Journal of Hazardous Materials 318 (2016) 623–630

Contents lists available at ScienceDirect

Journal of Hazardous Materials

journal homepage: www.elsevier.com/locate/jhazmat

Theoretical study of nitrodibenzofurans: A possible relationship between molecular properties and mutagenic activity

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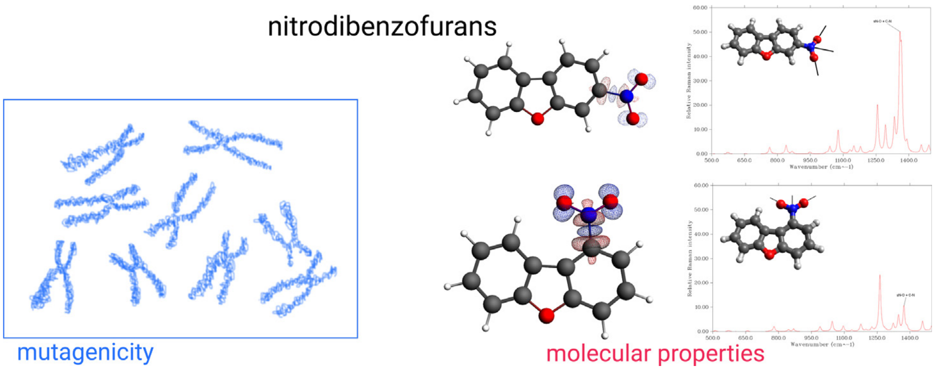
HIGHLIGHTS

- Molecular properties of nitrodibenzofurans are investigated theoretically.
- High quality DFT methods and EDA analysis are employed.
- Stability, ionization potential, electron affinity, and polarizability determined.
- Polarizability/mutagenic activity relationship is established.
- Relationship between vibrational properties and mutagenic activity is determined.

GRAPHICAL ABSTRACT



ARTICLE INFO

Article history:
Received 28 December 2015
Received in revised form 17 June 2016
Accepted 14 July 2016
Available online 16 July 2016

Keywords:
Nitrodibenzofurans
Dinitrodibenzofurans
Environmental pollutants
Density functional theory
Mutagenic activity

ABSTRACT

In this study we present a theoretical investigation of the molecular properties of nitrodibenzofurans (NDFs) and dinitrodibenzofurans (DNDFs) and their relation to mutagenic activity. Equilibrium geometries, relative energies, vertical ionization potentials (IP), vertical electron activities (EA), electronic dipole polarizabilities, and dipole moments of all NDFs and three DNDFs calculated by Density Functional Theory (DFT) methods are reported. The Ziegler/Rauk Energy Decomposition Analysis (EDA) is employed for a direct estimate of the variations of the orbital interaction and steric repulsion terms corresponding to the nitro group and the oxygen of the central ring of NDFs. The results indicate differences among NDF isomers for the cleavage of the related bonds and steric effects in the active site. The results show a good linear relationship between polarizability ($<\alpha>$), anisotropy of polarizability ($\Delta\alpha$), the summation of IR intensities (ΣI_{IR}) and the summation of Raman activities (ΣA_{Raman}) over all 3N-6 vibrational modes and experimental mutagenic activities of NDF isomers in *Salmonella typhimurium* TA98 strain. The polarizability changes with respect to the ν_{sNO+CN} vibrational mode are in correlation with the mutagenic activities of NDFs and suggest that intermolecular interactions are favoured along this coordinate.

1. Introduction

Nitro polycyclic aromatic compounds (NPACs) are ubiquitous air pollutants typically present in the atmosphere in the form of volatile particles and aerosols and they are recognized to be among the most hazardous environmental contaminants. Diben-

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http://dx.doi.org/10.1016/j.jhazmat.2016.07.035

zofuran (DF) was identified in air, groundwater, fuel gas, fly ash from municipal incinerators, diesel exhaust gas particulates and cigarette smoke. This molecule is one of the main components of the coal tar. DF in isolated lung mitochondria significantly increases the lag phase preceding mitochondrial repolarization, suggesting a decrease in the efficiency of the mitochondrial phosphorylative system [1]. Exposure to DF affects lung mitochondrial phosphorylative function causing an increase in the population of dysfunctional mitochondria and an impairment in the energetic status maintenance, therefore stimulating autophagy as a possible rescue mechanism in this cell line [2]. DF also interferes with the adenine nucleotide translocase (ANT) and so prevents Cyclophilin D (CypD) binding to ANT, causing decreased phosphorylative capacity and inhibiting the mitochondrial permeability transition (MPT) [3].

DF nitro isomers can be formed in the reaction of DF with nitrogen oxides NO_x under atmospheric conditions. It has been shown that 3-nitrodibenzofuran is a strong bacterial mutagen [4]. It was also detected in flame-grilled food [5]. On the other hand, the nitrodibenzofuran chromofore has been identified recently [6] as a new caging group for ultra-efficient photolysis in living cells [7,8] and has been used in various biochemical applications [9–12].

One of the crucial steps in the bacterial degradation of dibenzofuran, as well as of many others diaryl ethers, is a dioxygenolytic cleavage of the ether bond [13–15]. This process can be initiated by incorporating the molecular oxygen adjacent to the ether bridge and can be done by gram-negative bacteria such as *Sphingomonass* sp. [13,16,17] as well as gram-positive bacteria [14,15,18]. Harms and coworkers have analysed regioselectivity of the initial attack by *Sphingomonas* sp. strain HH69 on the monosubstituted dibenzofurans [19]. They proved that it can take place at the substituted aromatic ring, when final product is one of nitrosalicylic acids, and at nonsubstituted aromatic ring, when final metabolite is salicylic acid. They also argued that although initial attack may or may not show significant regioselectivity there is no evidence for any systematic influence of the substituents.

One of the structural factors that contributes to the mutagenicity of nitro polycyclic aromatic hydrocarbons (NPAHs) is planarity of the molecule [20–24]. Nitro-PAHs with a perpendicular (or nearly perpendicular) nitro group are considered to be weak direct-acting mutagens. Fu and coworkers stated that the decreased mutagenicity of nitrated PAHs with nitro group perpendicular to the aromatic ring may be due to their inability to fit into the active site of the nitroreductases because of steric interactions [21]. However there are cases where potent mutagenic responses are at variance with the statement of planarity [25]. The mutagenic potencies of nitro-PAHs were often related to O–N–C–C dihedral angles [21]. However, as it was shown in the study by Onchoke [26], this criterion is not sufficient for the prediction of mutagenicity of nitrobenzanthrones and there is only a qualitative agreement between the experimental and theoretical mutagenic trends.

In this study we want to link molecular properties with the mutagenic activity of all four NDFs and two dinitrodibenzofurans (DNDFs) detected in the reaction mixture of DF with nitrogen oxides (NO_x) under light irradiation determined by Watanabe and Hirayama [27]. For that purpose we use experimentally found bacterial mutagenicity [28] obtained by the Ames method [29] with the suspension assay modified by Yahagi [30]. Watanabe and coworkers found that all compounds except 1-NDF have exhibited mutagenicity in *Salmonella typhimurium* TA98 without S9 mix i.e. without mammalian metabolic activation system [28]. They also claimed that since in their experiments 3-NDF was more mutagenic than other NDFs, as well as 2,7-DNDF was more mutagenic than 2,8-DNDF, the nitro group at C3 or C7 position seemed to be predominant in the activation of NDFs and DNDFs by 'classical' nitroreductase which is the one that TA98 strain possesses [28]. It is well-known that the stronger NPAH-nitroreductase binding affinities is, the greater can be NPAH mutagenic activity. For that purpose we tend here to find which type of interaction is crucial for the formation of complex between NDFs and DNDFs and nitroreductase.

2. Methods

2.1. DFT calculations

The equilibrium geometries of all nitrobenzofuran isomers as well as 1,8-, 2,7- and 2,8- dinitrodibenzofurans were fully optimized using the B3LYP (Becke3-Lee-Yang-Parr) DFT method with the 6-311+G(2df,p) basis set. The optimizations were performed in the framework of the C_1 point group. The frequency calculations showed no imaginary values, confirming the true minima. The vertical first ionization potentials (IP) and vertical electron affinities (EA) were calculated according to the formulas:

$$IP = E_{cation} - E_{neutral} \tag{1}$$

$$EA = E_{neutral} - E_{anion} \tag{2}$$

where E_{cation}, E_{anion}, and $E_{neutral}$ are the energy of the cation, anion, and neutral, respectively. The energies were calculated using the optimized geometry of the neutral ground state at the B3LYP/6-311+G(2df,p) level of theory. The ground electronic state energies of the cation and anion were calculated using the unrestricted B3LYP method (UB3LYP), whereas neutral ground state energies were calculated employing the B3LYP level of theory. For calculation of the IP and EA values of the nitrobenzofuran and dinitrodibenzofuran isomers, the 6-311++G(2d,2p) basis set was employed. The relative energies of the isomers were determined at the B3LYP/6-311+G(2df,p) level of theory. The zero-point vibrational energies (ZPVE) were scaled by the scaling factor of 0.9889 determined for the B3LYP method and the 6-311+G(2df,p) basis set [31]. From the calculated components of the zero-frequency (static) dipole polarizability tensor along the principal axes, α_{xx}, α_{yy}, α_{zz}, at the B3LYP/6-311+G(2df,p) level, the following quantities [32] are obtained:

the electronic contribution to the average polarizability, $<\alpha>$:

$$<\alpha>= (\alpha_{xx}+\alpha_{yy}+\alpha_{zz})/3 \tag{3}$$

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

$$\Delta\alpha = \{[(\alpha_{xx}-\alpha_{yy})^2+(\alpha_{xx}-\alpha_{zz})^2+(\alpha_{yy}-\alpha_{zz})^2+6(\alpha_{xy}{}^2+\alpha_{xz}{}^2+\alpha_{yz}{}^2)]/2\}^{1/2} \tag{4}$$

The intensity of the peak corresponding to the vibrational mode *k* characterized by the normal coordinate Q_k in the Raman spectrum of molecule depends on the derivatives of the averaged polarizability and anisotropy of polarizability with respect to the normal coordinate Q_k [33]:

$$A_{Raman} \approx (45(\alpha')^2+7(\gamma')^2)/45 \tag{5}$$

where

$$\alpha' = (A_{xx}'+A_{yy}'+A_{zz}')/3 \tag{6}$$

$$(\gamma')^2 = 1/2[(A_{xx}'-A_{yy}')^2+(A_{yy}'-A_{zz}')^2+(A_{zz}'-A_{xx}')^2+6(A_{xy}'^2+A_{xz}'^2+A_{yz}'^2)] \tag{7}$$

$A_{pq}' = \partial A_{pq}/\partial Q_k$ (p,q = x,y,z) is the derivative of the component of polarizability tensor with respect to the normal coordinate Q_k. The dipole moment values were calculated at the B3LYP/cc-pVTZ level of theory. The calculations have been performed with the Gaussian 09 [34] and Gaussian 03 [35] program packages.