



Electronic properties of environmental pollutants and their mutagenic activity: Nitro derivatives of azaphenanthrenes



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HIGHLIGHTS

- We computed molecular properties of nitroazaphenanthrenes.
- DFT methods are employed.
- Several descriptors for distinguishing the investigated isomers are identified.
- Good linear relationship between mutagenic activities and ΣA_{Raman} was established.

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ABSTRACT

The physico-chemical properties of nitroazaphenanthrene isomers: 4-nitro-9-azaphenanthrene (4-N-9-Aph), 5-nitro-9-azaphenanthrene (5-N-9-Aph), 6-nitro-4-azaphenanthrene (6-N-4-Aph), 8-nitro-1-azaphenanthrene (8-N-1-Aph), and 8-nitro-4-azaphenanthrene (8-N-4-Aph) have been investigated theoretically using Density Functional Theory (DFT) calculations. Equilibrium geometries, relative stability, ionization potentials, electron affinities, molecular electrostatic potentials, dipole moments, electric polarizabilities, and vibrational properties of these isomers are presented. Averaged O–N–C dihedral angle, dipole moment, polarizability, the summation of IR intensities (ΣI_{IR}) and the summation of Raman activities (ΣA_{Raman}) over all 3N-6 vibrational degrees of freedom are sensitive to the structure of isomers. A very good linear relationship between ΣA_{Raman} values ($R = 1.00$) and the *Salmonella typhimurium* strain TA98(–S9) mutagenic activity of the investigated nitroazaphenanthrene isomers (Tokiwa et al., 2003) reveals a very important role of inductive and dispersive forces on the mutagenic pathways of the investigated isomers.

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1. Introduction

Aristolochic acids used earlier for anti-inflammatory agents in pharmaceutical preparations are derivatives of nitrophenanthrene carboxylic acid. It was found that they induced tumors (Schmeiser et al., 1987, 1990; Arlt et al., 2002). Nitrophenanthrenes were detected in the particles emitted from diesel engines. They are formed in the combustion process and the reactions in the atmosphere between phenanthrene and nitrogen oxides and many of them exhibit strong mutagenic properties (Sera et al., 1995). Nitroazaphenanthrenes as well as their N-oxide derivatives show pronounced mutagenic activities (Tokiwa et al., 2003; Sera et al., 2004).

The mutagenic activities of nitro derivatives of arenes may depend on structural factors of molecule like dimensions of the

molecule, the position of the nitro group, the angle between the nitro group and the aromatic system as well as the stabilization of the reactive nitrenium ion (Vance and Levin, 1984). The reduction of the nitro group is an important metabolic pathway for the mutagenic activation of nitro-polycyclic aromatic hydrocarbons (nitro-PAHs) (Debnath et al., 1991). This step is controlled by formation of the enzyme-substrate complex between the enzyme nitroreductase and the molecule nitro-PAH (Debnath et al., 1991). It was assumed that if the nitro group is in the same plane as the rings of the aromatic system, the molecule may penetrate easier into the enzyme cavity compared to the isomer with a non-planar orientation of the nitro group (Fu et al., 1985). The aromaticity of aza-analogues of phenanthrene was investigated both experimentally and theoretically (Stępień et al., 2004). It was concluded that the replacement of one or two C–H units by nitrogen in phenanthrene, changed the π -electron delocalization moderately. The aza-analogues usually exhibit more effective π -electron delocalization compared to phenanthrene. However, for

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nitroazaphenanthrenes, *ab initio* or DFT theoretical studies of molecular properties have not been published so far.

In this paper we provide an analysis of the geometrical parameters, relative energies, ionization potentials, electron affinities, dipole moments, molecular electrostatic potentials, polarizabilities, and vibrational properties of 4-nitro-9-azaphenanthrene (4-N-9-Aph), 5-nitro-9-azaphenanthrene (5-N-9-Aph), 6-nitro-4-azaphenanthrene (6-N-4-Aph), 8-nitro-1-azaphenanthrene (8-N-1-Aph), and 8-nitro-4-azaphenanthrene (8-N-4-Aph) employing the Density Functional Theory (DFT) method with different basis sets. The mutagenic activity/physico-chemical property relationships are discussed.

2. Computational methods

The equilibrium geometries of 4-N-9-Aph, 5-N-9-Aph, 6-N-4-Aph, 8-N-1-Aph and 8-N-4-Aph were fully optimized using the B3LYP (Becke3–Lee–Yang–Parr) DFT method (Becke, 1993; Lee et al., 1988) with the cc-pVTZ and 6-311 + G(2df,p) basis sets which consist of 622 and 626 contracted basis functions, respectively, on the carbon, hydrogen, nitrogen and oxygen atoms. We performed the optimizations in the framework of the C_1 point group. The frequency B3LYP/cc-pVTZ and B3LYP/6-311 + G(2df,p) calculation showed no imaginary values, implying that the structures are minima on the potential energy surface of the ground electronic state. For the determination of the relative energies of the isomers the zero-point vibrational energies (ZPVE) were scaled using the scaling factor of 0.9889 determined for the B3LYP method and the 6-311 + G(2df,p) basis set (Merrick et al., 2007).

The first ionization potentials (*IP*), electron affinities (*EA*), chemical hardness (η) (Parr and Pearson, 1983), electronegativity (χ) (Parr et al., 1978), and electrophilicity index (κ) (Parr et al., 1999) were calculated according to the formulas:

$$IP = E_{\text{cation}} - E_{\text{neutral}} \quad (1)$$

$$EA = E_{\text{neutral}} - E_{\text{anion}} \quad (2)$$

$$\eta = (IP - EA)/2 \quad (3)$$

$$\chi = (IP + EA)/2 \quad (4)$$

$$\kappa = \chi^2/2\eta \quad (5)$$

where E_{cation} , E_{anion} , and E_{neutral} are the energy of the cation, anion, and neutral, respectively, calculated using the optimized geometry of the neutral ground state at the B3LYP/6-311 + G(2df,p) level of theory. The energies of the ground electronic states of the cation and anion were calculated using the unrestricted B3LYP method (UB3LYP) while neutral ground state energies were calculated employing the B3LYP level of theory. In the calculations the spin contamination in the UB3LYP procedure was acceptably low. The calculated $\langle \hat{S}^2 \rangle$ values do not differ much from the exact $S(S+1)$ value: the spin contamination values were under 0.77 before and under 0.7502 after annihilation in the worst cases. The dipole moment values were calculated at the B3LYP/cc-pVTZ level of theory.

In order to reach better description of the polarizability and Raman activity which rely on the electronic polarizability derivative components, we employed the data from the geometry optimizations of 4-N-9-Aph, 5-N-9-Aph, 6-N-4-Aph, 8-N-1-Aph and 8-N-4-Aph using the 6-311 + G(2df,p) basis set with diffuse and polarization functions. From the calculated components of the zero-frequency (static) dipole polarizability tensor along the principal axes, α_{xx} , α_{yy} , α_{zz} , the following quantities (Long, 1982) are obtained:

the electronic contribution to the average polarizability, $\langle \alpha \rangle$:

$$\langle \alpha \rangle = (\alpha_{xx} + \alpha_{yy} + \alpha_{zz})/3 \quad (6)$$

and the electronic contribution to the polarizability anisotropy, $\Delta\alpha$:

$$\Delta\alpha = \left\{ \left[(\alpha_{xx} - \alpha_{yy})^2 + (\alpha_{xx} - \alpha_{zz})^2 + (\alpha_{yy} - \alpha_{zz})^2 + 6(\alpha_{xy}^2 + \alpha_{xz}^2 + \alpha_{yz}^2) \right] / 2 \right\}^{1/2} \quad (7)$$

To predict the reactive sites for electrophilic and nucleophilic attack for the investigated isomers, the electrostatic potential (ESP) calculations were carried out at the B3LYP/6-31G* and B3PW91/6-31G** levels of theory. The maps of molecular electrostatic potential were generated using the program Multiwfn (Lu and Chen, 2012). For generating the isosurfaces of ESP the program Molekel was employed (Varetto, 2009). All calculations have been performed with the Gaussian program package (Frisch et al., 2004).

3. Results

3.1. Geometries and relative energies

The geometries of 4-N-9-Aph, 5-N-9-Aph, 6-N-4-Aph, 8-N-1-Aph, and 8-N-4-Aph fully optimized at the B3LYP/6-311 + G(2df,p) level of theory are presented in Fig. 1. The phenanthrene aromatic rings in 6-N-4-Aph are in planar arrangement while in 4-N-9-Aph, 5-N-9-Aph, 8-N-1-Aph, and 8-N-4-Aph show some distortion of planarity with the biggest deviation of the C–C–C dihedral angles varying from 3° (in 8-N-4-Aph) to 8° (in 5-N-9-Aph). The isomers are characterized with different orientations of the nitro group with respect to the plane of the rings. The averaged O–N–C–C dihedral angles are calculated to be 64° for 4-N-9-Aph, 60° for 5-N-9-Aph, 0° for 6-N-4-Aph, 37° for 8-N-1-Aph, and 34° for 8-N-4-Aph. The distance between the oxygen atom of the nitro group and the closest hydrogen atom are 2.205 Å for 8-N-4-Aph, 2.221 Å for 8-N-1-Aph, 2.389 Å for 6-N-4-Aph, 2.435 Å for 5-N-9-Aph, and 2.443 Å for 4-N-9-Aph. The steric hindrance effects are especially pronounced in 8-N-4-Aph and 8-N-1-Aph isomers. The C–N bond lengths of the nitro group are 1.478 Å for 4-N-9-Aph and 5-N-9-Aph, 1.474 Å for 6-N-4-Aph, 1.476 Å for 8-N-1-Aph, and 1.475 Å for 8-N-4-Aph. The two N–O bond lengths from the nitro group are 1.221 Å and 1.219 Å for 4-N-9-Aph, 1.222 Å and 1.220 Å for 5-N-9-Aph, 1.224 Å and 1.222 Å for 6-N-4-Aph, 1.223 Å and 1.222 Å for 8-N-1-Aph, and 1.224 Å and 1.223 Å for 8-N-4-Aph.

The relative energy of these isomers calculated at the B3LYP/6-311 + G(2df,p) level show that these isomers differ in their stability (Table 1). The order of stability is 6-N-4-Aph < 8-N-4-Aph < 8-N-1-Aph < 5-N-9-Aph < 4-N-9-Aph. The relative energies were refined with zero-point vibrational energies based on harmonic vibrational frequencies calculated at the B3LYP/6-311 + G(2df,p) level of theory. The values for zero-point vibrational energies (ZPVE) energies were scaled by a factor of 0.9889 (Merrick et al., 2007) to compensate for the well known systematic overestimation of the normal frequencies, (ZPVEsc). The relative energies based on the most stable isomer calculated from the scaled ZPVE corrected energies are denoted by ΔE_{ZPVEsc} . After introduction of the ZPVEsc correction, the order of stability at the B3LYP/6-311 + G(2df,p) level is the same: 6-N-4-Aph < 8-N-4-Aph < 8-N-1-Aph < 5-N-9-Aph < 4-N-9-Aph. The introduction of the ZPVEsc correction decreases the stability of the investigated isomers by 0.05–0.10 kcal/mol. Of all investigated isomers the 6-N-4-Aph isomer is the most stable while 4-N-9-Aph is the least stable isomer by 11.56 kcal/mol. The relative energy of 5-N-9-Aph is 10.69 kcal/mol and both 4-N-9-Aph and 5-N-9-Aph are characterized by the nitro group in the phenanthrene bay-region.

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