

Full-dimensional Molecular Dynamics Simulation of Electronic Absorption Spectra of Ethyl 1,4-Dihydro-4-Oxoquinoline-3-Carboxylate and its 6-Fluoro and 8-Nitro Derivatives in Dimethyl Sulfoxide

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Abstract

A systematic and comparative theoretical study based on the DFTB+ and ZINDO methods has been performed on the set a of four recently prepared oxo-quinoline derivatives possessing a variety of biological activities. The main goal of this work was the computation of the vibrational broadening of absorption spectra using representative samples of molecular structures created by means of molecular dynamics simulations. Our simulations predicted the uniform distribution of solvent molecules over and under the plane of oxo-quinoline skeleton for all four model molecules solvated in dimethylsulfoxide. Although theoretical electronic energies of the transitions are underestimated, the shapes of the simulated absorption spectra are in good accordance with the experimental UV/Vis data. The employed technique can represent a useful and effective tool for spectra simulations and their deconvolution.

Keywords: Fluoroquinolones; Photosensitive drugs; DFTB; ZINDO; Molecular Dynamics

Introduction

1,4-Dihydro-4-oxoquinoline derivatives (4-quinolones) substituted at pyridone or benzene rings have received great attention due to their possible applications in medicine. They possess a variety of biological activities including antimicrobial, antiviral, antimycotic, antiprotozoal and antimalarial effects. Here, the specific position belongs to fluoro-substituted 1,4-dihydro-4-oxoquinoline-3-carboxylic acids (fluoroquinolones) due to their worldwide therapeutic application (Andersson and MacGowan 2003, Hooper and Wolfson 1989).

However, the photoexcitation of fluoroquinolone drugs results in the undesirable side effects: phototoxic and photoallergic responses caused predominantly by the production of Reactive Oxygen Species (ROS), as it has been confirmed previously *via in vitro* and *in vivo* experiments (Spooner et al. 1999). It was experimentally evidenced that UVA excitation of ethyl 1,4-dihydro-8-nitro-4-oxoquinoline-3-carboxylate (**QN**) in aerated (DMSO) led to the efficient activation of molecular oxygen. The generation of superoxide radical anion and singlet oxygen has been observed using Electron Paramagnetic Resonance Spectroscopy (Rimarčík et al. 2010)

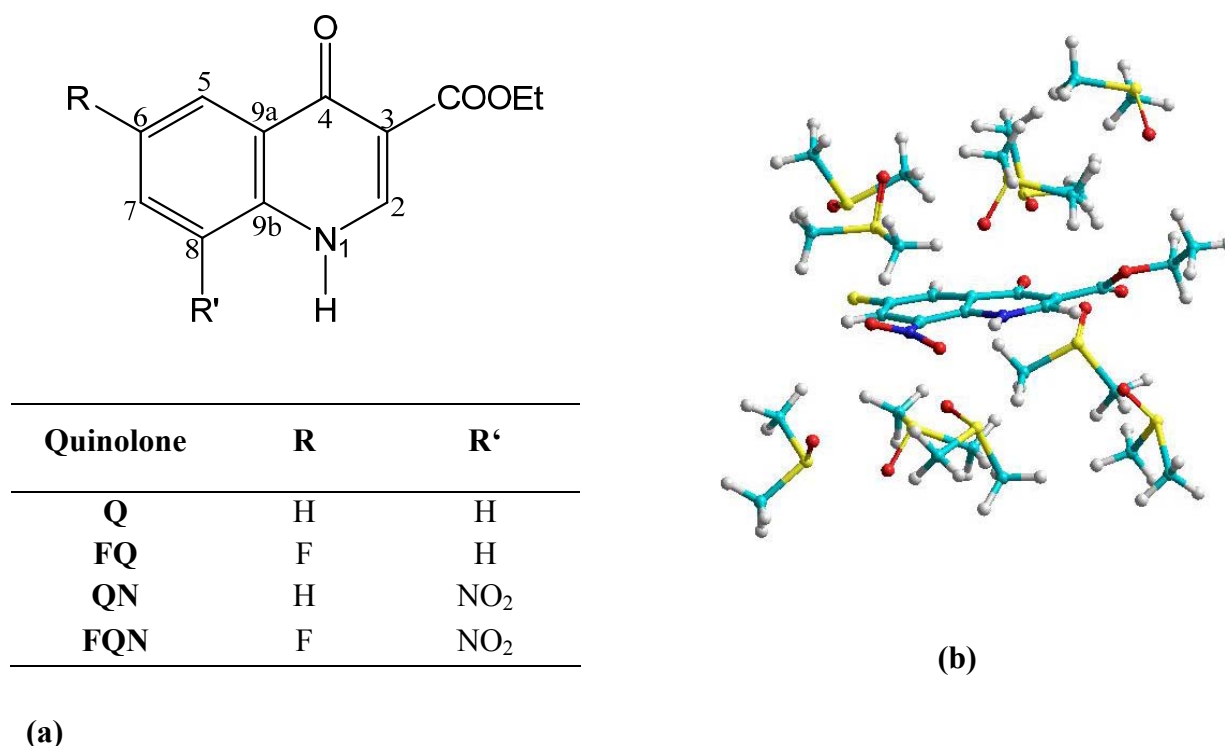


Fig. 1. Schematic structure, numbering and notation of studied molecules (a), the representative arrangement of ten DMSO molecules surrounding the **FQN** molecule (b).

To gain deeper insight into the effect of 4-oxoquinoline structure on the photo-physical properties, we focused on the quantum chemical calculations of model ethyl 1,4-dihydro-4-oxoquinoline-3-carboxylate and its 6-fluoro and 8-nitro derivatives (see Fig. 1) in the gas phase and polar aprotic solvent DMSO. Therefore, the picosecond molecular dynamics (MD) simulations will be performed using Tight Binding Density-Functional based method (DFTB+) (Elstner et al. 1998, Aradi et al. 2007). The UV/Vis spectra will be evaluated from the vertical electronic transitions which were calculated on the basis of the structures extracted from the MD.

The physical origin of the lowest electronic transition for the gas phase will be explained using molecular orbital analysis. Finally, the calculated electronic spectra will be compared with the experimental optical absorption spectra. Moreover, the applicability of the suggested combined MD approach with the inclusion of dispersion contributions will be discussed.

Calculation and experimental details

Calculation methods

The electronic ground state geometries of selected molecules were optimized using the DFTB+ approach. This method is comparable in its computational efficiency to the popular semi-empirical methods, e.g. AM1 or PM3, but it is based on Density Functional Theory instead of Hartree-Fock theory (Dewar and Thiel 1977). The classical molecular dynamics simulations based on the DFTB+ Hamiltonian have been carried out using the DFTB+ code with inclusion of dispersion interactions (Aradi et al. 2007). The Velocity-Verlet integration scheme (Verlet 1968) was used to integrate the equations of motion. Using one femtosecond time step, the dynamics run for 60 ps after the equilibration time of 20 ps. The temperature of 300 K was controlled by the Andersen thermostat (Andersen 1980).

Absorption electronic spectra for the model systems were simulated by the first sampling of the ground-state configuration space with an ensemble of thermally equilibrated nuclear geometries. The geometries used were generated by the above mentioned molecular dynamics simulations. The random geometrical points based on the normal distribution function (10000) were picked up after the MD thermostatization to sample the configuration space. For the selected geometries, the first forty ZINDO/S (Zerner's parametrization for Intermediate Neglect of Differential Overlap for Spectroscopy) (Zerner et al. 1980) vertical transition energies and oscillator strengths between the initial and final state were computed. These quantities were used to compute the Einstein coefficient for absorption. A gaussian broadening function was attributed to each transition having the non-vanishing height respectively to Einstein coefficient and with a phenomenological broadening constant of 0.05 eV. The sum of all Gaussian functions plotted against the transition energy gives a post Franck-Condon semi-classical approximation of the spectrum (Barbatti et al. 2006 and 2007). The semiempirical ZINDO calculations were performed using Gaussian 03 program package (Frisch et al. 2003).

UV/Vis experiments

The substituted 1,4-dihydro-4-oxoquinoline derivatives were synthesized and purified in our laboratory as described in Ref. (Černuchová et al. 2004). Quinolone structures and substituents characterization are summarized in Fig. 1. UV/Vis spectra of investigated quinolones in dimethylsulfoxide (DMSO; SeccoSolv[®] Merck) were recorded using a UV-3600 UV/Vis spectrometer (Shimadzu, Japan) with 1 cm square quartz cell.

Results and Discussion

The mutual effect of fluorine and nitro substituents on the structure of ethyl 1,4-dihydro-4-oxoquinoline-3-carboxylate (**Q**) primary affects the intramolecular distances. The optimal DFTB+ gas phase bond lengths in the two rings are compiled in Fig. 2. If we compare the optimal geometry of pristine **Q** molecule with the substituted derivatives, the presence of the weak electron-acceptor fluorine in position 6 or an strong electron-acceptor NO₂ group in position 8 have different effects. The fluorine atom added to the quinolone skeleton on the C₆ atom in **FQ** leads to a small elongation of the C₆–C₇ and C₆–C₅ bonds, by ca 0.001 Å. The presence of the strong electron-acceptor nitro group at the C₈ carbon in **QN** molecule leads to the elongation of C₇–C₈ (by 0.013 Å) and C₈–C_{9b} (by 0.015 Å) bonds. These geometrical changes are compensated with the significant shortening of the N₁–C_{9b} bond by 0.013 Å. As illustrated in Fig. 2, the combined effect of F and NO₂ substituents in **FQN** molecule has the strongest impact on the geometry changes in comparison with the non-substituted **Q** molecule.

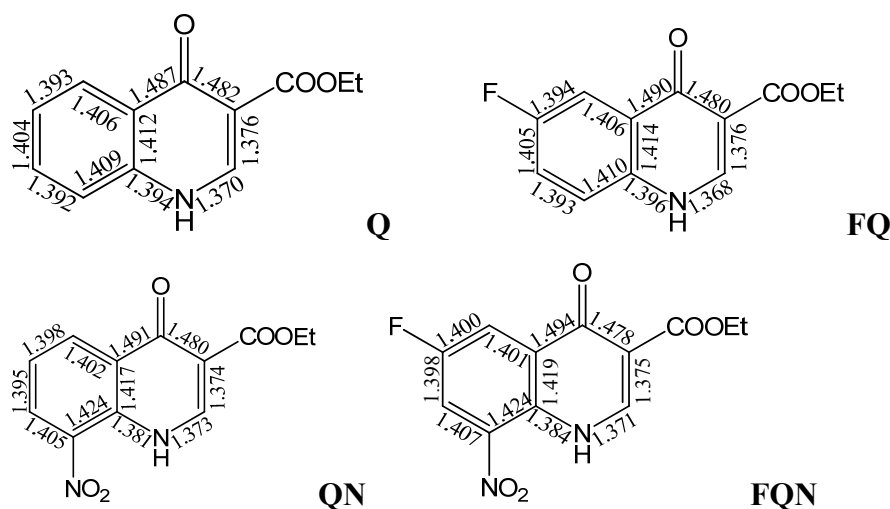


Fig. 2. DFTB+ gas-phase optimal structures of studied molecules. All distances are in Å.

The structural changes induced by the studied F or NO₂ groups are also reflected in the vertically excited singlet electronic states. The first ten calculated ZINDO//DFTB+ vertical transitions for the gas phase are compiled in Table 1. The lowest vertical excitation energy ($S_0 \rightarrow S_1$) starts at 2.32 and 2.34 eV for **FQN** and **QN** molecules, and at 2.93 and 2.95 eV for **FQ** and **Q** molecules, respectively. However, their oscillator strengths are negligible. The order of the optical transitions with a non-negligible oscillator strength is three for **Q** and **FQ** molecules and four for **QN** and **FQN** molecules. If we compare the energies of the first relevant transition ($f > 0$), the pristine molecule **Q** has the highest value of 4.05 eV. The fluorine substitution leads to a decrease in energy by 0.05 eV for **FQ**. On the other hand, the substitution with nitro group induces strong bathochromic effect. The decrease by 1.00 eV is predicted for **QN** and by 1.05 eV for **FQN**. The effect of substitution is also apparent in the further evaluated optical transitions. The first six vertical excitation energies with non-negligible oscillator strengths ($f > 0.03$) are depicted in Fig. 3.

Table 1 The first ten ZINDO//DFTB+ vertical excitation energies (in eV) and oscillator strengths f (in parentheses) for the studied molecules in gas phase

Molecule	Q	FQ	QN	FQN
1	2.95 (0.000)	2.93 (0.000)	2.34 (0.000)	2.32 (0.000)
2	3.53 (0.000)	3.52 (0.000)	2.71 (0.000)	2.70 (0.000)
3	4.05 (0.331)	4.00 (0.274)	2.92 (0.000)	2.90 (0.000)
4	4.15 (0.059)	4.07 (0.129)	3.05 (0.262)	3.00 (0.253)
5	4.80 (0.124)	4.75 (0.120)	3.51 (0.000)	3.50 (0.000)
6	5.06 (0.001)	5.07 (0.005)	3.82 (0.058)	3.84 (0.030)
7	5.11 (0.363)	5.10 (0.285)	4.17 (0.124)	4.14 (0.132)
8	5.33 (0.193)	5.31 (0.382)	4.39 (0.323)	4.35 (0.322)
9	5.45 (0.059)	5.41 (0.067)	4.57 (0.012)	4.48 (0.014)
10	5.59 (0.636)	5.61 (0.583)	4.63 (0.000)	4.62 (0.000)

For all studied molecules, the lowest energy transitions with non-negligible oscillator strengths are connected with the electron excitations from the Highest Occupied (HOMO) to the Lowest Unoccupied (LUMO) Molecular Orbitals. The delocalization of electrons within the oxo-quinoline moiety is also dependent on the present substituents. The chromophoric nitro group has a strong influence on the electron distribution. As it can be seen in Fig. 4, the HOMO and LUMO orbitals of **FQN** molecule are delocalized over the oxo-quinoline part. However, the lobes of the HOMO orbitals are spread over C5-C6-C7, C8-C9a-C9b, C2-C3-

C4, N1 and O4 atoms, whereas the LUMO orbitals are delocalized between C5, C7, C9b atoms and NO₂ group. The HOMO–LUMO transition has $\pi \rightarrow \pi^*$ character and it includes the electron transfer from the central part to NO₂ group. As illustrated in Fig. 4, further transitions are connected with higher unoccupied orbitals (LUMO+1, LUMO+2 and LUMO+4).

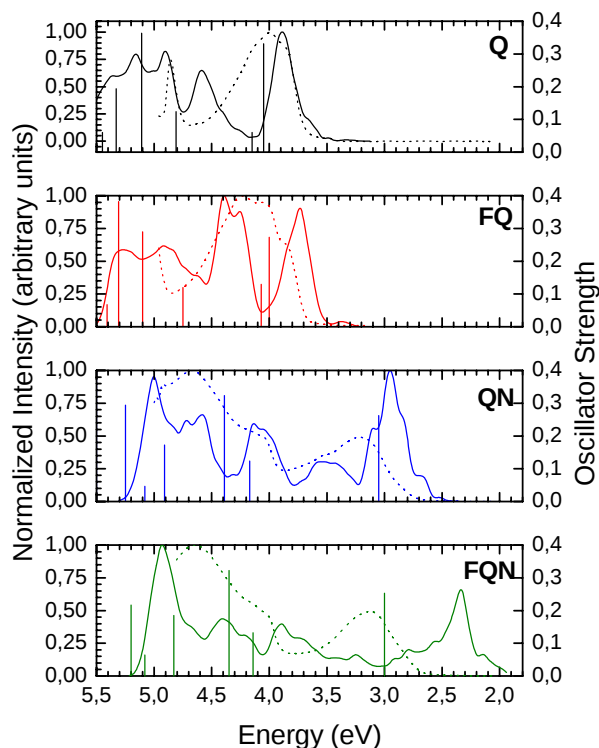
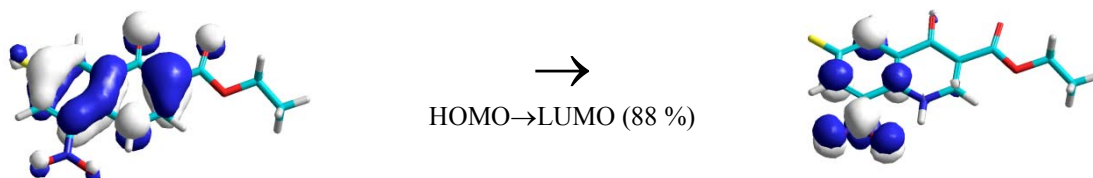


Fig. 3. UV/Vis experimental and simulated ZINDO//DFTB+-MD spectra of the studied molecules with 10 DMSO molecules. The ZINDO//DFTB+ vertical transitions for the gas phase molecule are depicted in the right y-axis (with their oscillator strengths). --- simulated spectrum, measured spectrum.

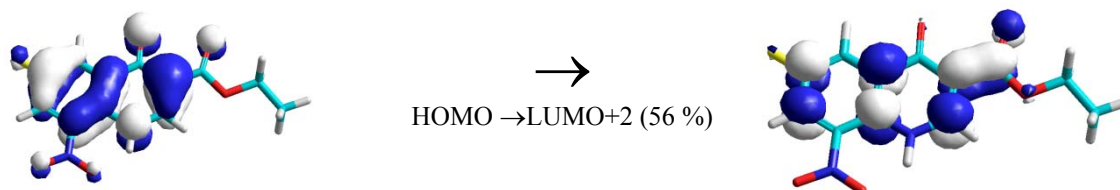
The quantum chemical calculations of the solvated molecules are restricted due to high computational demands. In this context, we have chosen the model with ten DMSO molecules. The molecular dynamics simulations performed after the thermostatzation period (20 ps) showed the uniform distribution of solvent molecules over and under the plane of oxo-quinolone skeleton for all four studied molecules. As it is depicted in Fig. 1b, for the evaluated snapshot of **FQN**...(DMSO)₁₀ with the lowest total DFTB+ energy, the resulting space orientation is affected by solvent-solute interactions and by mutual interactions between solvent molecules. The distribution of the distances evaluated for the selected pairs of atoms can help us to characterize the space distribution of DMSO molecules surrounding the individual solute molecule. They enable a rough estimation of the radii of solvation shells.

This might be demonstrated for N(1)...SO(CH₃)₂ distances. As it is shown in Fig. 5, the histogram for pristine **Q** molecule exhibits three well distinguished bands. The first band represents the accessibility of DMSO molecules to the N1 reaction center. The band is broad and it is located over the distances from 3.5 to 5.0 Å. The second broader band (corresponding to the first solvation shell radius) starts at the distance of 5.0 and ends at 6.7 Å. The last band is very small and it is located at 8.4 Å. This distance reflects the second solvation shell of the studied molecule. It seems that the interchange of the solvent molecules between the first and second solvation shell is restricted. The addition of the substituents, in general, shifts all three bands to lower distances. The first bands are shifted by about 0.5 Å comparing to **Q** molecule and their probabilities are decreased.

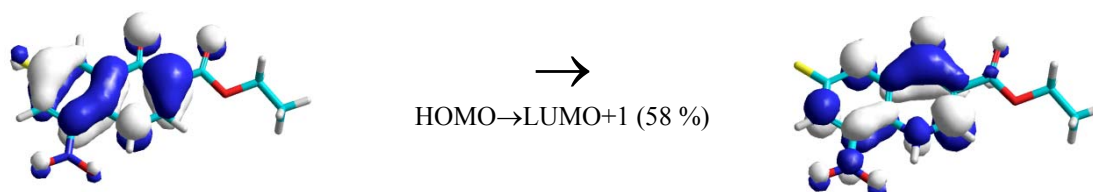
3.00 eV (0.253):



4.14 eV (0.132):



4.35 eV (0.322):



4.83 eV (0.185):

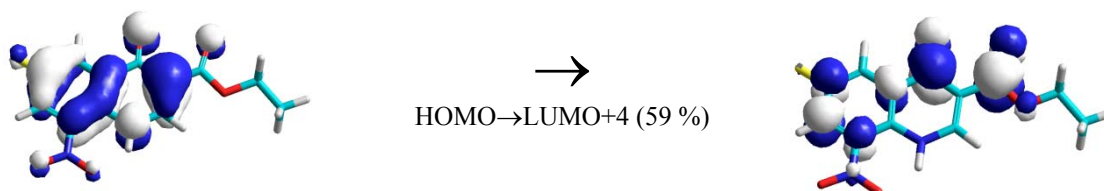


Fig. 4. Plots of the ZINDO molecular orbitals with significant contribution to the first four lowest energy transitions with oscillator strengths $f > 0.050$ for **FQN** molecule in gas phase for the optimal DFTB+ geometry. Oscillator strengths are in parentheses, percentages represent contributions of individual transitions for presented excitations.

The second bands are most populated and in the case of **QN** molecule it has the tendency to split-off. For **FQ** molecule, the presence of fluorine atom is reflected with the strong contraction of the second solvation shell. The maximum appears at 6.5 Å distance. The presence of NO₂ group in **QN** molecule has a minimal effect on the distances corresponding to the second solvation shell.

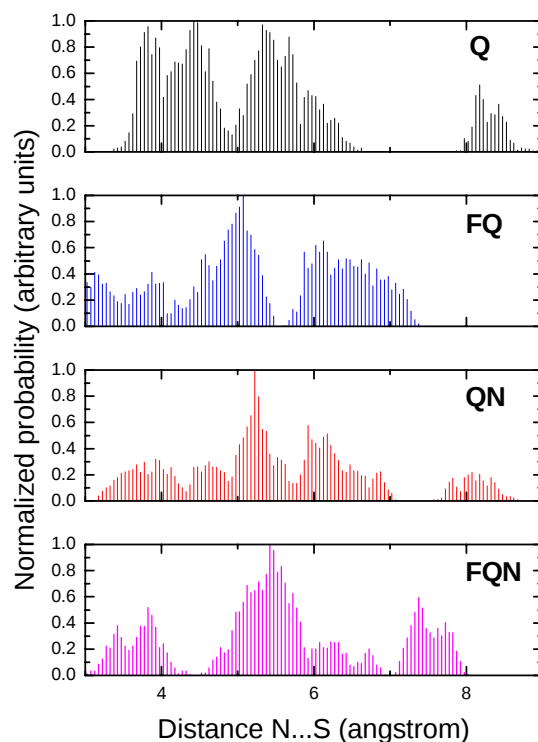


Fig. 5. The distribution of N(1)...SO(CH₃)₂ distances between the solvated molecule and solvent molecules.

The simulated absorption spectra for the studied systems based on MD geometries in DMSO are shown in Fig. 3 together with the experimental spectra measured in DMSO. The application of aprotic DMSO allows the sufficient solubility of the investigated quinolone derivatives. On the other hand, the strong absorption of radiation by DMSO above 250 nm (4.96 eV) limits the high energy threshold of experimental spectra to 4.76 eV (260 nm; Fig. 3). The general shape of theoretical spectra for **Q**, **FQ** and **FQN** within the investigated energy region (up to 5.5 eV) is in the agreement with the experimental ones. However, the ZINDO energies are shifted to lower values by 0.25 eV (**Q**), by 0.5 eV (**QN**) and by 0.8 to 1.0 eV (**FQN**). These shifts are related to the fact that the semiempirical methods do not take into

the account the nuclear repulsion from the Coulomb law. Therefore, in the case of the weak interaction, this parameterization has the dominant effect on the energetics of the solvent sensitive transitions. This artificial underestimation of the energy of the first band is more significant in the case of nitro derivatives. If we compare the width of obtained bands, the calculated bands are narrower by about 10 % in comparison with the experimental ones. This band narrowing originates in the thermostatzation of the molecule at the temperature of 300 K which produces cold vibration modes. The energies of these modes may be even below the zero point energy because of the classical trajectory approximation. In this situation, many geometrical points in the configuration space are artificially too close to the equilibrium structure. Despite the above mentioned problems, the theoretically evaluated bands give a clear picture how the experimental bands are composed. This information is very important for the possible deconvolution of experimental spectra.

Conclusions

A systematic and comparative theoretical study based on the DFTB+ and ZINDO methods has been performed for the set of four 4-oxo-quinoline derivatives. The DFTB+ calculations of optimized gas phase structures show the different effects of the weak electron acceptor fluorine and strong electron acceptor nitro group on the bond lengths within the 4-oxo-quinoline moiety. In this work, we have simulated the vibrational broadening of absorption spectra using representative samples of molecular structures created by means of molecular dynamics simulations. Molecular dynamics based on DFTB+ approach can help us to find the possible mutual orientations of the solute molecule with interacting DMSO molecules. After the thermostatzation period, the uniform distribution of solvent molecules above and under the plane of 4-oxo-quinoline skeleton for all four solvated molecules was observed. Depending on the molecular structure, the obtained theoretical absorption bands show more than three main peaks (maxima) in the region ranging from 1.8 to 5.5 eV. The intensity of the shoulder appearing at the lowest energies (long wavelengths) is significantly affected by the intermolecular interaction. Although too strong decrease in excitation energies in the presence of NO₂ group was observed, the general shapes of simulated absorption spectra are in accordance with the experimental results for **Q**, **FQ** and **QN** molecules, while **FQN** shows large deviations from experiment. Despite the above mentioned deficiencies, the

molecular dynamics based DFTB+ method combined with ZINDO Hamiltonian can represent a useful and effective technique applicable in spectra simulations and deconvolutions.

Acknowledgement

This study was financially supported by Scientific Grant Agency (VEGA Projects 1/0137/09, 1/0774/08, 1/0225/08 and 1/0018/09) and Research and Development Agency of the Slovak Republic (contracts Nos. APVV-0055-07, LPP 0230-09, SK-AT-0002-08 and SK-AT-0016-08) and by the Austrian Academic Exchange Service program Wissenschaftlich-Technische Zusammenarbeit Austria-Slovakia under contract No. ÖAD WTZ 11/2009.

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