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Experimental and DFT analysis of structural and spectroscopic features of nitroterephthalic acid, and computational insights into its molecular interactions with hER-α via molecular docking

Fehmi Bardak

Department of Physics, Manisa Celal Bayar University, Manisa, Turkey

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ABSTRACT

It has become clear that the exposure to the ubiquitous xenoestrogens are the first line causatives for human breast cancer. Besides, terephthalic acid (TPA), the major chemical constituent in the synthesis of polyethylene terephthalate (PET), also shown to have carcinogenic effects. Nitroterephthalic acid (NTPA) modified PET or polyethylene glycol (PEG) polymers are suggested to have lower risk, however little known about the reactive nature of NTPA especially in terms of its interactions with estrogen receptors. Therefore, this study focuses on the investigation of structural and spectroscopic features of NTPA through experimental and theoretical methods, and the exploration of interactions with human estrogen receptor alpha (hER-α) in comparison with that of benzoic acid (BA), phthalic acid (PA), and terephthalic acid (TPA) by using molecular docking methodology. Essential quantum descriptors obtained for NTPA include electrostatic potential surface, electrophilicity and nucleophilicity from Fukui analysis, aromaticity indexes from nuclear independent chemical shift (NICS) analysis, and electronic properties like band gap and ionization potentials from population analysis. Infrared, Raman, and UV spectra are presented both experimentally and via ab initio density functional theory calculations obtained at the B3LYP 6-311++G(d,p) level of theory. Ligand-enzyme interactions were discussed within a dependency on the structural variations in four ligands in docking analysis. NTPA was found to behave like phthalic acid and highly rich in terms of conformations in monomeric and dimeric forms.

1. Introduction

Chemical exposure to cancer causative agents has been accounted as the most common reason in many types of cancer and related diseases because of their release from multiple sources starting from the naturally occurring infectious agents to industrially created pollutions, hormone drugs, immune system suppressing compounds, and etc … All can be in charge of either starting a cancer incident or aggravation of the disease. Besides the chemical exposure, lifestyle reasons like tobacco usage and physical activity or mediclinic treatments like radiation therapy have been shown to lead cancer as well [1]. Upon growing technology with polymer based manufacturing, chemical content of the materials become highly questionable. Probably the most suspicious and vital one is the bottles made from polyethylene terephthalate (PET). Although the PET has not been seen (or ignored) to be a source of endocrine disruptors and used worldwide as the main ingredient in plastic containers, evidence from experiments released that PET bottles may yield endocrine disruptors even under normal conditions [2–4]. On the other hand, PET is used excessively due to its immerse amount of applications. To improve the properties of PET further, or to overcome its some drawbacks such as poor dyeability, pilling, and brittleness, chemical modifications have been attempted [5]. The common way in the modification is to introduce copolymerizing compounds with functional groups either more or different type than carboxyl group.

An interesting PET modifier is the nitroterephthalic acid (NTPA) (Fig. 1) that has been implemented successfully [6]. NTPA is also used in the modification of polyethylene glycol to be used as capillary gas chromatography column [7]. With an enrichment of a nitro group to terephthalic acid, NTPA clearly seems to have a higher reactive nature; however, how it differs from terephthalic acid (TPA) and phthalic acid (PA), or their base structure benzoic acid (BA) has not been explained in detail. Thus, we aim to explain the structural properties of NTPA such as electronic and

E-mail address: fehmi.bardak@cbu.edu.tr.

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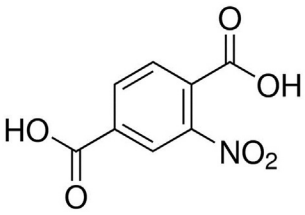

Fig. 1. 2D chemical structure of nitroterephthalic acid.

spectroscopic features and dimerization characteristics, and obtain reactivity parameters exhaustively. Over and above, we intend to investigate and compare the cancer causative nature of mentioned compounds because decision making about whether to improve the material properties or to reduce health hazards is critical.

This work is organized as follows: Section 2 contains the details of experimental techniques used in determination of structural and spectroscopic features of NTPA. Section 3 presents the calculations of these features and the molecular docking of NTPA to the hER-α in comparison with that of TPA, PA, and BA. Results and discussion section starts with the conformational search for NTPA. Two possible monomeric and five possible dimeric stable structure parameters of NTPA found via quantum chemical calculations are compared with the x-ray crystallographic data from the literature. Binding characteristics and critical points are obtained via reduced density gradient analysis and topology analysis are presented. Electrostatic properties such as atomic charges potential energy surfaces and Fukui analysis are presented to reveal reactive sites. UV–Vis spectrum and calculated electronic properties presented, and chemical reactivity parameters obtained on the basis of frontier molecular orbital analysis. FT-IR and FT-Raman spectroscopic features are presented to reveal the effect of nitro group on the vibrational characteristics of the molecule. Reactivity and toxicity parameters of NTPA are predicted and compared to that of TPA, PA, and BA. Finally, molecular docking properties of four compounds are presented and residue based interaction profile of NTPA with hER-α is produced.

2. Experimental

NTPA molecule is supplied from Across Organics Company in solid state with a purity of 99% and used without any further purification. The FT-IR (4000-400 cm^{-1}) spectrum is recorded in Perkin-Elmer FT-IR System Spectrum BX spectrometer by using a KBr disc technique with a scanning speed of 10 cm^{-1} min^{-1} and the spectral resolution of 4.0 cm^{-1}. FT-Raman (3500–10 cm^{-1}) spectrum of the title molecule is recorded in Bruker RFS 100/S FT-Raman instrument using 1064 nm excitation from an Nd:YAG laser with a liquid nitrogen cooled Ge detector by accumulating five hundred scans at 4 cm^{-1} resolution at a laser power of 100 mW. UV–Vis (200–400 nm) spectrum in water was recorded by using Shimadzu UV-2101 PC, UV–VIS recording Spectrometer.

3. Computational details

All quantum chemistry calculations presented in this study were performed by using Gaussian 16 software [8] and GaussView 6 [9]. Potential energy surface (PES) scan with 2197 points by the rotation of two carboxyl groups and nitro group was performed semi-empirically at PM6 level. Optimized geometries for two monomeric and five dimeric forms were computed by using DFT B3LYP method with 6–311++G (d, p) basis set because this combination has been proven to be the most suitable in terms of accuracy and computational expense [10–14]. Vibrational characteristics for the lowest energy monomeric form of NTPA were calculated at the same level of theory. Fundamental vibrational modes corresponding to the harmonic frequencies were characterized by potential energy distribution (PED) analysis with the help of VEDA4 program [15] and visual representations of GaussView 6. Reactive site determination via Fukui function analysis was performed by using Multiwfn 3.3.9 [16]. The reduced density gradient (RDG) of the title molecule (monomer and dimer forms) are graphed by Multiwfn [16] and plotted by VMD program [17].

The UV–Vis spectra and related electronic properties of presented molecule for the gas phase and in water and ethanol solvent environment of the Polarizable Continuum Model (PCM) using the integral equation formalism variant (IEFPCM) were achieved by utilizing time-dependent DFT (TD-DFT) [18–20] method with B3LYP/6-311++G(d,p) method/basis set. Group contributions to molecular orbitals and molecular orbital interactions within those groups were analyzed by TDOS, PDOS, and OPDOS spectra obtained via GaussSum3.0 [21].

Non-covalent interactions were obtained mapping the reduced density gradient (RDG)

$$RDG(\boldsymbol{r}) = \left[1\Big/2\left(3\pi^2\right)^{1/3}\right]\Big/\left[|\nabla\rho(\boldsymbol{r})|\Big/\rho(\boldsymbol{r})^{4/3}\right]$$

onto the $\rho(\boldsymbol{r}).\mathrm{sign}(\lambda_2)$ quantity as suggested by Johnson et al. [22] using Multiwfn_3.3.6 [16]. Visualization of these interactions in a color coded pattern was produced in VMD [17] program.

Protein structure of hERa-LBD (Y537S) in complex with estradiol (pdb: 3uud) [23] was obtained from the Research Collaboratory for Structural Bioinformatics (RCSB) Protein Data Bank. The structure was cleared from water molecules and pre-existing ligand. The polar hydrogens and Kollman partial charges corresponding electrostatic potential using quantum mechanics were added in AutoDockTools [24] to assign appropriate ionization states for the amino acid residues. Submitted ligand structures were obtained from DFT calculations at the B3LYP 6-311++G(d,p) level of theory. Docking calculations were performed at two different platforms. Introductory binding affinity estimation was achieved by using Autodock Vina [25] with Lamarckian Generic Algorithm (LGA) at default settings. Advanced docking and post screening analysis of ligand-enzyme interactions are performed by using via iGEMDOCK graphical environment [26] on the basis of GEMDOCK (Generic Evolutionary Method for DOCKing Molecules) scoring function [27]. Accurate docking settings suggested by the program with the following setting; population size of 800, number of generations of 80, and number of solutions of 10 was used. During the calculations, the ligand intramolecular energies are excluded from total energy calculation. The visual representations of ligands in docked state were obtained via PyMol (Schrödinger, LLC, Cambridge, MA, USA) [28] interface. Residue based interaction profile for NTPA with hER-α was created in Discovery Studio 4.1 developed by Accelrys (Dassault Systemes, BIOVIA Corp., San Diego, CA, USA).

4. Results and discussion

4.1. Energy conformers

PES investigation by the rotation of two carboxyl groups and nitro group presented in Fig. 2 indicates that there are multiple possible conformations represented by the minima on black curve. However, the red curve gives more abstract view of more stable conformations. The left most and the right most minima are equivalent while the minimum at the middle is slightly at higher