O bond breaking in **NTO**. While electron lose causes shortening of N-C bond in **FMN** from 1.41 Å through 1.34 Å to 1.29 Å, that facilitates the proton release.

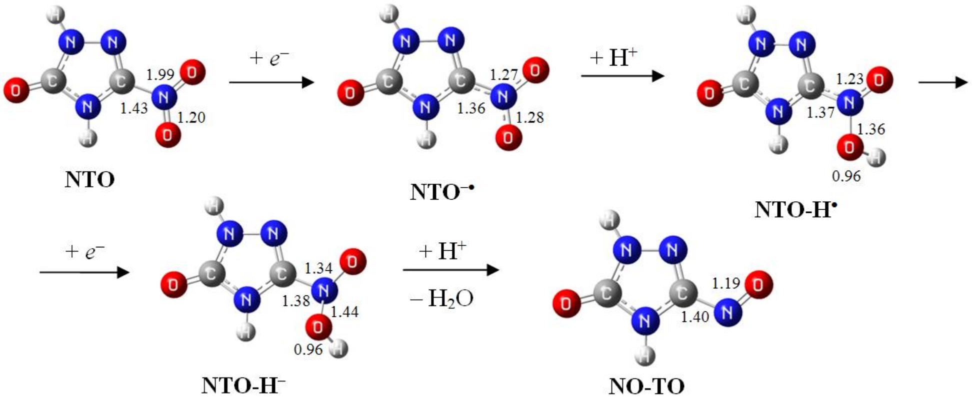

Fig. 1. Optimized structures of the reactive species on the $2e^-/2H^+$ reduction pathway of NTO

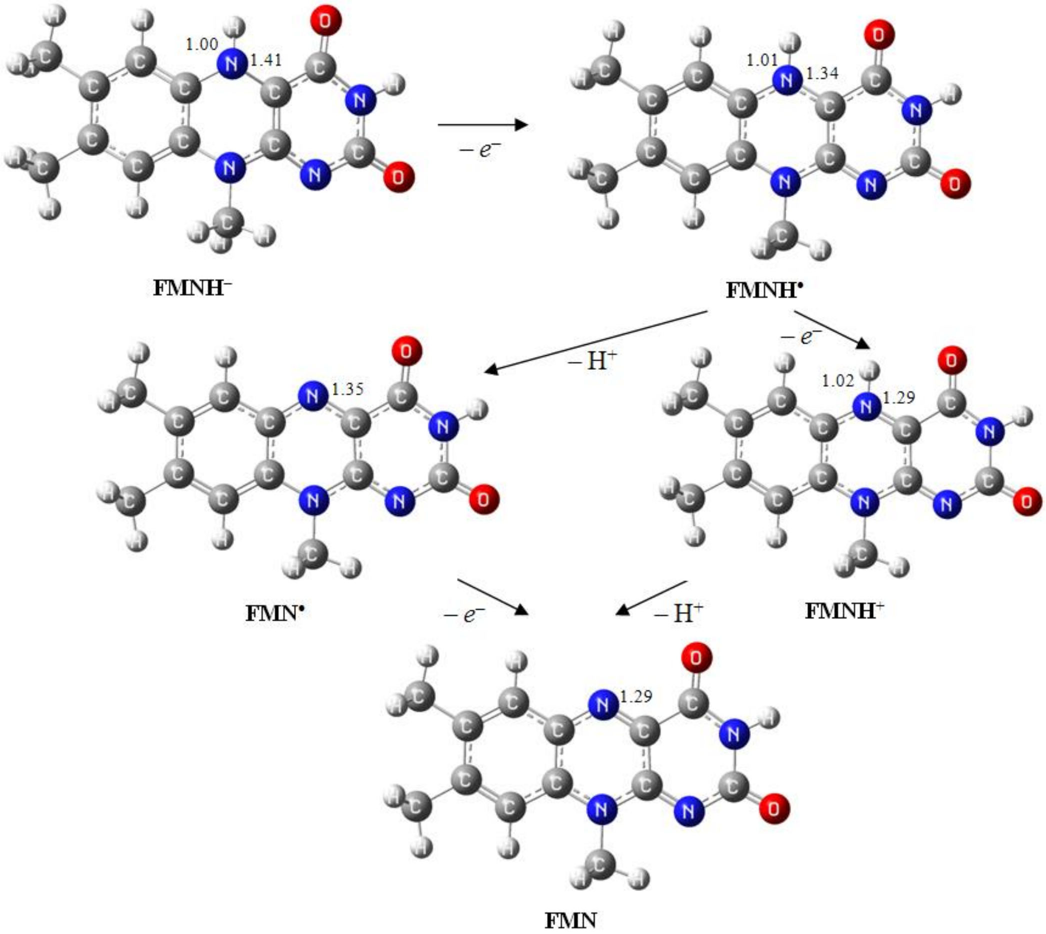

Fig. 2. Optimized structures of the reactive species on the $2e^-/1H^+$ oxidation pathway of $FMNH^-$

Conclusions

Reduction mechanism of nitro group to nitroso group for **NTO**, **DNAN**, **DNT**, **TNT**, and **ANTA** by **FMN** was studied at MPWB1K/tzvp level. Calculations show that mechanism consists of consecutive electron and proton transfers. The order of proton transfer is critical: the first proton transfer occurs from aqueous solution, the second one – from FMN. Overall process for studied compounds is accompanied of 56–59 kcal/mol free energy release. Electron attaching reflects in increasing of N–O bond length in nitrocompounds that is facilitates its breaking. While electron losing causes decrease of C–N bond length in FMN that is promotes proton elimination.

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