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Density Functional Theory Study of Semiquinone Radical Anions of Polychlorinated Biphenyls in the Syn- and Anti-like Conformation

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Abstract

Polychlorinated biphenyls can be metabolized to reactive metabolites, such as PCB semiquinone radical anions ($SQ^{\bullet-}$), whose structure and role in PCB-induced toxicity are difficult to investigate due to their relative instability. The unrestricted UB3LYP/6-311G** method was used to investigate several molecular descriptors of the syn- and anti-like conformation of $SQs^{\bullet-}$. The bond lengths and angles of the quinone moiety of the $SQs^{\bullet-}$ were in between the values reported for PCB quinones and hydroquinones, which is consistent with the distribution of the α -HOMO. The dihedral angles between the two ring systems increased in the presence of *ortho* chlorine substituents and were smaller compared to the corresponding PCB quinones. The ground state energies indicate that the anti-like conformation of the $SQs^{\bullet-}$ is more favorable than the syn-like conformation. Molecular descriptor used for modeling of quantitative structure-activity relationships displayed some dependence on the conformation. These findings suggest that $SQs^{\bullet-}$ in both the syn- and anti-like conformation may interact differently with target molecules, which may have implications for the toxicity of PCBs.

Keywords

Environmental contaminants; PCB quinones; dihedral angle; molecular structure; density functional theory

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Supporting Information

Bond lengths and bond angles calculated at the UB3LYP/6-311G** level of theory for PCB quinones (Q) and the corresponding semiquinone radicals ($SQ^{\bullet-}$); Mulliken atomic spin densities in semiquinone radical anions; linear polarizabilities, first order hyperpolarizabilities and octupole moments. This material is available free of charge via the Internet at <http://pubs.acs.org>.

Introduction

Polychlorinated biphenyls (PCBs) are abundant and persistent environmental pollutants. PCBs were used, for example, as coolants, lubricants, stabilizing additives in flexible PVC coatings of electrical wiring, electronic components, and are still in use as dielectric fluids in transformers and capacitors.^{1,2} Although the production of PCBs was banned in the 1970s due to environmental and human health concerns, recent studies demonstrate that PCBs are formed inadvertently as byproducts of industrial processes and can be found as byproducts in paints.³ Environmental monitoring studies also demonstrate that environmental PCB levels, for example in the Great Lakes, have only slowly decreased over the past decade.⁴ As a result, exposure to PCBs still represents a human health hazard that has been associated with multiple diseases including cancer, heart disease, developmental neurotoxicity and immunotoxicity.^{1,2}

PCB congeners with a low degree of chlorination are readily metabolized by mammalian cytochrome P450 enzymes to hydroxylated metabolites (OH-PCBs).^{5,6} The OH-PCBs can be conjugated by glucuronosyltransferases⁷ or sulfotransferases⁸ to facilitate their excretion as the corresponding glucuronide or sulfate, or are further oxidized by cytochrome P450 enzymes to form dihydroxylated PCB metabolites.^{9,10} These dihydroxylated PCBs may undergo autooxidation or enzymatic oxidation to reactive *ortho* or *para* PCB quinones.^{9,11} *In vitro* studies have shown that PCB quinones may cause Arylhydrocarbon receptor (AhR)-mediated toxicity¹² and inactivate topoisomerases.^{13–15} They readily react with glutathione^{9,15,16} and other cellular target molecules, including DNA.^{9,17} PCB quinones can redox-cycle and, thus, contribute to the production of reactive oxygen species *in vitro* and in cells in culture.^{11,18,19} *In vivo* studies demonstrate that PCB quinones play a role in the carcinogenicity of lower chlorinated PCB by displaying initiating activity in the resistant hepatocyte model.²⁰

Although PCB quinones themselves are reactive and toxic species, they can also undergo one electron reductions by both enzymatic and spontaneous reduction processes to form PCB semiquinone anion radicals ($SQ^{\bullet-}$).^{11,18} $SQs^{\bullet-}$ can also be formed by one electron oxidation of the corresponding dihydroxylated PCB metabolites.^{11,21} These $SQs^{\bullet-}$ have been implicated in the toxicity of PCBs and their quinone metabolites;^{11,16–18,21} however, little is known about the structure and reactivity of $SQs^{\bullet-}$, and few studies have investigated the role of PCB quinones versus PCB $SQs^{\bullet-}$ in the toxicity of PCB metabolites. $SQs^{\bullet-}$ are relatively unstable and can only be generated *in situ*, for example by one-electron reduction of PCB quinones in high pH buffers, by one-electron reduction with Xanthine oxidase, or via a comproportionation reaction of the PCB quinone and hydroquinone.¹¹ Therefore, it is difficult to investigate the molecular structure of $SQs^{\bullet-}$ and their interaction with potential target molecules in the laboratory.

Density functional theory (DFT) studies are frequently employed to examine the effect of the one electron reduction of quinones on the molecular geometry and electronic properties of the resulting $SQs^{\bullet-}$.^{22–33} In addition, the structure of the highest occupied molecular orbital (HOMO), the lowest unoccupied molecular orbital (LUMO) and the spin densities are commonly used molecular descriptors in relating structure of PCB congeners with their reactivity.³⁴ Modeling QSARs using dispersion interactions between environmental contaminants and receptors has also gained immense attention. In particular, the stacking interaction model developed by McKinney et al.³⁵ has been widely used to study receptor binding interactions with PCBs using DFT-derived descriptors of isolated molecules, such as polarizabilities and multipole moments.³⁶ Despite extensive studies of the mechanisms of toxicity of PCB quinones and $SQs^{\bullet-}$, the $SQs^{\bullet-}$ under consideration in the present study have never been investigated with regards to developing QSARs.

In the present study, we determine selected molecular descriptors for a series of PCB SQs^{•-} and the corresponding quinones in both the syn- and anti-like conformation and use the optimized geometries and the calculated descriptors to evaluate the robustness of QSAR models developed by other groups.³⁶ These computational studies not only contribute to our understanding of molecular structure of SQs^{•-}, but also provide fundamental insights into the role of SQs^{•-} in the toxicity of PCBs.

Experimental Section

Computational Details

The PCB quinone and semiquinone radical structures were built in Argus Lab 4.0.³⁷ The quinone structures were assigned a singlet ground state and a molecular charge of zero while doublet ground state and a charge of -1 was assigned to the radical structures. After the initial geometry optimization using the AM1 method in ArgusLab, these structures were re-optimized at the UB3LYP/6-311G** levels of theory using Gaussian 03,³⁸ followed by vibrational frequency calculations to ascertain the stability of the geometric structures based on the absence of any imaginary frequencies. All parametric entities provided in this study, viz. single point energies, HOMO/LUMO energies and atomic spin densities were calculated using the UB3LYP/6-311G** method. The molecular orbitals were generated using the cubegen utility of Gaussian 09 package.³⁸ The resulting geometric and electronic structures were visualized using Argus Lab³⁷ and Gabedit 2.2,³⁹ respectively. The mean of linear polarizabilities, first order hyper polarizabilities and octupole moments were calculated at the same level of theory using the keyword 'Polar'. The mean of linear polarizability ($\bar{\alpha}$) and polarizability anisotropy ($\Delta\alpha$) were calculated using the expressions provided by Gu et al.:³⁶

$$\bar{\alpha} = \frac{1}{3}(\alpha_{xx} + \alpha_{yy} + \alpha_{zz})$$

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

Total first order hyperpolarizability (β) was calculated from its individual components as follows:^{40,41}

$$\beta = [(\beta_{xxx} + \beta_{xyy} + \beta_{xzz})^2 + (\beta_{yyy} + \beta_{yzz} + \beta_{yxx})^2 + (\beta_{zzz} + \beta_{zxx} + \beta_{zyy})^2]^{1/2}$$

All of the Gaussian calculations were performed on an Intel Xeon based IBM HS21 blade cluster of University of Kentucky high performance computing facility. All computations were performed for isolated molecules in vacuum.

Results and Discussion

Molecular Geometry of PCB Semiquinone Radical Anions

The B3LYP method uses a hybrid functional which favorably balances the tendency of Hartree-Fock (HF) calculations to overestimate localization of electrons and of DFT to overestimate delocalization in organic cations with two nitrogen redox centers (which are

electronically similar to semiquinones⁴²), as discussed by Kaupp et al.⁴³ Kaupp and coworkers have shown that refined hybrid functionals with increased HF exchange contributions or with local mixing functions give somewhat more precise predictions (e.g., 5–10% differences in predicted polarizabilities) for organic mixed-valence compounds,^{43–45} but the (U)B3LYP method has been widely used for (semi)quinones^{22,24–29}. The B3LYP functional has been used to predict geometries,²⁹ electron affinities,^{24,46} and hyperfine coupling constants^{26,31} consistent with experiment observations of semiquinone compounds. When comparisons have been made between functionals, UB3LYP has been shown to predict g-tensors comparable or superior to UBP86 (which was previously shown to perform well^{30,33}) and UBPE0.^{31,32} For electron affinity calculations, B3LYP has been shown to be superior to HF for a set of naturally occurring quinone metabolites,²³ and comparable but intermediate between BLYP and BHLYP for a set of benzo-, naphtho- and anthra-quinones.²⁴ Based on this survey of prior work, B3LYP was selected as the DFT method for the present study.

In our own studies, we have recently shown that the unrestricted UB3LYP/6-311G** method provides a good approximation of the molecular structure of the PCB quinones shown in Figure 1.⁴⁷ Here we employ the same computational approach to investigate the molecular structure of the corresponding SQs^{•−} in comparison to the structure of the parent PCB quinones. The choice of basis set is justified because aside from the work of Witwicki et al.^{30–33} (which was geared specifically towards prediction of EPR parameters) all prior reports of DFT calculations of semiquinones used basis sets of double zeta quality and above, as originally recommended by O'Malley and Collins.²⁶ Satisfactory results were reported with 6-31G*,^{23,25,27} 6-311G**^{22,29,46} or 6-311G(2d,p)²⁸. Recently, Frontana et al. reported that improved correlations with experimental redox potentials can be found for semiquinones when diffuse functions are added to the 6-31G** basis set,²⁴ so additional calculations were performed for comparison using the 6-311++G** basis set for the 2'-Cl-2,5-(S)Q and 2',5',-Cl-2,5-(S)Q systems. Calculations were performed for the syn- and anti-like conformation of quinones with an unsymmetrical substitution pattern in the phenyl ring (Figure 2). Overall, the bond lengths and bond angles of the syn and anti-like conformation of the SQs^{•−} were comparable and, if not mentioned otherwise, only the data for the syn-like conformation are discussed below (Tables 1 and 2; the corresponding data for the anti-like conformation are presented in Tables S1-S2).

Bond length predictions

The two C-O bond distances (i.e., C2-O2 and C5-O5) increased by 0.039 to 0.041 Å due to the one electron reduction (Table 1). Only 3,4',6-Cl-2,5-Q displayed a somewhat less pronounced elongation of the C-O bond length, with C2-O2 increasing by 0.037 and C5-O5 increasing by 0.035 Å. This is not unexpected because the addition of one electron to a benzoquinone moiety formally converts one double bond into a single bond (i.e., C=O + e[−] → C-O^{•−}). Similar changes in the C-O bond lengths have been reported for 1,4-benzoquinone^{48–51} and other 1,4- benzoquinone derivatives using a variety of computational approaches.^{52,53} For example, Boesch and Wheeler predicted an increase of the C-O bond lengths of 1,4-benzoquinone and 2,3,5,6-tetrachloro-1,4- benzoquinone (*p*-chloranil) by 0.041 and 0.033 Å, respectively,⁵³ whereas an more pronounced lengthening of one C-O bond (0.047 Å) has been predicted for ubiquinones.⁵² An increase of 0.041 Å in the C-O bond length has also been reported for the reduction of 1,2-benzoquinone to the corresponding semiquinone radical anion at the UB3LYP/6-311G** level of theory.⁵⁴ In our study, the effect of the one electron reduction of the C-O bonds of 3,4',6-Cl-2,5-Q was in between the effect observed for benzoquinone and 2,3,5,6-tetrachloro-1,4-benzoquinone due to the two chlorine substituents in the PCB quinone. The single phenyl substituent appeared

to have little effect on the C-O bond length since the changes observed in this study are comparable to the value reported by Boesch and Wheeler for 1,4- benzoquinone.⁵³

The one electron reduction resulted in bond lengths in the benzoquinone moiety of the SQs^{•-} that are closer to the typical bond length of an aromatic C-C bond of 1.40 Å.⁵⁵ The lengths of the C1-C6 and C3-C4 double bonds of the benzoquinone ring increased by 0.022–0.037 Å and 0.034–0.037 Å, respectively. This effect was less pronounced for 3,4',6-Cl-2,5-Q, where in particular the C1-C6 bond increased only by 0.028 Å. Similarly, one electron reduction of *p*-chloranil resulted in a smaller increase in the C-C double bond length in the semiquinone radical anion compared to benzoquinone (0.022 Å versus 0.028 Å, respectively) due to the presence of four chlorine substituents, as predicted using the B3P86 hybrid Hartree-Fock/density functional method with a 6-31G(d) basis set.⁵³ At the same time, the four single bonds of the PCB quinones were shortened by 0.031 to 0.041 Å. The most pronounced bond shortening was observed for C1-C2 (0.037–0.041 Å), followed by C5-C6 (0.034–0.037 Å), C2-C3 (0.029–0.033 Å) and C4-C5 (0.030–0.031 Å). 3,4',6-Cl-2,5-Q was an exception and its SQ^{•-} displayed the most pronounced decrease in the bond length following the rank order C2-C3 (0.047 Å) > C5-C6 (0.041 Å) > C1-C2 (0.032 Å) > C4-C5 (0.027 Å). Overall, comparable changes in the bond lengths have been predicted with different DFT methods for the one electron reduction of 1,4-benzoquinone and other quinones to the semiquinone radical anion BQ^{•-}.^{48–53}

The effect of the addition an electron on the Cl-C bond length of PCB quinones was investigated because it may predict how easily this bond can be cleaved. The Cl-C bond lengths in the phenyl ring were weakened by the addition of one electron and increased by 0.005 to 0.023 Å in length. An even more pronounced weakening of the Cl-C bonds was observed for the two chlorine substituents of the benzoquinone moiety of 3,4',6-Cl-2,5-Q, which increased by 0.037 and 0.044 Å for Cl-C3 and Cl-C6, respectively. Similarly, Boesch and Wheeler predicted an increase on the Cl-C bond length of *p*-chloranil by 0.031 Å.⁵³ The addition and removal of one electron similarly affects the Cl-C bond length of PCBs. In particular PCB cations display stronger Cl-C bonds, whereas PCB anions display weaker Cl-C bonds.^{56,57}

In comparison to the benzoquinone moiety, the one electron reduction only slightly affected the bond lengths in the phenyl substituent, with only a small elongation of the C1'-C2' and C1'-C6' bonds (0.009 Å) being observed. Otherwise, the bond lengths were essentially unchanged. Interestingly, the one electron reduction resulted in no change in the interring (i.e., C1-C1') bond lengths. This observation is intriguing because a previous computational study by Arulmozhiraja et al. predicted that the interring bond length of PCBs is strengthened by the addition or removal of electrons due to an increase in the double bond character of the interring bond.⁵⁷

Bond angle predictions

As shown in Table 2 for the syn-like conformation, the changes in the bond length were accompanied by changes in the bond angles that mirror changes predicted previously for BQ^{•-} compared to 1,4-benzoquinone.^{48,49,51} The C1-C2-C3 and C4-C5-C6 bond angles decreased by 2.21 ° to 2.63 °, whereas the remaining four bond angles in the benzoquinone moiety increased by 0.84 ° to 1.75 °. The only exception was 3,4',6-Cl-2,5-Q, where the C1-C2-C3 and C4-C5-C6 bond angles decreased by 3.15 ° and 3.06 °, respectively, due to the presence of the chlorine and phenyl substituents. This change is comparable to *p*-chloranil, where the C-C(=O)-C bond angle decreased by 3.2 °, as predicted using the B3P86 hybrid Hartree-Fock/density functional method with a 6-31G(d) basis set.⁵³ The other bond angles in the benzoquinone moiety of 3,4',6-Cl-2,5-Q increased by 0.95 ° to 2.32 °. In comparison, the C-C=C bond angles of *p*-chloranil increased by 1.9 °.⁵³ There were also slight changes

in the bond angles of the phenyl ring of $\text{SQs}^{\bullet-}$, with the $\text{C6}'\text{-C1}'\text{-C2}'$ being consistently smaller by 1.5° to 1.9° compared to the PCB quinone in the same conformation. All other bond angles in the phenyl ring displayed small change in the bond angle due to the one electron reduction, with no systematic change discernible for this series of compounds.

Dihedral angle predictions

Although structure-activity relationship studies investigating interactions of $\text{SQs}^{\bullet-}$ or their parent PCB quinones with target molecules are essentially nonexistent, the dihedral angle is likely an important structural determinant for these interactions.⁵⁸ Similar to the parent quinones, *ortho* chlorine substituents increased the predicted dihedral angles between the two ring systems of the $\text{SQs}^{\bullet-}$ (Table 3). In the syn-like conformation, $\text{SQs}^{\bullet-}$ without *ortho* chlorine substituent in the phenyl ring displayed dihedral angles ranging from 24.30° to 26.98° , whereas $\text{SQs}^{\bullet-}$ with one *ortho* chlorine substituent had larger dihedral angles ranging varying from 45.40° to 51.51° . The dihedral angles of $\text{SQs}^{\bullet-}$ in the anti-like conformation were slightly larger compared to the angles observed in the syn-like conformation and displayed the same effect of *ortho* chlorine substitution (Table 3).

The dihedral angles of the $\text{SQs}^{\bullet-}$ were smaller compared to the respective PCB quinones (Table 3). Similarly, the dihedral angles of PCB cations and anions are smaller compared to the corresponding parent PCB^{57,59} due to an increase in the interring $\text{C1-C1}'$ π -bond character in the PCB ions.⁵⁷ In the case of PCB $\text{SQs}^{\bullet-}$, the extent of this change seemed to be more pronounced in the absence of an *ortho* chlorine substituent. Specifically, the dihedral angles of the two $\text{SQs}^{\bullet-}$ without *ortho* chlorine substituents in the phenyl ring were 13° to 14° smaller compared to the PCB quinones, whereas the dihedral angles of the $\text{SQs}^{\bullet-}$ with an *ortho* chlorine substituent were only 6° to 10° smaller. Furthermore, the change in the dihedral angle was more pronounced for *ortho* chlorine substituted $\text{SQs}^{\bullet-}$ in the anti- compared to the syn-like conformation, whereas the opposite was true for non-*ortho* chlorine substituted $\text{SQs}^{\bullet-}$.

Ground state energies of $\text{SQs}^{\bullet-}$

We and others have shown that, depending on the substitution pattern, the ground state energy between the syn- and anti-like conformations of PCBs and PCB quinones differs by 0.2 to 2 kJ/mol.^{57,60} The ground state energies of both conformations were essentially identical for non-*ortho* substituted $\text{SQs}^{\bullet-}$ (Table 4). However, the anti-like conformation of two $\text{SQs}^{\bullet-}$ with *ortho* chlorine substituents was 5.0 kJ/mol more favorable compared to the syn-like conformation. The opposite is true for *ortho* chlorine substituted PCBs and PCB quinones, where the syn-like conformation is slightly more stable compared to the anti-like conformation.^{57,60} It is currently unclear to which extent these energy differences between the syn- and anti-like conformations need to be considered when investigating the interaction of $\text{SQs}^{\bullet-}$ with potential target molecules, such as the AhR. Computational investigations suggest that the ground state structure is not necessarily the conformation of the PCB or PCB metabolite bound to the target molecule.^{34,58,61}

Structures and energies of molecular orbitals

The energies of the highest occupied molecular orbital (HOMO) and the lowest unoccupied molecular orbital (LUMO) were calculated for both PCB quinones and $\text{SQs}^{\bullet-}$ to provide further insights into the changes in the molecular structure upon addition of a single electron to the LUMO of the respective PCB quinone (Table 5). Furthermore, HOMO and LUMO energies as well as the HOMO-LUMO gap are frequently used quantum chemical parameters in qualitative structure-activity studies.⁶² In the present study, the molecular orbitals were calculated using a spin-unrestricted formalism and, thus, are one electron constructs. Formally, the HOMO-LUMO gap of the $\text{SQs}^{\bullet-}$ is the gap between the α -HOMO

and β -LUMO. However, a given pair of α - and β -spin orbitals is almost identical in terms of their density distribution (Figures 3B versus 3C and 3D versus 3E) and can be thought of as describing the corresponding two electron orbital. Thus, the α -HOMO- α -LUMO gap should be considered to be the physically significant HOMO-LUMO gap in these systems.⁶³

In particular the density distribution of the α -HOMO and to a lesser extent the β -LUMO are comparable to the LUMO of the parent PCB quinone (Figure 3). Furthermore, the α -HOMO and β -LUMO of the SQs^{•-} are similar and mostly distributed across the benzoquinone moiety (Figures 3D and 3E); however, the α -HOMO is distributed to a much smaller extent across the C1-C1' interrering bond and the phenyl ring compared to the β -LUMO. The α -HOMO and β -LUMO displayed an out-of-phase, anti-bonding interaction between the atoms in the C=O and C=C bonds and an in-phase, bonding interaction between the C-C atoms. These bonding and anti-bonding interactions are consistent with the above mentioned lengthening of the C=O and C=C bonds and the shortening of the C-C bonds predicted for the reduction of the quinones to the corresponding SQs^{•-}. The localization of the α -HOMO is in agreement with the observation that the one electron reduction did not alter the interrering bond length of the SQs^{•-} relative to the parent PCB quinone and had little effect on the molecular geometry of the chlorinated phenyl ring. The limited distribution of the α -HOMO across the phenyl ring is also consistent with our previous finding that the hyperfine splittings with the hydrogen substituents on the (chlorinated) phenyl ring contribute little to the features in the EPR spectra of the six SQs^{•-}.^{11,21}

The orbital energies of selected molecular orbitals of the SQs^{•-} and the corresponding parent quinones are listed in Table 5. The HOMO-LUMO gap of the mono- and di-chlorinated PCB quinones ranges from 3.23 to 3.48 eV. A comparable HOMO-LUMO gap of 3.23 eV has been reported for 3,6-di-*tert*-butyl-1,2-benzoquinone.⁵⁴ The presence of the chlorine substituents in the benzoquinone moiety in 3,4',6-Cl-2,5-Q results in a smaller HOMO-LUMO gap of 3.00 eV. The position of the chlorine substituent in the phenyl ring seemed to influence the HOMO-LUMO gap, which decreased in the order 2'-Cl-2,5-BQ > 3'-Cl-2,5-BQ > 4'-Cl-2,5-BQ. The one electron reduction drastically alters the α -HOMO- β -LUMO gap, which is independent of the conformation and ranges from 1.90 to 1.99 eV for all six SQs^{•-}. The corresponding HOMO-LUMO gap reported previously for the semiquinone radical anion of 3,6-di-*tert*-butyl-1,2-benzoquinone, also determined at the UB3LYP/6-311G** level of theory, was essentially identical (1.95 eV).⁵⁴ The α -HOMO- α -LUMO gap displays more pronounced differences between the SQs^{•-} and ranges from 2.59 to 3.08 eV. In particular the 3,4',6-Cl-2,5-Q has a larger α -HOMO- α -LUMO gap compared to the five quinones with no chlorine substituents in the benzoquinone moiety.

Distribution of Mülliken Atomic Spin Densities

The Mülliken atomic spin densities were investigated to assess if there are any changes in the location of the spin densities as a function of the chlorine substitution pattern. Table 6 shows only small differences in the distribution of the spin densities between the syn- and anti-like conformations. In both conformations, the spin densities of the SQs^{•-} are primarily located at the two oxygen atoms, with a higher spin density present at O5 (0.26–0.30) compared to O2 (0.23–0.20). The only exception is the almost comparable spin densities of 3,4',6-Cl-2,5-Q (0.26 for O2 versus 0.28 for O5). These values qualitatively agree with the oxygen spin densities obtained from ¹⁷O hyperfine couplings determined using EPR spectroscopy.⁶⁴ Some spin density (0.04 to 0.09) is present at the carbon atoms of the benzoquinone ring system, with a fairly large spin density (values of 0.15 to 0.18) present at C6. Only 3,4',6-Cl-2,5-Q has a slightly different localization of the spin densities, with C6 displaying the smallest value (0.12) observed for this series of compounds. Wheeler and colleagues predicted comparable location of Mülliken atomic spin densities for several 1,4- and 1,2-benzoquinones using different computational methods.^{52–54} In all SQs^{•-} essentially

no spin density is located in the phenyl ring or the chlorine substituents, including the chlorine substituents in the benzoquinone ring of 3,4',6-Cl-2,5-Q. This observation is in agreement with the distribution of the single occupied molecular orbital over the benzoquinone moiety, for example of 2'-Cl-2,5-Q (Figure 3) and, thus, consistent with observed lack of hyperfine splitting with the hydrogen substituents on the (chlorinated) phenyl ring.^{11,21}

Effects of diffuse functions in the basis set

To observe the effects of including diffuse functions in the basis set, a set of calculations were carried out for syn-like PCB quinones and SQs^{•-} with 2'-Cl and 2',5'-Cl substitution at the UB3LYP/6-311++G** level of theory. Table 7 summarizes the ground-state energy differences and band gap results for these systems. While the individual orbital energies show significant differences due to the inclusion of diffuse functions, the differences in ground state energy are similar to those predicted using the 6-311G** basis set. They differ by 8–10%, which is significant but well below the increases of 20–35% reported by Frontana et al. upon switching from 6-31G** to 6-31++G**. ²⁴ The changes in estimated band gap for the compounds are even less, with negligible changes for the α -HOMO to β -LUMO gap and only 3.5–5.4% changes for the α -HOMO to α -LUMO gap. Given that band gaps are the primary observable quantities and that electron affinities are treated primarily using linear correlations with observable redox potentials,²⁴ diffuse functions are probably more important for precise quantitative predictions than for experimental correlations with respect to substitution within the quinone compounds.

Linear polarizabilities, hyperpolarizabilities and octupole moments

Components of linear polarizabilities, first order hyperpolarizabilities and octupole moments have been used in QSARs of polychlorinated dibenzofuran toxicity³⁶ and, therefore, may also be useful descriptors for formulating QSARs for PCB quinones and SQs^{•-} using the stacking interaction model of McKinney and coworkers. ³⁵ These parameters were investigated to assess how they change due to the one electron reduction and chlorine substitution pattern.

The mean of linear polarizabilities ($\bar{\alpha}$) were essentially independent of the conformation for both PCB quinones and SQs^{•-}, whereas the polarizability anisotropy ($\Delta\alpha$) values depended on the conformation (Tables S5 and S6). The largest effect of the conformation on $\Delta\alpha$ was observed for 2'-Cl-2,5-Q, which had a 2.1-times larger $\Delta\alpha$ value in the anti- compared to the syn-like conformation. The $\Delta\alpha$ values for SQs^{•-} in the syn- and anti-like conformation were similar, with $\Delta\alpha$ of 2'-Cl-2,5-SQ in the anti-like conformation being only 1.2-times larger than in the syn-like conformation. There appeared to be a linear relationship for $\Delta\alpha$ and $\bar{\alpha}$ for PCB quinones and SQs^{•-} with the same number of chlorine substituents, with $\Delta\alpha$ and $\bar{\alpha}$ typically increasing as chlorine substituents move from *ortho* to *meta* to *para* position (Figure 4). Both $\Delta\alpha$ and $\bar{\alpha}$ were slightly larger for SQs^{•-} than for the parent quinones (Tables S5 and S6). The observed magnitudes and the linear correlation between $\Delta\alpha$ and $\bar{\alpha}$ are similar to those reported for polychlorinated dibenzofuran congeners.³⁶

There was only a small difference in β between compounds in the syn- and anti-like conformation, with the most pronounced differences being observed for *ortho* substituted PCB quinones. For example, β for 2'-Cl-2,5-Q was 1.5-times smaller in the syn-like compared to the anti-like conformation. This difference was less pronounced for SQs^{•-}, with β of anti-2'-Cl-2,5-SQ being only 1.2-times larger than β of syn-2'-Cl-2,5-SQ. Figure 5 compares β of PCB quinones and the corresponding SQs^{•-}. Except for the 3,4',6-Cl-2,5-Q, the hyperpolarizability of SQs^{•-} for both conformations was larger than the value predicted for the parent quinones. In particular on the syn-like conformation, a comparatively large

difference in β was observed between PCB quinones and the corresponding SQs $^{\bullet-}$ with chlorine substituent in the *ortho* position (Figure 5a). For example, the hyperpolarizability of 2',5'-Cl-2,5-SQ was 8-times larger compared to the hyperpolarizability calculated for 2',5'-Cl-2,5-Q.

All components of β and Ω were larger when compared to the values calculated for polychlorinated dibenzofurans (Tables S7-S10).³⁶ These values fall well outside of the ranges of β and Ω used to develop the QSAR of Gu et al. and therefore extrapolation to predict pEC50 values for AhR-mediated toxicity is not reasonable. Although *in vitro* studies have shown that PCB quinones cause AhR-mediated toxicity,¹² the significant differences in the first order hyperpolarizabilities and octupole moments of PCB quinones on one hand and polychlorinated dibenzofurans on the other hand suggest that the toxicity of PCB quinones and SQs $^{\bullet-}$ is most likely not mediated by a direct interaction with AhR. Alternatively, the QSAR model described for binding interactions with AhR for polychlorinated dibenzofurans³⁶ may need to be reparameterized to be applicable for the quinone compounds considered in the present study.

While the effects of including diffuse functions on calculated energy differences are modest (Table 7), they are expected to have a larger impact on quantities related to long-range electron correlations such as polarizabilities. Table S11 summarizes the polarizabilities, first-order hyperpolarizabilities, and octupole moments calculated using the 6-311++G** basis set for 2'-Cl-2,5-(S)Q and 2',5'-Cl-2,5-(S)Q congeners. All of the calculated quantities change significantly because of including diffuse functions in the basis set. The changes are substantial (for instance, on the order of 30% differences in the polarizabilities) but the reported values are of the same order of magnitude as calculations with 6-311G**. This shows that basis sets with diffuse functions should be used for accurate predictions of these quantities, but in Figure S1, we show that linear relationships exist between the values calculated with the 6-311++G** basis set and those calculated with the 6-311G** basis set. These relationships can be used to translate the results of faster calculations made with 6-311G** into the more detailed calculations with diffuse functions. For polarizabilities and octupole moments, good linear relationships are found ($R^2 = 0.9766$ and 0.9958 , respectively) that match the combined results from both quinones and semiquinones. For hyperpolarizabilities, slightly different linear correlations are made for quinones and semiquinones, but both are good correlations ($R^2 > 0.99$ in both cases). These results suggest that while predicting exact values of polarizabilities, hyperpolarizabilities and octupole moments requires a good choice of basis set (most likely with diffuse functions), calculations without diffuse functions provide trends among congeners that can still be utilized to construct a meaningful QSAR. The conclusions about the effects of chlorine substitution on polarizabilities, hyperpolarizabilities and octupole moments remain unchanged by using the 6-311++G** basis set.

Conclusions

SQs $^{\bullet-}$ are an important, but poorly investigated group of reactive PCB metabolites that may play a crucial role in their toxicity. The DFT calculations completed the present study predicted significant changes in the bond length and bond angles of the benzoquinone moiety of the SQs $^{\bullet-}$ and the dihedral angle between both ring systems compared to the parent PCB quinone. The changes in the molecular geometry of the benzoquinone moiety were comparable to the structural changes predicted for simple quinones and can be explained with the structure of the α -HOMO. Analogous to the PCB quinones, *ortho* chlorine substituents increased the dihedral angle of the SQs $^{\bullet-}$; however, compared to PCB quinones, the one electron reduction caused a clear decrease in the dihedral angle between both ring systems that depended on the chlorine substitution pattern and was most

pronounced for SQs^{•-} without *ortho* chlorine substituents. Furthermore, the ground state energies of the anti-like conformation of *ortho* substituted SQs^{•-} were more stable than the syn-like conformation, whereas the opposite is true for the parent PCB quinones. Molecular descriptors, such as $\Delta\alpha$ and β , display some dependence on the conformation, especially for *ortho* substituted SQs^{•-}. Thus, the predicted molecular structures of SQs^{•-} may result in different conformation-dependent affinities of SQs^{•-} to target molecules. Furthermore, the interaction of SQs^{•-} with cellular targets is likely to be different compared to the parent PCB quinones.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.
Chemical structures and numbering scheme of PCB quinones.

Figure 2. Molecular structure of 2',5'-Cl-2,5-Q in the syn- and anti-like conformation. (A) Syn-like conformation shown perpendicular to the C1-C1' interring bond and (B) along the C1-C1' interring bond. (C) Anti-like conformation shown perpendicular to the C1-C1' interring bond and (D) along the C1-C1' interring bond.

PCB quinone

(A) HOMO (MO 64)

(B) LUMO (MO 65)

PCB semiquinone radical anion

(C) β -HOMO (64 β) (D) α -HOMO (65 α) (E) β -LUMO (MO 65 β) (F) α -LUMO (66 α)

Figure 3. Comparison of the (A) HOMO and (B) LUMO of 2',5'-Cl-2,5-Q in the syn-like conformation with the (C) β -HOMO (MO 64 β), (D) α -HOMO (MO 65 α), (E) β -LUMO (MO 65 β) and (F) α -HOMO (MO 66 α) of the corresponding semiquinone anion radical 2',5'-Cl-2,5-SQ $^{\bullet-}$. Molecular orbitals (MO) were visualized using Gabedit with an isosurface value of 0.02.

Figure 4. Relationship between the mean of linear polarizability, $\bar{\alpha}$, and anisotropy, $\Delta\alpha$, of the calculated linear polarizabilities for PCB SQs $^{\bullet-}$ and the corresponding quinines in the (a) syn- and (b) anti-like conformation. The labels in the plot indicate the chlorine substitution pattern. The units are all in a.u. (1 a.u. = 0.148×10^{-30} m 3). MCQ: mono-chlorinated quinone; DCQ: di-chlorinated quinone; TCQ: tri-chlorinated quinone; MCSQ: mono-chlorinated SQ $^{\bullet-}$; DCSQ: di-chlorinated SQ $^{\bullet-}$; TCSQ: trichlorinated SQ $^{\bullet-}$.

Figure 5. Total first order hyperpolarizabilities (β) of PCB quinones and SQs $^{\bullet-}$ in the (a) syn- and (b) anti-like conformation. The labels on the x-axis indicate the chlorine substitution pattern. The units of β are in a.u. (1 a.u. = 3.206×10^{-53} C m 3 J $^{-2}$).

Table 1

Comparison of bond lengths calculated at the UB3LYP/6-311G** level of theory for PCB quinones (Q) and the corresponding semiquinone radicals (SQ⁻) in the syn-like conformation.

Bond	2'-Cl-2,5-Q		3'-Cl-2,5-Q		4'-Cl-2,5-Q		2',5'-Cl-2,5-Q		3',4'-Cl-2,5-Q		3',4',6-Cl-2,5-Q	
	Q	SQ ⁻	Q	SQ ⁻	Q	SQ ⁻	Q	SQ ⁻	Q	SQ ⁻	Q	SQ ⁻
C2-O2	1.216	1.255	1.217	1.257	1.218	1.259	1.215	1.254	1.218	1.257	1.210	1.247
C5-O5	1.219	1.260	1.220	1.260	1.220	1.260	1.219	1.259	1.220	1.259	1.213	1.248
C1-C2	1.505	1.464	1.509	1.470	1.508	1.471	1.505	1.465	1.509	1.471	1.508	1.476
C1-C6	1.344	1.378	1.350	1.386	1.351	1.385	1.344	1.379	1.350	1.387	1.352	1.380
C1-C1'	1.485	1.484	1.480	1.480	1.478	1.480	1.485	1.481	1.479	1.478	1.482	1.485
C2-C3	1.486	1.453	1.486	1.456	1.485	1.454	1.486	1.453	1.484	1.455	1.501	1.454
C3-C4	1.337	1.364	1.337	1.361	1.337	1.362	1.338	1.363	1.338	1.360	1.336	1.358
C4-C5	1.484	1.4536	1.484	1.453	1.483	1.452	1.484	1.454	1.483	1.453	1.477	1.450
C5-C6	1.483	1.448	1.478	1.443	1.477	1.443	1.483	1.446	1.477	1.442	1.501	1.460
C1'-C6'	1.401	1.406	1.403	1.409	1.404	1.409	1.398	1.406	1.403	1.409	1.400	1.402
C1'-C2'	1.400	1.404	1.404	1.412	1.404	1.410	1.401	1.406	1.401	1.409	1.400	1.401
C2'-C3'	1.391	1.392	1.387	1.385	1.389	1.392	1.390	1.391	1.391	1.389	1.389	1.393
C3'-C4'	1.392	1.392	1.391	1.389	1.390	1.389	1.391	1.391	1.398	1.395	1.391	1.388
C4'-C5'	1.392	1.393	1.392	1.395	1.391	1.388	1.390	1.388	1.394	1.392	1.391	1.388
C5'-C6'	1.391	1.390	1.390	1.389	1.389	1.391	1.389	1.385	1.386	1.386	1.390	1.392
Cl-C	1.758	1.763	1.760	1.782	1.757	1.780	1.754	1.758	1.747	1.764	1.732	1.776
							1.756	1.775	1.744	1.763	1.756	1.773
											1.736	1.773

The Cl-C bond lengths are listed in the following order: Cl-C2' and Cl-C5' for 2',5'-Cl-2,5-Q, Cl-C3' and Cl-C4' for 3',4'-Cl-2,5-Q, and Cl-C3, Cl-C4', and Cl-C6 for 3,4',6-Cl-2,5-Q.

Table 2

Selected bond angles (°) calculated at the UB3LYP/6-311G** level of theory for PCB quinones (Q) and the corresponding semiquinone radicals (SQ^{•-}) in the syn-like conformation.[†]

Bond	2'-Cl-2,5-Q		3'-Cl-2,5-Q		4'-Cl-2,5-Q		2',5'-Cl-2,5-Q		3',4'-Cl-2,5-Q		3,4',6-Cl-2,5-Q	
	Q	SQ ^{•-}	Q	SQ ^{•-}	Q	SQ ^{•-}	Q	SQ ^{•-}	Q	SQ ^{•-}	Q	SQ ^{•-}
O2-C2-C3	120.88	122.27	120.00	120.27	119.82	120.26	120.96	122.31	119.96	120.19	121.02	123.10
O2-C2-C1	121.72	122.94	122.23	124.17	122.31	124.14	121.64	122.92	122.23	124.16	121.40	122.46
O5-C5-C4	121.51	122.73	121.36	122.58	121.35	122.61	121.54	122.66	121.41	122.55	120.76	121.97
O5-C5-C6	121.24	122.59	121.34	122.57	121.39	122.55	121.16	122.66	121.25	122.53	122.23	124.09
C2-C1-C6	119.51	121.26	118.52	119.37	118.37	119.32	119.69	121.33	118.41	119.25	119.08	120.32
C2-C1-C1'	118.05	118.63	119.63	120.73	119.60	120.63	117.90	118.40	119.71	120.78	116.22	116.08
C6-C1-C1'	122.32	119.95	121.85	119.90	122.02	120.05	122.32	120.14	121.87	119.97	124.69	123.60
C1-C2-C3	117.38	114.78	117.77	115.56	117.87	115.59	117.38	114.75	117.81	115.65	117.59	114.44
C2-C3-C4	121.97	123.30	122.25	123.63	122.22	123.63	121.93	123.24	122.30	123.59	121.87	124.19
C3-C4-C5	121.01	122.38	120.69	121.76	120.70	121.77	121.01	122.43	120.61	121.78	121.53	122.48
C4-C5-C6	117.25	114.68	117.30	114.85	117.25	114.84	117.30	114.68	117.34	114.92	117.00	113.94
C5-C6-C1	122.70	123.58	123.47	124.88	123.58	124.82	122.56	123.53	123.52	124.77	122.89	124.56
C6'-C1'-C1	119.72	119.40	119.83	120.99	119.73	120.96	119.30	119.01	119.99	121.17	124.69	120.79
C6'-C1'-C2'	117.75	116.01	118.86	117.14	118.17	116.68	118.21	116.40	118.35	116.73	118.74	117.73
C1-C1'-C2'	122.53	124.59	121.29	121.87	122.08	122.36	122.49	124.59	121.65	122.10	120.55	121.44
C1'-C2'-C3'	121.48	122.24	119.53	119.84	120.94	121.68	121.18	122.02	120.80	121.28	120.94	121.67
C2'-C3'-C4'	119.60	120.07	121.78	123.11	119.47	119.50	120.10	120.57	120.19	120.91	119.15	118.89
C3'-C4'-C5'	120.09	119.33	118.65	117.24	121.02	120.85	119.08	118.06	119.37	118.72	121.10	121.21
C4'-C5'-C6'	119.75	119.78	120.51	120.91	119.01	121.04	121.04	121.67	120.35	120.38	119.24	119.09
C5'-C6'-C1'	121.32	122.55	120.67	121.74	121.38	122.26	120.39	121.27	120.94	121.97	120.82	121.41

[†]See text for a discussion of bond angles highlighted in bold.

Table 3

Selected dihedral angle averages (°) calculated at the UB3LYP/6-311G** level of theory for PCB quinones (Q) and the corresponding semiquinone radicals (SQ^{•-}) in the syn- and anti-like conformation.[†]

Quinone	Syn-like Conformation		Anti-like Conformation	
	Q	SQ ^{•-}	Q	SQ ^{•-}
2'-Cl-2,5-Q	66.46	60.26	55.27	47.20
3'-Cl-2,5-Q	40.10	26.56	40.21	27.54
4'-Cl-2,5-Q	38.68	26.98		
2',5'-Cl-2,5-Q	67.60	58.97	55.43	45.40
3',4'-Cl-2,5-Q	38.28	24.30	39.19	25.73
3,4',6-Cl-2,5-Q	55.98	51.51		

[†]The *in silico* dihedral angles are the average of the four dihedral angles involving the Cl-Cl' bond between the benzene and the quinone rings.

Table 4

Ground state energies E calculated at the UB3LYP/6-311G** level of theory for PCB quinones (Q) and the corresponding semiquinone radicals ($SQ^{\bullet-}$) in the syn- and anti-like conformation.

Quinone	$E_{syn}(SQ^{\bullet-})$ (10^6 kJ/mol)	$\Delta E_{syn}(Q) - E_{syn}(SQ^{\bullet-})$ (kJ/mol)	$E_{anti}(SQ^{\bullet-})$ (10^6 kJ/mol)	$\Delta E_{anti}(Q) - \Delta E_{anti}(SQ^{\bullet-})$ (kJ/mol)	$\Delta E_{syn}(SQ^{\bullet-})$ E _{anti} (SQ ^{•-}) (kJ/mol)	$E_{anti}(SQ^{\bullet-})$ (kJ/mol)
2'-Cl-2,5-Q	-2.82	200	-2.82	194	5.0	5.0
3'-Cl-2,5-Q	-2.82	213	-2.82	213	0.0	0.0
4'-Cl-2,5-Q	-2.82	212				
2',5'-Cl-2,5-Q	-4.02	217	-4.02	210	5.5	5.5
3',4'-Cl-2,5-Q	-4.02	226	-4.02	226	-0.1	-0.1
3,4',6-Cl-2,5-Q	-5.23	258				

Table 5

Comparison of the HOMO and LUMO energies of PCB quinones (Q) and the corresponding semiquinone radicals (SQ^{•-}) in the syn- and anti-like conformation calculated at the UB3LYP/6-311G** level of theory. The respective molecular orbitals are listed in parentheses.[†]

Compound	PCB quinone		SQ ^{•-}						
	E _{HOMO} [eV]	E _{LUMO} [eV]	ΔE _{HOMO-LUMO} [eV]	E _{β-HOMO} [eV]	E _{α-HOMO} [eV]	E _{β-LUMO} [eV]	E _{α-LUMO} [eV]	ΔE _{α-HOMO-β-LUMO} [eV]	ΔE _{α-HOMO-α-LUMO} [eV]
(A) Syn-like conformation									
2'-Cl-2,5-Q	-7.13 (56a)	-3.65 (57a)	3.48	-2.14 (56β)	-0.39 (57a)	1.60 (57β)	2.39 (58a)	1.99	2.78
3'-Cl-2,5-Q	-7.13 (56a)	-3.79 (57a)	3.34	-2.39 (56β)	-0.66 (57a)	1.25 (57β)	2.13 (58a)	1.91	2.79
4'-Cl-2,5-Q	-7.00 (56a)	-3.78 (57a)	3.23	-2.38 (56β)	-0.65 (57a)	1.26 (57β)	2.15 (58a)	1.92	2.80
2',5'-Cl-2,5-Q	-7.12 (64a)	-3.80 (65a)	3.32	-2.33 (64β)	-0.59 (65a)	1.37 (65β)	2.00 (66a)	1.96	2.59
3',4'-Cl-2,5-Q	-7.15 (64a)	-3.90 (65a)	3.25	-2.56 (64β)	-0.84 (65a)	1.06 (65β)	1.86 (66a)	1.90	2.70
3,4',6-Cl-2,5-Q	-7.14 (72a)	-4.14 (73a)	3.00	-3.06 (72β)	-1.21 (73a)	0.74 (73β)	1.87 (74a)	1.95	3.08
(B) Anti-like conformation									
2'-Cl-2,5-Q	-7.11 (56a)	-3.69 (57a)	3.42	-2.20 (56β)	-0.47 (57a)	1.50 (57β)	2.31 (58a)	1.97	2.78
3'-Cl-2,5-Q	-7.11 (56a)	-3.79 (57a)	3.32	-2.38 (56β)	-0.65 (57a)	1.26 (57β)	2.12 (58a)	1.91	2.77
2',5'-Cl-2,5-Q	-7.10 (64a)	-3.84 (65a)	3.26	-2.40 (64β)	-0.69 (65a)	1.26 (65β)	1.93 (66a)	1.94	2.62
3',4'-Cl-2,5-Q	-7.14 (64a)	-3.90 (65a)	3.25	-2.55 (64β)	-0.83 (65a)	1.07 (65β)	1.85 (66a)	1.90	2.68

[†] See text for a discussion of parameters highlighted in bold.

Table 6

Selected Mulliken atomic spin densities in semiquinone radical anions.[/]

Atom	2'-Cl-2,5-Q		3'-Cl-2,5-Q		4'-Cl-2,5-Q		2',5'-Cl-2,5-Q		3',4'-Cl-2,5-Q		3,4',6-Cl-2,5-Q	
	syn	anti	syn	anti	syn	anti	syn	anti	syn	anti	syn	anti
C1	0.08	0.06	0.06	0.06	0.06	0.06	0.08	0.06	0.06	0.06	0.08	0.08
C2	0.05	0.07	0.06	0.06	0.07	0.07	0.05	0.07	0.06	0.06	0.06	0.06
C3	0.08	0.07	0.06	0.06	0.06	0.06	0.07	0.07	0.06	0.06	0.07	0.07
C4	0.07	0.08	0.06	0.07	0.07	0.07	0.06	0.07	0.06	0.06	0.09	0.09
C5	0.05	0.04	0.04	0.04	0.04	0.04	0.04	0.04	0.03	0.03	0.04	0.04
C6	0.13	0.15	0.17	0.17	0.16	0.16	0.15	0.17	0.18	0.18	0.12	0.12
O2	0.26	0.25	0.23	0.24	0.24	0.24	0.26	0.24	0.23	0.23	0.26	0.26
O5	0.29	0.30	0.29	0.29	0.29	0.29	0.29	0.30	0.29	0.30	0.28	0.28

[/] See Figure 1 for the atom numbering scheme. Additional Mulliken atomic spin densities are presented in Tables S3 and S4. See text for a discussion of Mulliken atomic spin densities highlighted in bold.

Table 7

Energy results for selected syn-like PCB quinones and semiquinone radical anions calculated at the UB3LYP/6-311++G** level of theory. Percentages in parentheses indicate differences from calculations at the UB3LYP/6-311G** level of theory.

Compound	$\Delta E_{\text{syn}}(\text{Q}) - E_{\text{syn}}(\text{SQ}^{\cdot-})$ (kJ/mol)	PCB quinone		$\text{SQ}^{\cdot-}$						
		E_{HOMO} [eV]	E_{LUMO} [eV]	$\Delta E_{\text{HOMO-LUMO}}$ [eV]	$E_{\beta\text{-HOMO}}$ [eV]	$E_{\alpha\text{-HOMO}}$ [eV]	$E_{\beta\text{-LUMO}}$ [eV]	$E_{\alpha\text{-LUMO}}$ [eV]	$\Delta E_{\alpha\text{-HOMO-}\beta\text{-LUMO}}$ [eV]	$\Delta E_{\alpha\text{-HOMO-}\alpha\text{-LUMO}}$ [eV]
2'-Cl-2,5-Q	220 (+10%)	-7.21 (56a)	-3.83 (57a)	3.38 (-2.9%)	-2.53 (56 β)	-0.75 (57a)	1.22 (57 β)	1.88 (58a)	1.97 (-1.0%)	2.63 (-5.4%)
2',5'-Cl-2,5-Q	235 (+8.1%)	-7.16 (64a)	-3.97 (65a)	3.19 (-3.9%)	-2.69 (64 β)	-0.92 (65a)	1.03 (65 β)	1.76 (66a)	1.95 (-0.5%)	2.68 (+3.5%)