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The role of molecular properties of mononitrofluoranthenes to their mutagenic activity: Insight from *ab initio* and DFT calculations

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Abstract: The molecular properties of the environmental mutagens nitrofluoranthenes (NFs; 1-, 2-, 3-, 7- and 8-NF), such as (hyper)polarizability, dipole moment, molecular electrostatic potential (MEP), spectroscopic characteristics, magnetic index (NICS) and others, obtained by means of *ab initio* (MP2) and density functional theory (DFT) approaches have been correlated with the observed mutagenic activities. A very good linear correlation (R_{av} = 0.99) between average polarizability (<α>) and experimental mutagenic activities of NFs in different *Salmonella typhimurium* strains from two independent experimental studies (Vance and Levin, *Environ. Mutagen.* **6** (1984) 797 and Zielinska *et al.*, *Mutation Res.* **206** (1988) 131) was established. Higher values of polarizability derivatives with respect to the ν_{sNO+CN} vibrational coordinate for 8-NF and 3-NF compared to 1-NF and 7-NF and, consequently, higher Raman activities in the spectra that are in correlation with mutagenic activities, implicate significant intermolecular interactions along this vibrational coordinate. The results indicate that the binding of NFs to enzymes is the main step in mutagenic pathway of these nitro derivatives.

Keywords: nitro polycyclic aromatic hydrocarbons; (hyper)polarizability; Raman spectra; dipole moment; NICS; environmental pollutants.

INTRODUCTION

From the environmental perspective, fluoranthene (FLU) is one of the principal polycyclic aromatic hydrocarbons (PAHs) in contaminated sediments[1] and is classified as a priority control organic pollutant. Among its nitrated derivatives, there are species with pronounced mutagenic activities and there is considerable interest in the fate of these compounds in the environment. 2-Nitrofluoranthene is considered to be the most abundant nitro-PAH bound to particles in ambient atmospheres.[2,3] The mutagenic activities of mononitrofluoranthenes

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(NFs) have been investigated in several studies.[4–9] Vance and Levin suggested that additional aromaticity obtained by adding the aromatic ring to nitrofluorene influences the mutagenic activity of NFs and indicated to an optimum length of NFs for their mutagenicity.[4] Maynard *et al.* found that the energies of the lowest unoccupied molecular orbital (LUMO) of these isomers follow the trend in observed mutagenic activity although 8-NF is more mutagenic than 3-NF.[5] Zielinska *et al*. indicated to the role of nitro reduction and ring oxidation in the mutagenic activation of some NFs.[6] Nitrofluroanthenes have also been investigated theoretically.[10–13] The simulated IR and Raman were assigned, analysed and compared with available experimental data.[10] Onchoke also obtained good agreement between simulated and observed UV/Vis spectra of NFs.[12] However, only slight correlations were observed between mutagenicity and the investigated properties, and polarizability was not taken into consideration.

In the present work, attention was focused on the physico-chemical properties of nitrofluoranthene isomers: structure, stability, oxidoreduction properties, nucleus-independent chemical shift (NICS), molecular electrostatic potential (MEP), dipole moment, (hypo)polarizability, as well as spectroscopic characteristics such as vibrational wavenumbers, normal mode assignment, Raman activities and polarizability derivatives. The main aim of this study was to explore whether the observed mutagenic activities could be ruled by some specific molecular properties of these isomers calculated by *ab initio* and density functional theory (DFT) based approaches.

COMPUTATIONAL METHODS

Calculations with full geometry optimization using the DFT functionals (B3LYP,[14] CAM-B3LYP[15]) have been performed. During the geometry optimizations, no symmetry constraints were imposed and a normal mode analysis yielded no imaginary frequencies confirming that the optimized geometries are minima on the potential energy surface. The relative energies of NFs were determined at the B3LYP/6-311+G(2df,p) and MP2/aug-cc-pVDZ levels of theory. The energies were corrected to the zero-point vibrational energies (*ZPVE*) scaled employing the corresponding scaling factor.[16] Vertical ionization potential (*IP*) was obtained as the energy difference between energy of the cation and energy of the neutral, while vertical electronic affinity (*EA*) was obtained as the energy difference between the energy of the neutral and energy of the anion. For the calculation of the ground state energies of the cation and anion, the unrestricted method (UB3LYP) was employed. The calculations were realized with the help of Gaussian 09 program package.[17] The vibrational band assignment, simulated spectra, and the visualization of the MEP surfaces generated at the isolelectronic density surface were made by the Gaussview 6 program.[18] The analysis of the local minima and maxima on the MEP surfaces were obtained with the help of the program Multiwfn.[19]

Two approaches were employed for the polarizability calculations: DFT and *ab initio* (second-order Møller–Plesset perturbation theory (MP2)). The polarizability components (α_{xx}, α_{yy}, α_{zz}) in the MP2 approach were calculated using a finite-field method with a parabolic fit. The convergence of the SCF calculations up to 10^{-14} a.u. was used, which ensures a high accuracy of the MP2 energies. Steps of 0.001 a.u. were used for the added external electric

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field. The MOLPRO program package[20] was used for the MP2 calculations. The Raman intensity of the peak corresponding to the vibrational mode p characterized by the normal coordinate Q_p can be given as the Raman scattering factor. It depends on the derivatives of the averaged polarizability and anisotropy of the polarizability with respect to the normal coordinate Q_p:

$$S_{\text{Raman}} = 45(\alpha')^2 + 7(\gamma')^2 \quad (1)$$

where

$$a' = \frac{\left(a'_{xx} + a'_{yy} + a'_{zz}\right)}{3} \quad (2)$$

$$(\gamma')^2 = 1/2\left[(a'_{xx} - a'_{yy})^2 + (a'_{yy} - a'_{zz})^2 + (a'_{zz} - a'_{xx})^2 + 6\left(a'_{xy}{}^2 + a'_{xz}{}^2 + a'_{yz}{}^2\right)\right] \quad (3)$$

$\alpha'_{mn} = \partial\alpha_{mn}/\partial Q_p$ $(m,n = x,y,z)$ represents the derivative of the component of the polarizability tensor with respect to the normal coordinate Q_p. The first-order hyperpolarizabilities were obtained using the CAM-B3LYP approach, a level of theory that provides a reasonable approximation of the trends in hyperpolarizability.[21]

The *NICS(1)* values were calculated employing the GIAO-B3LYP method. Values of the magnetic index based on the total molecular orbital (MO) contribution to the out-of-plane (zz) component of the NICS tensor ($NICS_{zz}$)[22-24] are presented.

RESULTS AND DISCUSSION

Among the investigated isomers, 2-NF and 8-NF possess planar arrangement of the nitro group with respect to the plane of the aromatic rings (Fig. 1). The equilibrium geometries of 1-NF, 3-NF and 7-NF are characterized by a nonplanar configuration of the nitro group. At the B3LYP/6-311+G(2df,p) level, the nitro group of 3-NF is calculated to be twisted about 16° with respect to the aromatic system, while the nitro group of 1-NF and 7-NF is twisted about 28° relative to the aro-

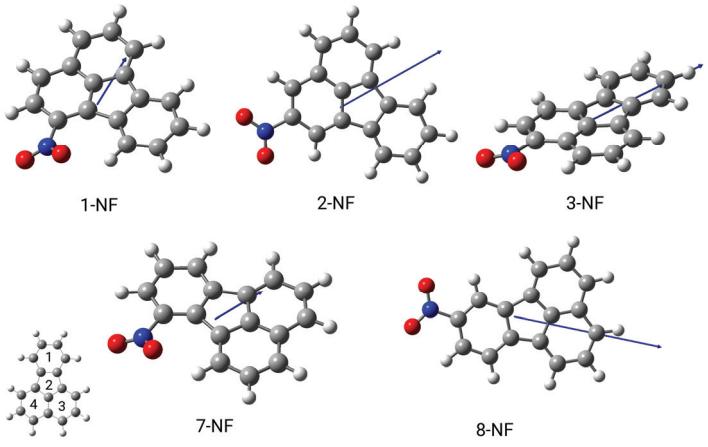

Fig. 1. Optimized geometries of the investigated NFs at the B3LYP/6-311+G(2df,p) level of theory, dipole moment vectors and numbering of the rings. Colours: white (hydrogen), grey (carbon), blue (nitrogen), red (oxygen).

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matic system plane. The criterion based on the C–C–N–O dihedral angle that states that planar nitro polycyclic aromatic hydrocarbons (NPAHs) intercalate more effectively in the active site of the enzyme nitroreductase and show therefore higher mutagenicity, cannot explain the differences in mutagenic activities of NFs (Table I).

TABLE I. Relative energy of nitrofluoranthene calculated from the scaled zero-point vibrational energy (ΔE_{ZPVEsc}), the ZPVE energy and relative energy calculated at the MP2 level (in kcal* mol^{-1}), vertical ionisation energy (*IP*, in eV), vertical electron affinity (*EA*, in eV), dipole moment (μ, in D**), averaged static dipole polarizability ($<\alpha>$), polarizability anisotropy ($\Delta\alpha$), static first-order hyperpolarizability (total (β_{tot}) and aligned along the direction of dipole moment (β_μ), in a.u.), and the experimental[4,6] mutagenic activities (in revertants nmol^{-1}). *IP* and *EA* are values of fluoranthene (FLU)

Molecule	ΔE_{ZPVEsc}[a]	*ZPVE*[a]	ΔE_{MP2}	*IP*[b]	*EA*[b]	μ[a]	$<\alpha>$[a]	$<\alpha>$[h]	$\Delta\alpha$[a]	β_{tot}[i]	β_μ[i]	Mutagenic activity TA98-S9
1-NF	4.49	130.82	2.34	8.07	1.57	4.97	217.32	218.27	178.90	423	395	500[f]
2-NF	0.88	130.73	0.72	8.14	1.48	5.56	218.71	219.46	188.79	544	544	1030[g]
3-NF	3.45	130.84	2.51	8.13	1.68	5.50	221.68	221.25	205.83	1044	1044	8500,[f] 7700[g]
7-NF	4.23	130.86	1.73	8.06	1.28	4.82	215.80	217.05	181.08	703	459	47[f]
8-NF	0.00	130.79	0.00	8.13	1.52	6.42	223.43	222.60	209.55	1721	1707	11000[f] 18200[g]
FLU	–	–	–	7.65 7.9[c] 7.68[d]	0.64 0.63[e]	0.34	196.47	194.99	–	–	–	–

[a]B3LYP/6-311+G(2df,p) (scaling factor 0.9889 from Ref. 16); [b]B3LYP/6-311++G(2d,2p)//B3LYP/6-311++G(2df,p); [c]exp. value from time-resolved photoionization from Ref. 26; [d]from Ref. 27; [e]exp. value from gas-phase electron-capture method from Ref. 25; [f]from Ref. 4; [g]from Ref. 6; [h]MP2/aug-cc-pVDZ values from the finite-field approach; [i]CAM-B3LYP/6-311+G(2d,p) level of theory

The calculations establish that 8-NF is the most stable isomer. The next most stable isomer is 2-NF lying above 8-NF by 0.72 kcal mol^{-1} at the MP2/aug-cc-pVDZ level of theory. The order of stability of the next three isomers is 7-NF (1.73 kcal mol^{-1}) > 1-NF (2.34 kcal mol^{-1}) > 3-NF(2.51 kcal mol^{-1}). The order of stability obtained at the B3LYP/6-311+G(2df,p) level of theory (Table I) is: 8-NF (0.00 kcal mol^{-1}) > 2-NF (0.88 kcal mol^{-1}) > 3-NF (3.45 kcal mol^{-1}) > 7-NF (4.23 kcal mol^{-1}) > 1-NF (4.49 kcal mol^{-1}). This is the same as the order of stability of NFs presented in the study by Onchoke[12] where relative energies where calculated at the B3LYP/6-311+G(d,p) level of theory. The MP2 relative energies differ from the B3LYP relative energies showing the impact of electron correlation and higher level of calculations on energy comparisons.[28]

In order to estimate the oxidative and reductive properties of the isomers,[29] the ionization energies and electron affinities of NFs were calculated. To check the accuracy of the applied methods, the values of *IP* and *EA* for fluoranthene for

* 1 kcal = 4184 J

** 1 D = 3.33564×10^{-30} C m

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which the corresponding experimental values are available, were calculated (Table I). The vertical electron affinity of fluoranthene, 0.64 eV, is in very good agreement with the experimental value of 0.63 eV obtained from the gas-phase electron--capture method.[25] The *IP* and *EA* values of NFs are presented in Table I. *IP* varies only slightly along the series of isomers (0.08 eV) while *EA* decreases by 0.4 eV on passing from 3-NF to 7-NF. Nevertheless, by inspection of the *IP* and *EA* values and the experimental mutagenic activities,[4,6] it could be noticed that the *IP* and *EA* values cannot be correlated with the observed mutagenicity of the NFs.

The $NICS_{zz}$ value computed 1 Å above the ring centroid ($NICS(1)_{zz}$) for each of the four rings of every NF isomer was calculated at the B3LYP/6-311+G(2df,p) optimized geometry (Table II). Rings 1, 3 and 4 have negative $NICS(1)_{zz}$ values, indicating their aromatic character. The five-membered ring of the investigated isomers possesses positive $NICS(1)_{zz}$ value (although not largely positive). For ring 3 and ring 4 of isomers 3-NF and 8-NF, the difference between the $NICS(1)_{zz}$ values is significant at 3.0 and 2.4 ppm, respectively, which may help in their identification through experimental NMR shifts. For isomers 1-NF and 7-NF, the difference between the $NICS(1)_{zz}$ values for ring 3 is even larger, 3.9 ppm. However, it could be noticed that the results based on *NICS* values are not consistent with the noticeable mutagenicity enhancement on going from 7-NF to 8-NF.

TABLE II. The NICS data ($NICS(1)_{zz}$ in ppm) for the rings of nitrofluoranthenes (for numeration of the rings see Fig. 1) obtained using the GIAO method and B3LYP/6-311+G(d,p) level of theory on the B3LYP/6-311+G(2df,p) optimized geometries

Molecule	Ring 1	Ring 2	Ring 3	Ring 4
1-NF	–19.58	12.57	–20.39	–22.44
2-NF	–20.96	8.10	–22.03	–21.76
3-NF	–19.32	11.77	–20.57	–21.77
7-NF	–20.37	5.77	–24.25	–23.61
8-NF	–19.39	5.18	–23.61	–24.15

Owing to its arrangement of atoms, the dipole moment of fluoranthene is relatively small while the polarities of nitrofluoranthenes are high due to the charges over the nitro group. B3LYP/6-311+G(2df,p) level of theory predicts the following order of μ values for NFs: 7-NF < 1-NF < 2-NF ≈ 3-NF < 8-NF (Table I). The directions of the dipole moment vectors of NFs are displayed in Fig. 1. The isomer with highest mutagenic activity, 8-NF, (11000 revertants $nmol^{-1}$)[4] has the largest dipole moment (6.42 D) while the isomer with lowest observed mutagenic activity, 7-NF (only 47 revertants $nmol^{-1}$)[4] possesses the lowest dipole moment (4.82 D). The calculated dipole moments are in good linear correlation (R = 0.93 and 0.97) with the observed mutagenic activity in *Salmonella typhimurium* strains TA98 and TA98NR,[4] respectively (Fig. 2). Therefore, in the enzyme–ligand complexes of nitrofluoranthenes, the dipole moment of the particular NF iso-

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mer can contribute to intermolecular interactions through both electrostatic and inductive terms.

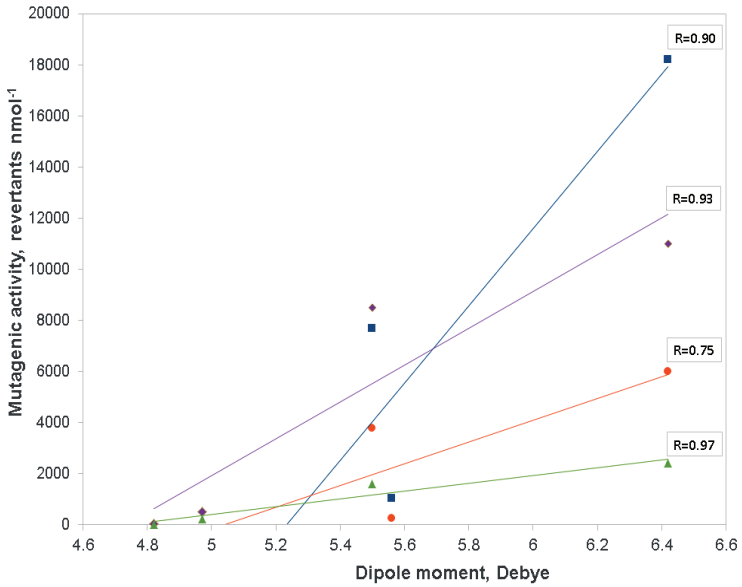

Fig. 2. The linear relationship between dipole moment calculated at the B3LYP/6-311+G(2df,p) level and mutagenic activity of NFs in *Salmonella typhimurium* strains obtained in two independent mutagenic assays (■: TA98,[6] ●: TA98NR,[6] ♦:TA98[4] and ▲: TA98NR[4]).

The molecular surface electrostatic potentials of NFs calculated at the B3LYP/6-31++G(2d,2p) level of theory were mapped on an isodensity surface of 0.004 e bohr^{-3} (Fig. 3). Different regions with increasing electrostatic potential in the order red (negative) < orange < yellow < green < blue (positive) could be noticed. The quantitative analysis of the molecular electrostatic potential surfaces of NFs was performed and the results are given in the Supplementary material to this paper (Figs. S-1–S-5 and Tables S-I–S-V). The data show that the isomer 8-NF with the highest value of mutagenic activity (18200 revertants nmol^{-1} in *S. typhimurium* strain TA98)[6] possesses two minima with a value –35.7 kcal mol^{-1} depending on the side of the molecule where the nitro group is located. On the other hand, the two least active isomers in the *S. typhimurium* strain TA98,[6] 7-NF and 1-NF (47 and 500 revertants nmol^{-1}, respectively), show electrostatic similarity – they have minima on the nitro group of lower values compared to 8-NF and 3-NF (–31.7 and –32.7 kcal mol^{-1} for 7-NF and –32.3 and –33.2 kcal mol^{-1} for 1-NF). Isomer 3-NF that possesses higher mutagenic potency compared to 1-NF and 7-NF, has minima in the region of the nitro group with higher values: –34.5 and –34.8 kcal mol^{-1} for 3-NF. These data corroborate the import-

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ance of the electrostatic characteristics for the interactions between NF isomers and their biomacromolecular target.

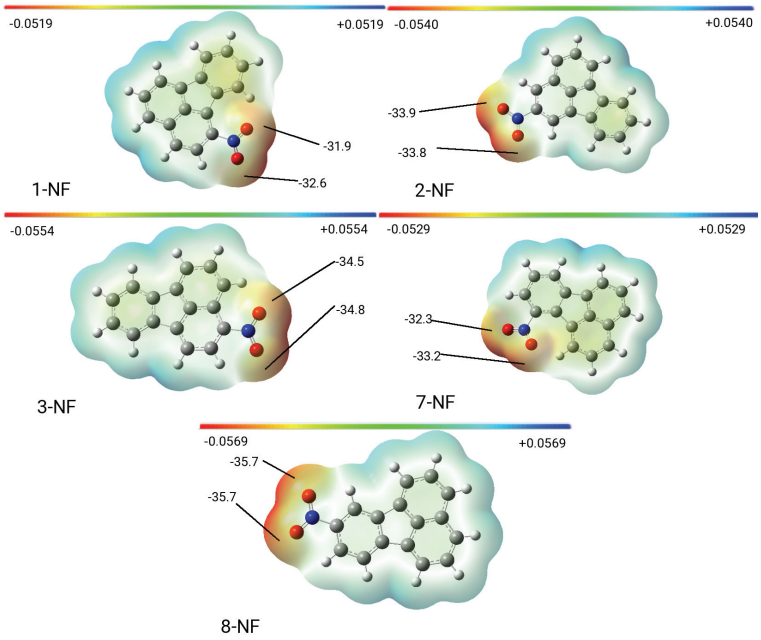

Fig. 3. The molecular electrostatic potential (isosurface value 0.004) of the NF isomers. The numerical values of the most negative values on the MEP surface (V_{min} in kcal mol^{-1}) calculated at the B3LYP/6-311++G(2d,2p) level are indicated. (Colour mapping toolbar with minimum and maximum values of the electrostatic potential energy in a. u. is also displayed.)

Results on mutagenicity in the Ames test of a large number of aromatic and heteroaromatic nitro compounds revealed that one of the main determinants of mutagenicity is hydrophobicity.[30,31] It was shown that polarizability is related to hydrophobicity and to other biological activities.[32–34] The importance of (hyper)-polarizability for quantitative structure property relationship (QSPR) was emphasized.[35] Different mutagenic behaviour, biodegradation rates, and toxicity of a series of substituted PAHs was elucidated based on molecular properties of a substrate that influence intermolecular interactions and its binding affinity to an enzyme.[36–52] The static electronic dipole polarizabilities of nitrofluoranthenes are presented in Table I. The introduction of the nitro group increases the $<\alpha>$ value of fluoranthene by 9–12 % (Table I). The largest $<\alpha>$ values were obtained for 8-NF and 3-NF. They are more polarizable, 5–7 a.u., compared to 1-NF and 7-NF, which are characterized by lower polarizability values. It is both encouraging and interesting that two different approaches and levels of theory (MP2 and B3LYP) yielded similar values of polarizability for NFs. To investigate whether

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the polarizability correlates with different mutagenic potencies, the $<\alpha>$ values were plotted against experimentally observed mutagenicity in different *S. typhimurium* strains[4,6] (Table III). Very good correlations (averaged correlation coefficient R_{av} = 0.99) were obtained for two independent mutagenic assays: R(TA98) = 0.99 and R(TA98NR) = 0.99,[4] and R(TA98) = 0.96 and R(TA98NR) = = 1.00[6] (Fig. 4 and Table III).

TABLE III. Correlation of the average polarizability calculated at the B3LYP/6-311+G(2df,p) level of theory with the mutagenicity (, revertants nmol^{-1}) of NFs observed in different *Salmonella typhimurium* strains[4,6]

Isomer	TA98[a]	TA98NR[a]	TA98[b]	TA98NR[b]	TA98/1,8DNP$_6$[b]
1-NF	500	230	–	–	–
2-NF	–	–	1030	250	180
3-NF	8500	1600	7700	3800	1020
7-NF	47	18	–	–	–
8-NF	11000	2400	18200	6000	5400
R[c]	0.99	0.99	0.96	1.00	0.87

[a]Ref. 4; [b]ref. 6; [c]R is the Pearson's correlation coefficient

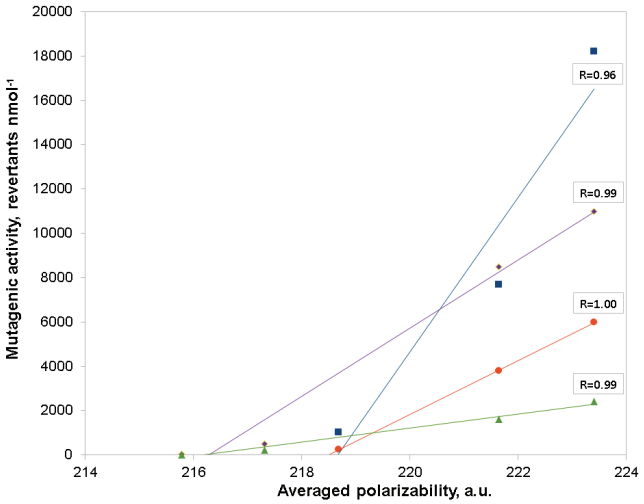

Fig. 4. Linear relationships between the averaged polarizability calculated at the B3LYP/6-311+G(2df,p) level and mutagenic activity of NFs in *Salmonella typhimurium* strains obtained in two independent mutagenic assays (■: TA98;[6] ●: TA98NR;[6] ♦: TA98;[4] ▲: TA98NR[4])

The results firmly support the argument that the polarizability of NFs could be one of the major factors in their ability to damage DNA and to induce mutations. Good correlations were also found for the hyperpolarizability of NFs. The static first-order hyperpolarizability values, total and aligned along the direction of the

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dipole moment, were calculated at the CAM-B3LYP/6-311++G(d,p) level of theory (Table I). The averaged correlation coefficient for the experimental mutagenic activities in *Salmonella typhimurium* was $R_{av} = 0.96$ (Fig. 5).

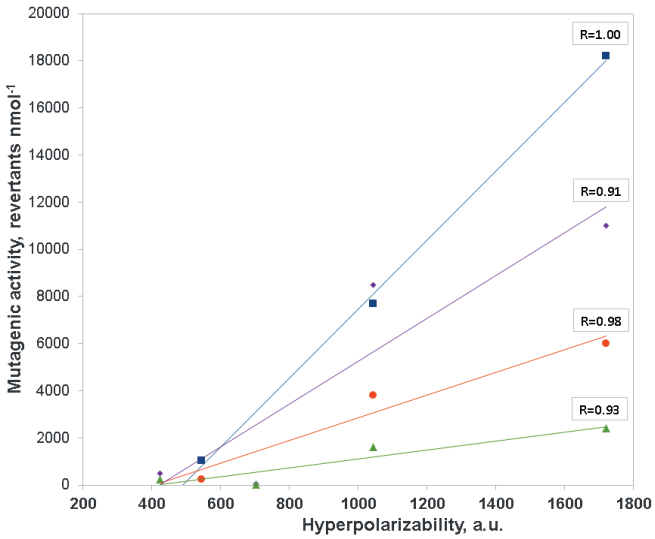

Fig. 5. Linear relationships between hyperpolarizability calculated at the CAM-B3LYP/6-311+G(2d,p) level and mutagenic activity of NFs in *Salmonella typhimurium* strains obtained in two independent mutagenic assays (■: TA98;[6] ●: TA98NR;[6] ♦: TA98;[4] ▲: TA98NR[4]).

On passing from 7-NF and 1-NF to 8-NF, the anisotropy of the polarizability value increases by 14–17 % (Table I and Fig. 6). Especially interesting are the values of the largest component of the polarizability tensor, α_{xx}, aligned along the longest molecular axis. These values are particularly large for the two isomers 8-NF and 3-NF characterized by the largest mutagenic activities, 11000 and 8500 revertants nmol^{-1}, respectively, presented in the study of Vance and Levine[4] and 18200 and 7700 revertants nmol^{-1}, respectively, presented in the study of Zielinska *et al.*[6]

On passing from 7-NF and 1-NF to 8-NF, the α_{xx} value increases by 13–20 %. The results on α_{xx} and $\Delta\alpha$ are consistent with the finding of Vance and Levine that nitroaromatics with the nitro group oriented along the longest molecular axis are more potent mutagens than those with the nitro group oriented along the shortest molecular axis.[4] The results point to the conclusion that in enzyme–substrate complexes that involve mononitrofluoranthenes, the polarizability as a measure of the change of the electronic density under application of external electric fields could contribute to intermolecular interactions through both inductive and dispersion terms.

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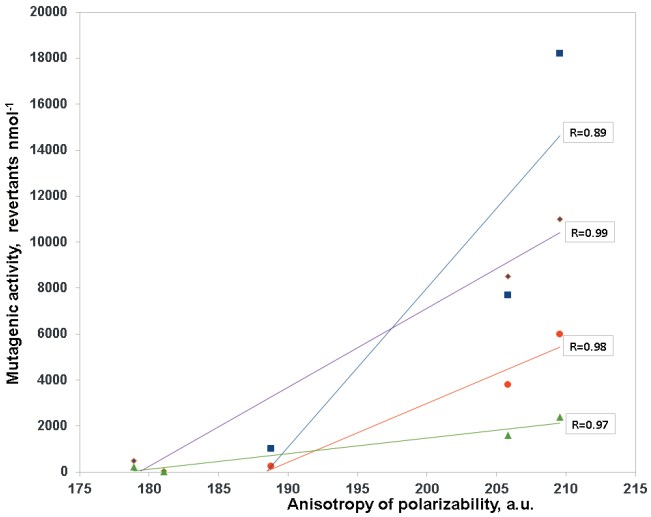

Fig. 6. The linear relationship between the anisotropy of polarizability calculated at the B3LYP/6-311+G(2df,p) level and mutagenic activity of the NFs in *Salmonella typhimurium* strains obtained in two independent mutagenic assays (■: TA98;[6] ●: TA98NR;[6] ♦: TA98;[4] ▲: TA98NR[4]).

In the Raman spectrum of 3-NF, the most intense peak in the range 500–1500 cm^{-1} corresponds to symmetric N–O bonds stretching coupled with C–N bond stretching (ν_{sNO+CN}). It is located at 1332 cm^{-1} by the scaled B3LYP/aug-cc-pVDZ calculations, in excellent agreement with the experimental value obtained by Onchoke[10] at 1329 cm^{-1} and the peak at 1332 cm^{-1} presented by Michl *et al.*[53] The most intense peak in the Raman spectra of 8-NF and 2-NF corresponds also to the ν_{sNO+CN} vibration and is located at 1343 (in agreement with the experimental value[53] of 1340 cm^{-1}) and 1345 cm^{-1}, respectively. The peaks of most intense bands in the Raman spectra of 1-NF and 7-NF correspond to the ring stretching vibration, ν_{ring}, and the ν_{sNO+CN} vibration. On passing from 7-NF to 8-NF, a noticeable effect occurs for the Raman activity of the band assigned to the ν_{sNO+CN} vibration (265.8 $Å^4$ $a.m.u.^{-1}$ for 7-NF; 282.3 $Å^4$ $a.m.u.^{-1}$ for 1-NF; 528.9 $Å^4$ $a.m.u.^{-1}$ for 2-NF; 1118.0 $Å^4$ $a.m.u.^{-1}$ for 3-NF; 1253.6 $Å^4$ $a.m.u.^{-1}$ for 8-NF), which increases by *ca*. 371 % from 7-NF to 8-NF. This is in line with the results of the observed mutagenic activities,[4,6] which show that 8-NF is the most active NF isomer while 7-NF is the least active isomer.

Additionally, calculations of derivatives of the averaged polarizability (α') and derivatives of the anisotropy of polarizability (γ') were also performed for this vibrational mode (Figs. 7 and 8). The ν_{sNO+CN} vibration is essentially attributed to the ν_{sNO} + ν_{CN} mode. The polarizability derivatives calculated at the B3LYP/6-311+G(2df,p) level for the ν_{sNO+CN} vibration are $\alpha' = 3.45$ $Å^2$ $a.m.u.^{-1/2}$ and $\gamma' = 10.04$ $Å^2$ $a.m.u.^{-1/2}$ for 8-NF, for 3-NF, they are $\alpha' = 3.28$ $Å^2$

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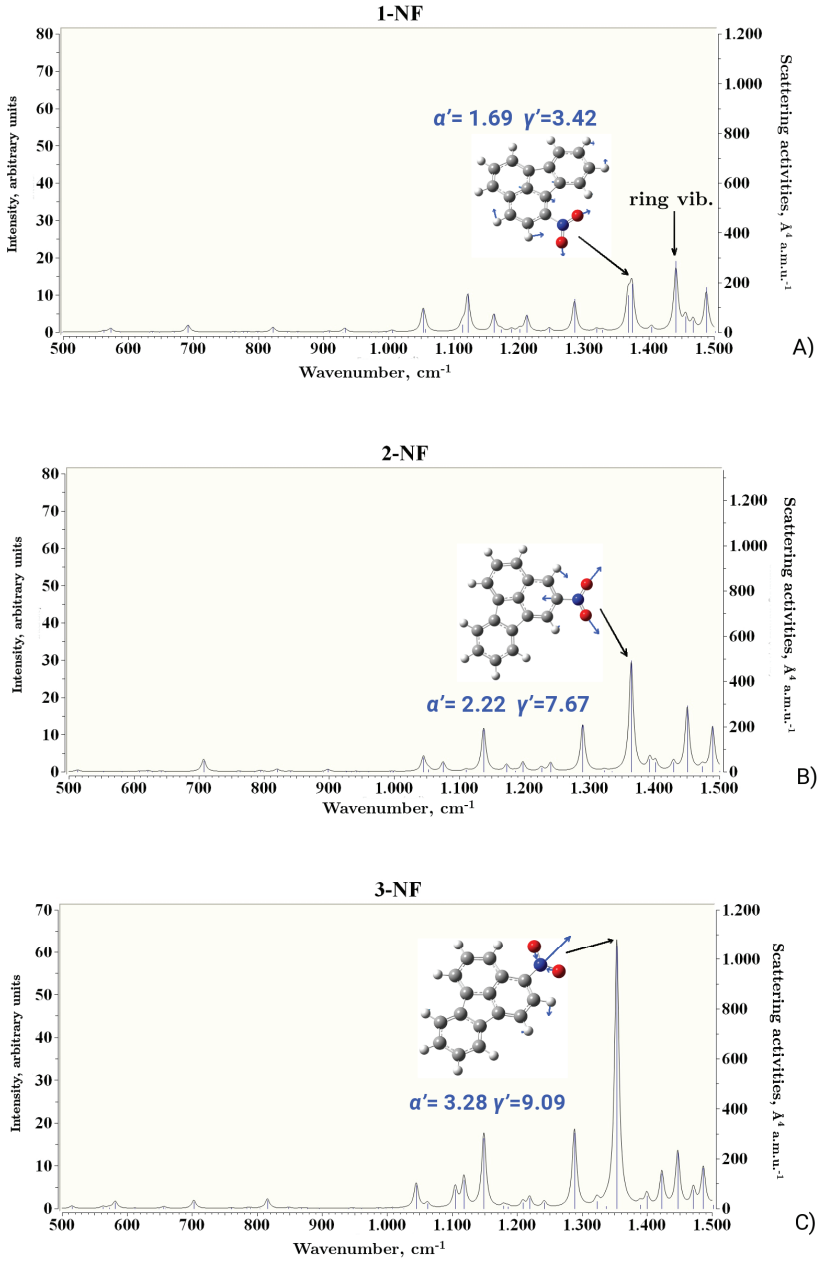

Fig. 7. The calculated B3LYP/6-311+G(2df,p) Raman spectra of 1-NF (A), 2-NF (B) and 3-NF (C) in the 500–1500 cm^{-1} region. The bands corresponding to the vibrational mode ν_{sNO+CN} and ring vibration are indicated. Atom vector displacements for the ν_{sNO+CN} normal mode are displayed along with the derivatives of averaged polarizability (α') and derivatives of anisotropy of polarizability (γ') for this vibrational mode.

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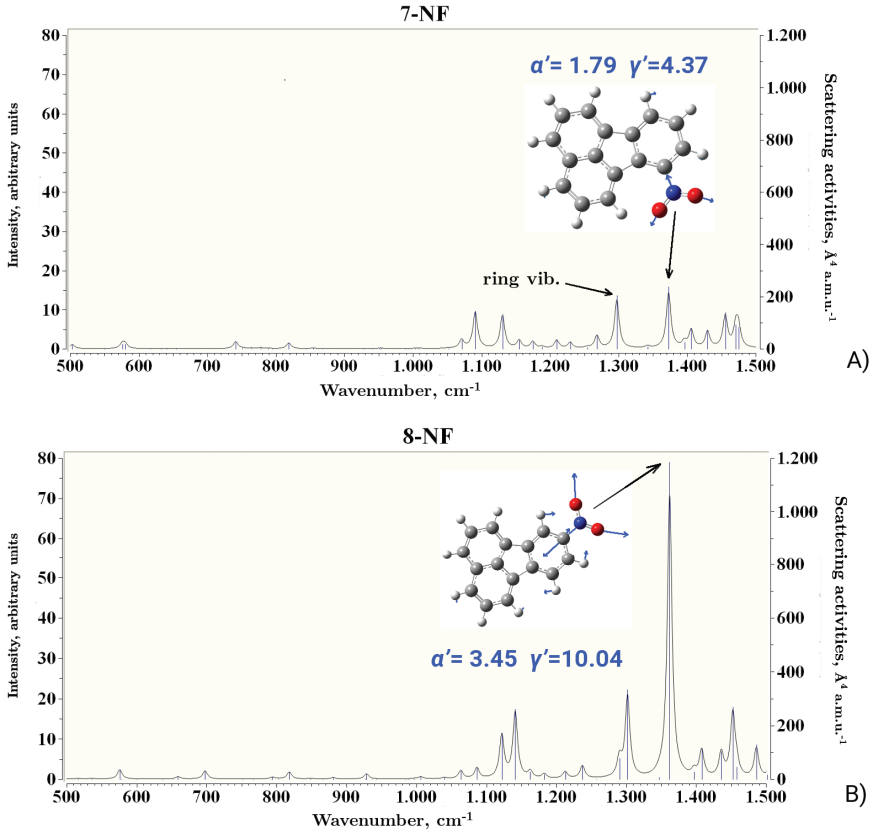

Fig. 8. The calculated B3LYP/6-311+G(2df,p) Raman spectra of 7-NF (A), and 8-NF (B) in the 500–1500 cm^{-1} region. The bands corresponding to the vibrational mode ν_{sNO+CN} and ring vibration are indicated. Atom vector displacements for the ν_{sNO+CN} normal mode are displayed along with the derivatives of averaged polarizability (α') and derivatives of the anisotropy of polarizability (γ') for this vibrational mode.

a.m.u.$^{-1/2}$ and $\gamma' = 9.09$ Å^2 a.m.u.$^{-1/2}$ while for 2-NF, they are $\alpha' = 2.22$ Å^2 a.m.u.$^{-1/2}$ and $\gamma' = 7.67$ Å^2 a.m.u.$^{-1/2}$. The ordering of these three NFs with respect to increasing polarizability derivatives α' and γ' is 2-NF < 3-NF < 8-NF and it follows the ordering of these isomers with respect to mutagenic activities that were estimated through the TA98-S9 test.[6] The α' and γ' values for 1-NF and 7-NF are lower compared to 8-NF, 3-NF and 2-NF. They are $\alpha' = 1.79$ Å^2 a.m.u.$^{-1/2}$ and $\gamma' = 4.37$ Å^2 a.m.u.$^{-1/2}$ for 7-NF and $\alpha' = 1.69$ Å^2 a.m.u.$^{-1/2}$ and $\gamma' = 3.42$ Å^2 a.m.u.$^{-1/2}$ for 1-NF. 7-NF is characterized by very low TA98 mutagenic activity, 47 revertants nmol^{-1} while the mutagenic activity of 1-NF is 500 revertants nmol^{-1}. These two isomers are of the lower mutagenic activity compared to 8-NF (18200 revertants nmol^{-1}), 3-NF (7700 revertants nmol^{-1}) and 2-NF (1030 revertants nmol^{-1}) and the polarizability derivatives ascribed to the symmetric stretching of

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N–O bonds along with the C–N bond stretching are in line with the observed mutagenic activities of these isomers.

For a given geometrical distortion along the N–O and C–N bonds, 8-NF is predicted to be the most susceptible to intermolecular interactions through dispersive contribution and is expected to exhibit higher binding capacity with the active site of the enzyme compared to 1-NF and 7-NF. Consequently, for geometrical distortion involving N–O bonds stretching along with C–N bond stretching, a prominent variation of polarizability could be associated with different mutagenic activities. Thee results suggest that inductive and dispersive forces play essential roles in the mechanism of the mutagenic activation of NFs. More details could be obtained from further analysis based on the quantum mechanics/ /molecular mechanics (QM/MM) approach that could take into account the active-site protein environment.

CONCLUSIONS

In order to establish a possible relationship between molecular properties and experimental mutagenic activities of mononitrofluroanthenes, the structures, stabilities, ionization potentials and electron affinities, NICS indexes, dipole moments, (hyper)polarizabilities, vibrational spectra and other related physicochemical properties of these isomers were calculated. Very good correlation was obtained between direct mutagenicity obtained in experiments with *Salmonella typhimurium* TA98 strain and $<\alpha>$ (R = 0.99), $\Delta\alpha$ (R = 0.99) and hyperpolarizability (R = 1.00). For different *S. typhimurium* strains from two independent mutagenic assays, it was found that excellent linear correlations (R_{av} = 0.99) exist between the calculated polarizability values of the NFs and their mutagenic potencies. On passing from 7-NF and 1-NF, isomers with low direct-acting TA98 mutagenic activity, to 8-NF, the isomer with the highest TA98 mutagenicity, the α_{xx} and $\Delta\alpha$ values increase by up to 20 and 17 %, respectively. The increments of the electric properties (α_{xx} and $\Delta\alpha$) are significant along the longest molecular axis, in consistency with the conclusion of Vance and Levine[4] for which direct-acting TA98 mutagenicity is maximized for nitrofluroanthene geometric isomers with the nitro group located along the longest molecular axis. The dipole moment values and quantitative analysis of the MEP surfaces of NFs show that electrostatic similarity exists among isomers of comparable mutagenic activity. From the vibrational spectra and derivatives of polarizability along the normal mode attributed to symmetrical N–O bonds stretching and C–N bond stretching, the noticeable variation of polarizability can be related to the strength of the intermolecular interactions in the enzyme–NF complex and, consequently, to different mutagenic activities of NFs. The results support the fact that binding to enzyme through intermolecular interactions is crucial in the metabolic pathways for the activation of mutagenicity of mononitrofluroanthenes.

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SUPPLEMENTARY MATERIAL

Additional data are available electronically from http://www.shd.org.rs/JSCS/, or from the corresponding author on request.

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ИЗВОД

УЛОГА МОЛЕКУЛСКИХ ОСОБИНА МОНОНИТРОФЛУОРАНТЕНА У ЊИХОВОЈ МУТАГЕНОЈ АКТИВНОСТИ: *AB INITIO* И DFT ПРИСТУП

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Молекулске особине мутагена нитрофлуорантена (NF; 1-, 2-, 3-, 7- и 8-NF) као што су (хипер)поларизабилност, диполни момент, молекулски електростатички потенцијал (MEP), спектроскопске карактеристике, магнетни индекс (NICS) и др., добијене *ab initio* (MP2) и DFT приступом, корелисане су са мутагеним активностима ових изомера. Установљена је врло добра линерана корелација (R_{av} = 0,99) између средње поларизабилности (<α>) и експериментално одређених мутагених активности нитрофлуорантена у различитим сојевима бактерије *Salmonella typhimurium* из две независне експерименталне студије (Vance and Levin, *Environ. Mutagen.* **6** (1984) 797 и Zielinska *et al., Mutation Res.* **206** (1988) 131). Веће вредности извода поларизабилности у односу на ν_{sNO+CN} вибрациону координату за 8-NF и 3-NF у поређењу са 1-NF и 7-NF и, следствено томе, веће вредности Раман активности у спектрима које су у корелацији са мутагеном активношћу, упућују на знатне молекулске интеракције дуж ове вибрационе координате. Резултати указују да је везивање изомера NF за активно место ензима главни корак у активацији мутагености код ових нитро деривата.

(Примљено 9. маја, прихваћено 14. маја 2019)

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