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APPLICATION OF QUANTUM-CHEMICAL METHODS TO ESTIMATE THE CARCINOGENIC PROPERTIES OF BENZOPYRENE METABOLITES

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Benzo[a]pyrene is a common environmental pollutant and a powerful carcinogen that can accumulate in various organs and tissues, causing DNA damage through the adducts' formation, which contributes to the development of neoplasms of various localization. This compound carcinogenic activity is well studied and proven to be related to the nature and electronic configuration of biologically activated metabolites. Since not all metabolites of benzo[a]pyrene show carcinogenic effects, in this study an attempt to theoretically investigate their spectral properties and to use the obtained data in establishing a correlation with the observed carcinogenic effect was made. In order to study the spectroscopic properties of benzo[a]pyrene metabolites which, depending on the transformation pathways, can form products with different carcinogenic activity, the energies of the lower electronically excited states of metabolite molecules were calculated using the semi-empirical PM3 method (Hyper Chem 7.5). To determine the features of the electron density distribution during the molecules' excitation, we used the values of the occupancy of the highest occupied molecular orbital and the lowest unoccupied molecular orbital, which participate in one-electron transitions.
The calculation results of the position of the benzo[a]pyrene absorption spectra satisfactorily correlate with the experimental data presented in the literature, which is a confirmation of the obtained data reliability regarding the spectral characteristics of its metabolites. The performed calculations made it possible to determine the position of the long-wavelength absorption bands of some metabolites, for which experimental data have not been currently determined. It has been established that the long-wave bands in the absorption spectra of carcinogenic metabolites of benzo[a]pyrene in the number: BP → BP 7,8-epoxide → BP 7,8-dihydrodiol → BP 7,8-dihydrodiol-9,10-epoxide are equally intense and sequentially shifted to the short-wavelength region relative to the benzo[a]pyrene absorption spectra.

Key words: *quantum-chemical calculations, metabolites, carcinogenic activity, molecular orbital population.*

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ВИКОРИСТАННЯ КВАНТОВО-ХІМІЧНИХ МЕТОДІВ ДЛЯ ОЦІНКИ КАНЦЕРОГЕННИХ ВЛАСТИВОСТЕЙ МЕТАБОЛІТІВ БЕНЗОПІРЕНУ

І. В. Короткова, Т. П. Ромашко

Бензо[а]пірен є поширеним забруднювачем навколишнього середовища та потужним канцерогеном, який може накопичуватися в різних органах і тканинах, зумовлюючі пошкодження ДНК шляхом утворення аддуктів, що сприяє розвитку новоутворень різної локалізації. Канцерогенна активність цієї сполуки добре вивчена і доведено, що вона пов'язана з природою та електронної конфігурацією біологічно активних метаболітів. Оскільки не всі метаболіти бензо[а]пірену виявляють канцерогенну дію, в даній роботі зроблено спробу теоретично дослідити їх спектральні властивості та використати отримані дані у встановленні кореляції з спостережуваною канцерогенною дією. З метою дослідження спектроскопічних властивостей бензо[а]пірену, який залежно від шляхів метаболізму може утворювати продукти з різною канцерогенною активністю, виконано розрахунок енергій нижчих електронно-збуджених станів молекул метаболітів за допомогою напівемпіричного методу PM3 (Hyper Chem 7.5). Для встановлення особливостей розподілу електронної густини при збудженні молекул використовували значення заселеності найвищої зайнятої молекулярної орбіталі і найнижчої вакантної молекулярної орбіталі, які беруть участь в одноелектронних переходах. Результати розрахунку положення спектру поглинання бензо[а]пірену задовільно корелюють з наведеними в літературі експериментальними даними, що є підтвердженням достовірності отриманих даних щодо спектральних характеристик його метаболітів. Виконані розрахунки дозволили визначити положення довгохвильових смуг поглинання деяких метаболітів, для яких на теперішній час експериментальні дані не встановлені. Показано, що довгохвильові смуги в спектрах поглинання канцерогенних метаболітів бензо[а]пірену в ряді: BP →BP 7,8-epoxide → BP 7,8-dihydrodiol → BP 7,8-dihydrodiol-9,10-epoxide рівноінтенсивні і послідовно зміщені в короткохвильову область відносно спектру поглинання бензо[а]пірену.

Ключові слова: *квантово-хімічні розрахунки, метаболіти, канцерогенна активність, заселеність молекулярних орбіталей.*

Introduction

Benzopyrene is a representative polycyclic aromatic hydrocarbons (PAH) formed as a by-product in various thermal processes and founded in almost all environmental objects. The main anthropogenic source of benzo[a] pyrene (BP), such as other PAH, is industry. Natural sources include mainly forest fires, reactions of humus compounds under the influence of soil microorganisms leading to the coal or oil formation, as well as biosynthesis carried out by bacteria, algae and plants. But these processes generate a relatively small percentage of PAHs compared to the amount of anthropogenic origin PAHs (Styszko et al., 2023). Most of PAHs with a high molecular weight are a potential long-term danger to human and animal health due to their high mobility, the ability to disperse in the biosphere, and slowly destruction. In particular, BP is recognized as one of the genotoxic carcinogens, which contributes to the tumors' initiation in almost all living organisms (Yemele et al., 2024). In addition, BP causes the immunotoxic, teratogenic effects and induces the cell apoptosis and proliferation, as well as enhanced DNA methylation.

When PAHs entering the human, the different transformations under the enzyme systems effect take place. Among all carcinogenic substances, the BP metabolism is most studied and presented in a number of modern reviews (Jiang et al., 2007; Garcia et al., 2023; Kim et al., 2024). It has been established the biological action of BP begins with the metabolic activation, and the first stage – oxidation by cytochrome P-450 dependent oxygenases takes place in the endoplasmic reticulum (Bukowska et al., 2022). However, the carcinogenic derivatives are produce not on the all routes of BP metabolism. At the first stage, many different BP metabolites are generated, such as epoxides and phenols. Phenols, which can be enzymatically transformed into quinones, are mainly weak carcinogens, except the highly carcinogenic 2-hydroxy-BP. Other phenols, for example, 6-hydroxy-BP, demonstrate only strong toxic properties. Epoxides via the epoxide hydrolase action are converted into the corresponding dihydrodiols, which further oxidized to BP-7,8-diol-9,10-epoxide. This compound is the final reactive form which generate the bulky DNA adducts – carcinogenesis initiators.

Adduct formation is the result of covalent binding between reactive BP metabolites (electrophilic substances) and nucleophilic sites in DNA and proteins, and evidence of these substances carcinogenic potential. Covalent DNA adducts formation in the presence of BP has long been used as a biomarker. The main adduct responsible for carcinogenesis is formed as a result of BP 7,8-dihydrodiol-9,10-epoxide transformations, the most mutagenic of the four possible enantiomers, and the N_2 position of guanine in the DNA structure was determined to be the best position for adduction (Madeen et al., 2019).

Ewa B. & Danuta M.Š. (2017) reported the biological activity of these compounds is related to their structural features, which affect the electron density distribution and, indirectly, the certain positions reactivity of the condensed system. Now, a number of biomonitoring methods have been developed to assess the BP and its metabolites effect on the human organism (Louro et al., 2022).

Take into account the ability of BP adducts with DNA and BP metabolites to fluorescence, the spectral-luminescence methods are widely used for their determination (Fan et al., 2018), and the synchronous scanning fluorescence method have a great importance among it (Zhang et al., 2015). Method provides the recording fluorescence spectra by simultaneously scanning excitation and emission wavelengths at the same speed (synchronously) and, maintaining a constant difference between the emission and the excitation wavelength (Silveira & Barbeira, 2022). This method allows the determination of relatively low adducts concentrations and separate their fluorescence spectra.

Despite remarkable progress in modern analytical methods, none of them can be recommended as the most informative and perfect to determination of DNA adducts or BP metabolites. Although experimental studies have a clear priority, the role of theoretical research is quite important for to obtain data which extremely difficult to determine experimentally.

In many cases, the studied systems parameters are easier to calculate using quantum chemistry methods, than to determine them based on a large set of experimental data. In this work, a quantum-chemical study of the BP metabolites spectral characteristics was carried out for the predicting their carcinogenic nature and to determine the absorption bands position of those metabolites for which there are no experimental data.

Material and Methods

To theoretically evaluate the carcinogenic properties of benzpyrene metabolites, a number of model compounds were created: 3,4-benzpyrene (BP), 4,5-benzpyrene (4,5-BP) and products of 3,4-benzpyrene metabolism:

1) 6-hydroxy-BP (6-OH-BP), 4,5-dihydrodiol-BP (4,5-BPD), 9,10-dihydrodiol- BP (9,10-BPD) are weak carcinogens;

2) 2-hydroxy-BP (2-OH-BP), BP 7,8-epoxide, BP (+)7,8-dihydrodiol, BP (–)7,8-dihydrodiol, BP (–)7,8-dihydrodiol-9,10-epoxide-1 (BPDE-1), BP (+)7,8-dihydrodiol-9,10-epoxide-2 (BPDE-2) are highly carcinogenic compounds.

Quantum-chemical calculations of energy parameters (energy of lowest electronic-excited states (singlet and triplet, Sππ* and Tππ*), oscillator strengths (f), configurational interaction coefficients (Ck)) of the studied compounds were performed in the frames of semi-empirical PM3 procedure using the HyperChem 7.5 program package (Young, 2001). Geometry of molecules have been optimized, taking into account the interaction of 15 once-excited electronic configurations of the ππ*-type 15 HOMO x 15 LUMO (where HOMO is the highest occupied molecular orbital, LUMO – lowest unoccupied molecular orbital).

In many computational studies, the semi-empirical PM3 method is most commonly used to calculate of organic systems, despite many limitations and inaccuracies. PM3 method on average predicts the energies and lengths bond' more accurately than AM1 or MNDO methods, what determines the main advantage of this method (Thiel, 2014; Christensen et al., 2016). We have previously shown the bond length with heteroatom in the chromophore fragment has a significant influence on the relative position of the energy levels of the lowest electronic-excited states and, as a consequence, on the molecules' spectral-luminescent properties (Sakhno & Korotkova, 1999; Sakhno et al., 2002). This determined the choice of calculation method the energy parameters of the studied systems.

Results and Discussion

Figure 1 fragmentary shows the diol epoxides formation from BP (Hecht & Hochalter, 2014), which are causes of the BP carcinogenic effect. The ability of BP dihydrodiols to initiate tumor formation has been established experimentally. It has been founded the carcinogenic effect

as BP (–)7,8-dihydrodiol as BP is almost the same. Other dihydrodiols – 4,5- and 9,10-dihydrodiols has much less activity than BP 7,8-dihydrodiols. When testing the enantiomers of BP 7,8-dihydrodiol, the (–) enantiomer was found to be more active relative with the (+) enantiomer (Rubin, 2021.

The strongest carcinogenic activity among all BP metabolites was found in its final metabolite 7,8-dihydrodiol-9,10-epoxide (7,8-BPDE), which can exist in the four enantiomer forms. It has been established that (+)7,8-dihydrodiol-9,10-epoxide-2 is more ~ 60% active tumor initiator compared to other enantiomers, i.e. BPDE-2 is the main BP carcinogenic metabolites (Fischer et al., 2018).

Table 1 presents the calculation results of electron-excited states of BP and its metabolites: phenols and diols by the PM3 method. As follows from the presented data, the lowest singlet states of the ππ*-type in the molecules of carcinogenic compounds are formed as a result of a one-electron transition from the highest occupied molecular orbital (HOMO) to the lowest unoccupied molecular orbital (LUMO) with a sizeable oscillator strength. The main role in the S2 state belongs by two electronic configurations.

Thus, in the phenol molecule 2-OH-BP, which has carcinogenic properties, the long-wave transition from HOMO to LUMO (49→50) is presented by an intense band (f=0.27) of 22753 cm^{-1} region. It should be noted the location proximity of this band to the BP absorption band (22814 cm-1). The formation of the second singlet state occurs due to two-electron transitions from 49→51 and 48→50 molecular orbitals (MO) with a small oscillator strength (f=0.07).

Carcinogenic phenol 2-OH-BP formation during the BP metabolism has almost no effect on the lowest singlet level position, but with the 6-OH-BP formation, which characterized only by toxic properties, the lowest singlet level energy decreases by ≈ 800 cm^{-1}. The value of energy singlet-triplet split (ES-T) of the ππ* levels in these compounds molecules is almost the same (12500 cm^{-1}). The energy of the lowest electronic-excited states in the dihydrodiols (4,5-BPD and 9,10-BPD) molecules with a moderate carcinogenic effect, also decreases relative to the carcinogenic BP: the energy of singlet levels – by 472 and 620 cm^{-1}, and triplet levels – by 906 and 336 cm^{-1}, respectively. The value of the Sππ* and Tππ* energy gap in these metabolites molecules also does not change (≈ 12500 cm^{-1}).

However, the highly carcinogenic BP 7,8-dihydrodiol formation leads to an increase in the energy of the lower singlet level on 410 cm^{-1}. The long-wavelength transitions in dihydrodiols molecules of 4,5-BPD and 9,10-BPD are represented by an intense bands (f=0.43) at 22342 and 22194 cm^{-1}, respectively, due to a one-electron transitions with 52→53 MO. This transition in the molecule of carcinogenic BP 7,8-dihydrodiol is presented by a band of the same intensity

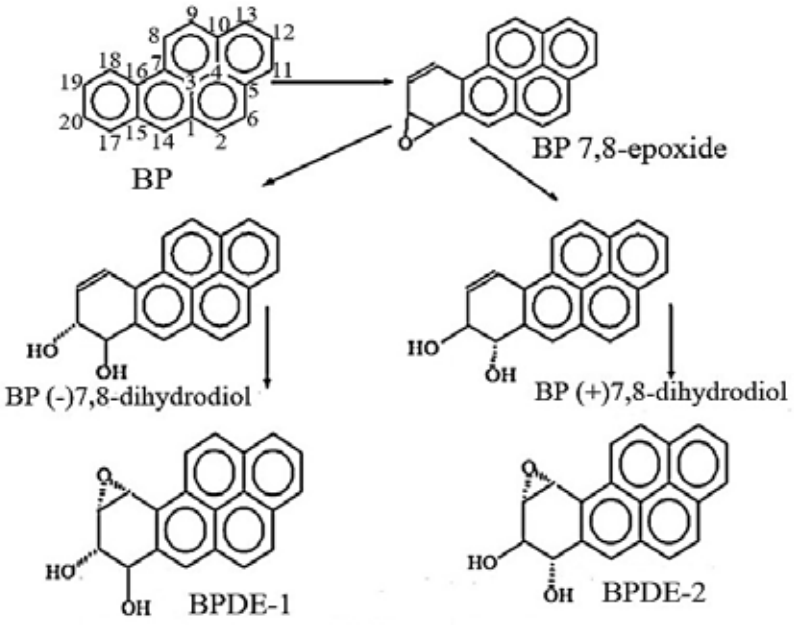

Fig. 1. Formation of benzopyrene carcinogenic metabolites

Table 1

PM3 analysis of the lowest energy transitions of BP molecule and its metabolites

Molecule	**State**	**E, cm^{-1}**	$\psi_N \rightarrow \psi^*_N$	$C_к$	**f**
BP	$S_1(\pi\pi^*)$	22814	46→47	0,61	0,40
	$S_2(\pi\pi^*)$	23212	46→48	-0,48	0,0025
			45→47	0,44	
	$T_1(\pi\pi^*)$	10291	46→47	0,61	
	$T_2(\pi\pi^*)$	17732	46→49	0,37	
			44→47	-0,33	
4,5-BP	$S_1(\pi\pi^*)$	24786	46→48	-0,46	0,0005
			45→47	-0,43	
	$S_2(\pi\pi^*)$	25174	46→47	0,52	0,11
			45→48	-0,38	
	$T_1(\pi\pi^*)$	13800	46→47	0,54	
	$T_2(\pi\pi^*)$	19754	46→50	-0,34	
			43→47	-0,31	
2-OH-BP	$S_1(\pi\pi^*)$	22753	49→50	0,54	0,27
	$S_2(\pi\pi^*)$	22897	49→51	-0,41	0,07
			48→50	0,42	
	$T_1(\pi\pi^*)$	10457	49→50	0,61	
	$T_2(\pi\pi^*)$				
6-OH-BP	$S_1(\pi\pi^*)$	22018	49→50	0,62	0,46
	$S_2(\pi\pi^*)$	22631	49→51	0,52	0,039
			48→50	-0,38	
	$T_1(\pi\pi^*)$	9461	49→50	0,62	
	$T_2(\pi\pi^*)$	17376	49→52	0,36	
			47→50	0,32	
4,5-BPD	$S_1(\pi\pi^*)$	22342	52→53	0,62	0,43
	$S_2(\pi\pi^*)$	23027	52→54	0,49	0,018
			51→53	-0,41	
	$T_1(\pi\pi^*)$	9385	52→53	-0,59	
	$T_2(\pi\pi^*)$	16095	50→53	0,34	
9,10-BPD	$S_1(\pi\pi^*)$	22194	52→53	-0,60	0,43
	$S_2(\pi\pi^*)$	22668	52→54	-0,49	0,016
				0,37	
	$T_1(\pi\pi^*)$	9955	52→53	-0,61	
	$T_2(\pi\pi^*)$	15719	52→53	-0,39	

(f=0.48), shifted to the short-wavelength region by ≈ 950 cm^{-1}.

Known, benzopyrene molecule has five benzene rings, and can exist in two isomeric forms exhibits different biological activity. Depending on the place of the fifth benzene ring attachment, isomers benzo[a]pyrene or 3,4-benzpyrene, which has characteristic carcinogenic properties, and benzo[e]pyrene or 4,5-benzpyrene with a weak carcinogen activity are distinguished (Mokrzyński et al., 2023).

The calculation results showed the absorption spectra of 4,5-BP is shifted to the long-wave region relative to the BP spectra by 2360 cm^{-1} and represented by a moderate intensity band (f=0.11), formed as a result of the electron transition from 46→47 MO, as in the BP spectra, but this band intensity in the BP spectra is significantly greater (f=0.40). The calculated position of the BP absorption spectra correlates with the experimental data presented by Han et al., (2023) with a correction for the solvent influence, since theoretical calculations describe the molecule in a vacuum.

To establish the features of the electron density distribution at the molecule's excitation, the population values of highest occupied molecular orbital (HOMO) and lowest unoccupied molecular orbital (LUMO) participating in once-electron transitions were used. This criterion we used in a number of previously studies to explain the spectral properties changes of heteroatomic molecules caused by the external factors effect (Korotkova et al., 1997; Sakhno & Korotkova, 1999). Molecular orbitals included in the main ππ*-type configurations are presented in Table 2. Since ππ*-type orbital has one component

(i=z), the Table 2 shows only d_β values of p_z-component of MO.

The excitation degree of the base molecule orbitals upon the introduction of one or two –OH groups was determined by the squares of the coefficient of MO expansion in the atomic orbitals (AO) studied compounds values. It was established that the introduction of the –OH group in the C2 position of the benzopyrene molecule does not significantly affect d_β^2 value. That is, if in BP molecule d_β^2 =0,038, then in 2-OH-BP d_β^2 = 0,021, which agreement with insufficient changes in the long-wave transitions location in these compounds' absorption spectra. However, when introduce an –OH group into C6 position (6-OH-BP), d_β^2 value increases almost threefold, which can serve as an explanation for the change of the lowest singlet level position compared to the BP molecule.

A comparison of the d_β^2 coefficients on the carbon atoms connected with –OH groups is confirms the established correlation: d_β^2 on the C2 atom in the molecule of carcinogenic phenol 2-OH-BP decreases by 1.1-fold compared to the BP molecule, and on the C6 atom in 6-OH-BP molecule with weak carcinogenicity increases by 1.2-fold.

Dihydrodiols generation, which have weakly expressed carcinogenic properties, that is, the introduction of two –OH groups, leads to a shift in the absorption spectra to the long-wave region relative to the BP spectra (Table 1). The obtained correlations cannot be explained by once-directional changes in the d_β^2 coefficients on carbon atoms bonded to –OH groups. Comparison d_β^2 values in the 4,5-BPD molecule showed an increase by almost 5-fold on C4 in the absence of significant changes on the C5 atom relative to BP molecule. In 9,10-BPD dihydrodiol molecule, d_β^2 value on C9 atom practically did not change, while on C10 it decreased by 1.8-fold.

Most active carcinogenic metabolites of BP, presented in the Scheme, occur from diol-epoxides. The energies of these compound's lowest electronic-excited states, derived from our PM3 computations, shown in Table 3.

Table 2

Computed structure of the main molecular orbitals involved in the lowest electronic-excited states of BP metabolites

№ atom	**BP**		**2-OH-BP**		**6-OH-BP**		**4,5-BPD**		**9,10-BPD**	
	ψ_{46}	ψ_{47}	ψ_{49}	ψ_{50}	ψ_{49}	ψ_{50}	ψ_{52}	ψ_{53}	ψ_{52}	ψ_{53}
1.	0,220	0,216	0,219	0,216	-0,260	-0,206	-0,195	0,212	0,213	-0,225
2.	-0,269	0,266	-0,260	0,274	0,252	-0,249	0,336	0,259	-0,246	-0,265
3.	-0,129	0,129	-0,135	0,128	0,115	-0,123	0,082	0,133	-0,140	-0,120
4.	0,019	0,019	0,033	0,009	-0,021	-0,014	-0,043	0,018	0,012	-0,023
5.	0,224	-0,223	0,209	-0,237	-0,202	0,209	-0,192	-0,224	0,207	0,216
6.	-0,260	-0,260	-0,263	-0,259	0,285	0,239	0,333	-0,252	-0,239	0,268
7.	-0,270	-0,270	-0,289	0,257	0,301	0,255	0,241	-0,270	-0,263	0,280
8.	0,195	-0,195	0,179	-0,206	-0,178	0,187	-0,170	-0,193	0,175	0,184
9.	0,289	0,291	0,301	0,282	-0,297	-0,274	-0,249	0,288	0,283	-0,282
10.	-0,091	0,089	-0,065	0,106	0,085	-0,085	0,095	0,086	-0,068	-0,091
11.	0,292	0,294	0,277	0,298	-0,297	-0,271	-0,291	0,292	0,267	-0,292
12.	-0,068	0,069	-0,069	0,080	0,059	-0,065	0,048	0,074	-0,071	-0,064
13.	-0,315	-0,317	-0,330	-0,305	0,315	0,293	0,299	-0,316	-0,290	0,313
14.	0,412	0,413	0,409	-0,416	-0,383	0,427	0,391	-0,411	0,393	0,409
15.	0,029	-0,030	-0,024	-0,034	-0,049	0,083	0,024	-0,031	-0,055	0,037
16.	-0,184	0,188	-0,174	0,194	0,164	-0,195	0,182	0,187	-0,143	-0,189
17.	-0,232	0,233	-0,237	0,230	-0,192	-0,264	0,209	0,233	-0,269	0,238
18.	0,179	0,177	0,191	0,169	-0,155	-0,204	-0,154	0,177	0,235	-0,185
19.	0,233	-0,226	0,222	-0,226	-0,180	0,254	0,205	-0,226	0,289	0,215
20.	-0,078	-0,076	-0,088	-0,069	0,092	0,079	0,066	-0,075	-0,049	0,085
			0,038	-0,029	0,214	-0,151	-0,167	-0,090	-0,130	0,066
							-0,167	0,088	-0,150	-0,070

Note: β *– is the atomic index;* $d_\beta(p_z)$ *– is the coefficient of MO expansion in the atomic orbitals (AO)*

Table 3

Energies of the lowest electronic-excited states, oscillator strengths of transitions in molecules of carcinogenic BP metabolites obtained by PM3 method

Molecule	$S_{\pi\pi^*}$	**f**	$T_{\pi\pi^*}$
BP	22814	0,41	10291
BP 7,8-epoxide	23000	0,002	10909
BP (–)7,8-dihydrodiol	23224	0,48	11184
BP (+)7,8-dihydrodiol	23229 23696	0,49 0,001	11157 17323
BPDE-2	24258	0,003	12234
BPDE-1	24273	0,008	12302

On the basis of our computation results, we can conclude that the long-wave bands in the absorption spectra of carcinogenic metabolites of BP are consistently shifted to the short-wave region, which is explained by a decreasing the longer a conjugated chain and the introduction of a heteroatom.

Conclusions

The PM3 calculations reported in this work have been performed using the Hyper Chem 7.5 program. We have performed calculations of the relative positions of the lowest electronic-excited states of 3,4-benzopyrene, its metabolites and its isomeric form for predicting carcinogenicity. It was established the decrease in the energy of the lower singlet level in molecules of non-carcinogenic compounds correlates with an increase in d_{β}^2 the coefficient on p_z-AO. In the absorption spectra of carcinogenic BP metabolites, the long-wavelength bands are of equal intensity and consistently shifted to the short-wavelength region relative to the BP spectra.

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