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Short communication

Generation and combined study on the chemical structure of nitrofurantoin radical anion

Angelina Popova, Simeon Stoyanov, DenitsaYancheva*

Institute of Organic Chemistry with Centre of Phytochemistry, Bulgarian Academy of Sciences, Acad. G. Bonchev Str., build. 9, 1113 Sofia, Bulgaria

Introduction

Nitrofurantoin (N-(5-nitro-2-furfurylidene)-1-aminohydantoin) is antimicrobial compound, used extensively as a prophylactic for urinary tract infections in humans and animals (Maaland and Guardabassi, 2011). It is reported that the modes of action underlying DNA damage or cytotoxicity induced by nitrofurantoin in rodent liver and lungs may involve ROS generation by reduction to nitro radical anion (Suntres and Shek, 1992). A recent study showed that the drug exhibits carcinogenicity in the kidneys of male rats and the structure of the nitro furan plays a key role in the induced genotoxicity (Kijima et al., 2015).

Most nitroaromatic drugs, containing nitroquinone, nitroimidazole or nitrofuran moiety, are considered to exert their toxic effect by nitro reduction (Boelsterli et al., 2006). One-electron reduction of the nitro group catalyzed by nitro-reductase gives rise to nitro anion radical, the chemical instability of which promotes production of various ROS such as superoxide anion and hydroxyl radical via its electron-donating ability (Wang et al., 2008).

Despite these drawbacks, new nitrofuran derivatives are still being developed as antimicrobial agents (Zorzi et al., 2014). Therefore, improved knowledge on the structure and reactivity of nitrofurantoin radical anion could help reduce the toxicity of the new nitrofuran antimicrobial agents.

This reports motivated us to generate electrochemically the nitro radical anion of nitrofurantoin and study its chemical structure by spectroscopic IR methods and DFT computations. The radical anion was electrochemically generated and the spectral and structural changes arising from the conversion were described based on IR spectra and DFT calculations. The structural variations, electron charge distribution over molecular fragments and IR frequency shifting were discussed.

Materials and methods

The electrochemical generation of the radical anion of nitrofurantoin was carried out in a special CaF_2 cell, provided with platinum electrodes build in the polyethylene spacer. 4.5 V were applied to the cathode in the solution cell containing 0.1 mol/l nitrofurantoin and equimolar amount of tetraethylammonium bromide in DMSO-d6. Electrochemical generation of the radical anion was continued for a period of 75 min and then the polarity of the electrolysis cell was reversed in order to regenerate the parent compound. The process of nitrofurantoin reduction and regeneration was monitored by recording IR spectra in 10 min intervals. The IR spectra were measured on a Brucker Tensor 27 FT spectrometer at a resolution of 2 cm^{-1} and 64 scans.

All theoretical calculations were performed using the Gaussian 09 package of programs. Geometry and vibrational frequencies of species studied were performed by analytical gradient technique without any symmetry constraint. All the results were obtained using the density functional theory (DFT), employing the B3LYP (Becke's three-parameter non-local exchange correlation) method in conjunction with 6-311+G(2df,p) basis set. In order to account for the ifluence of the medium, we used the Integral Equation Formalism Polarizable Continuum Model (IEF-PCM) on the same level of theory with inclusion of DMSO.

Results and discussion

The initial IR spectrum of nitrofurantion in DMSO-d6 solution, containing tetraethylammonium bromide as

* deni@orgchm.bas.bg

electrolyte salt, showed that the asymmetric and symmetric stretching vibrations of the nitro group are observed at 1521 and 1350 cm^{-1}. The stretching vibration of the N-C bond linking the nitro group to the furan ring is found at rather high wavenumber - 1211 cm^{-1}, respectively. A few minutes after applying the current, the solution in cathode space became brown, and the bands of the anion radical of nitrofurantoin appeared in the IR spectrum. More prolonged electrolysis (75 min) caused strong increase of the bands of the anion radical, while the bands of the neutral compound vanished. Reversal in the polarity of the electrolysis cell resulted in gradual decrease of the IR bands of the radical anion and reappearance of the neutral molecule absorptions. After 75 min of reversed electrolysis the initial spectrum of the parent compound was completely restored without the presence of any additional IR bands. This fact unambiguously demonstrates that the observed spectral changes are due to the reduction of nitrofurantoin to radical anion and not to other chemical transformations.

The conversion of nitrofurantoin into radical anion is related to strong frequency decreases in the assymetric N-O stretching: $\Delta vas(NO_2)$ = 220 cm^{-1}, strong frequency decreases in the symetric N-O stretching: $\Delta vs(NO_2)$ = 209 cm^{-1} and strong frequency increase in C-NO_2 stretching: Δv(C-NO2) = 273 cm^{-1}. Based on the calculated spin density, the odd electron is localized mainly on the nitro group (c.a. 70%) and in smaller extends – on the furan ring (c.a. 30%). The radical anion formation leads to simultaneous shortening of the C-N bond and lengthening of the N-O bonds.

Conclusion

The observed frequency shifts arising from the conversion of nitrofurantoin into radical anion are larger than those found with the conversion of dinitrobenzenes and cyanobenzonitriles. It is evidence that larger structural variations in the nitrofuran moiety occur upon conversion into radical anion than in case of dinitrobenzenes and nitrobenzonitriles. The localization of the spin density over the nitro group is a sign for high reactivity of the formed nitrofurantoin radical anion and strong ability to initiate production of various ROS via electron donation. The importance of aminohydantoin moiety for the stability and reactivity of the nitrofurantoin radical anion has to be elucidated by studying other nitrofuran derivatives with modified side chains.

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