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Crystal structure and density functional theory studies of toxic quinone metabolites of polychlorinated biphenyls

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ABSTRACT

Lower chlorinated polychlorinated biphenyls (PCBs) are readily metabolized via hydroxylated metabolites to reactive PCB quinones. Although these PCB metabolites elicit biochemical changes by mechanisms involving cellular target molecules, such as the aryl hydrocarbon receptor, and toxicity by interacting with enzymes like topoisomerases, only few PCB quinones have been synthesized and their conformational properties investigated. Similar to the parent compounds, knowledge of the three-dimensional structure of PCB quinones may therefore be important to assess their fate and risk. To address this gap in our knowledge, the gas phase molecular structure of a series of PCB quinones was predicted using HF/3-21G, B3LYP/6-31G** and UB3LYP/6-311G** calculations and compared to the respective solid state structure. All three methods overestimated the Cl–C bond length, but otherwise provided a reasonable approximation of the solid state bond angles and bond lengths. Overall, the UB3LYP/6-311G** level of theory yielded the best approximation of the molecular structure of PCB quinones in the solid state. Chlorine addition at the *ortho* position of both rings was found to increase the dihedral angle of the resulting quinone compound, which may have important implications for their interaction with cellular targets and, thus, their toxicity.

1. Introduction

PCBs are abundant and persistent environmental pollutants and were used as complex mixtures containing a large number of the possible 209 PCB congeners for a range of industrial applications, including as coolants, lubricants, stabilizing additives in flexible PVC coatings of electrical wiring and electronic components (Hansen, 1999; Robertson and Hansen, 2001). They are still in use as dielectric fluids in transformers and capacitors in the United States. The production of PCBs was banned in the 1970s due to environmental and human health concerns; however, recent studies demonstrate that PCBs are formed inadvertently as byproducts of industrial processes and can be found as byproducts in paints (Hu and Hornbuckle, 2010). Furthermore, environmental monitoring studies demonstrate that environmental PCB levels, for example in the Great Lakes, have only slowly decreased over the past decade (Hornbuckle et al., 2006). As a result, low level PCB exposures still represent a human health hazard that may be associated with multiple diseases, such as cancer, heart disease, developmental neurotoxicity and immunotoxicity in humans (Hansen, 1999; Robertson and Hansen, 2001).

In particular, lower chlorinated PCB congeners are readily metabolized by mammalian cytochrome P450 enzymes to mono- (Letcher et al., 2000; James, 2001) and subsequently dihydroxylated PCB metabolites (Amaro et al., 1996; McLean et al., 1996). These dihydroxylated metabolites can undergo one electron oxidations by both enzymatic and spontaneous reduction processes to form PCB semiquinone anion radicals (Song et al., 2008b; Venkatesha et al., 2008; Wangpradit et al., 2010) and, subsequently, be further oxidized to *ortho* or *para* PCB quinones (Amaro et al., 1996; Song et al., 2008b). *In vitro* studies have shown that some PCB quinones alter gene expression by interacting with the aryl hydrocarbon receptor (AhR) (Machala et al., 2004). PCB quinones also may inactivate enzymes, like topoisomerases (Srinivasan et al., 2002; Bender et al., 2006, 2007). They readily react with glutathione (Amaro et al., 1996; Srinivasan et al., 2002; Song et al., 2009) and other cellular target molecules, including DNA (Amaro et al.,

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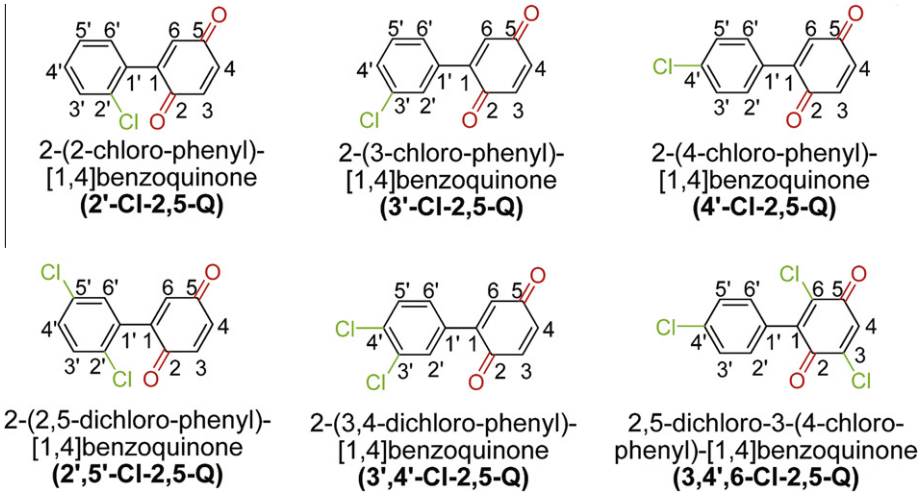

Fig. 1. Chemical structures, numbering scheme and nomenclature of PCB quinones.

1996; Arif et al., 2003). PCB quinones can redox-cycle and, thus, contribute to the production of reactive oxygen species (McLean et al., 2000; Song et al., 2008b; Venkatesha et al., 2008). *In vivo* studies demonstrate that PCB quinones play a role in the carcinogenicity of lower chlorinated PCBs by displaying initiating activity in the resistant hepatocyte model (Espandiari et al., 2004).

Despite the potential role of PCB quinones in the toxicity of lower chlorinated PCBs, few PCB quinones have been synthesized and little is known about their molecular structure. Considering the large number of PCB quinone metabolites that may be formed from the 209 possible PCB congeners, reliable approaches to predict their bond length and other structural parameters would aid in our understanding of their chemistry and, ultimately, toxicity. If accurate structure predictions can be made via computational chemistry, quantitative structure-activity relationships can be used to identify candidate compounds for toxicity generation from PCBs. Here we compare HF/3-21G, B3LYP/6-31G** and UB3LYP/6-311G** calculations to predict the molecular structure of six PCB quinones (Fig. 1) in both the syn- and anti-like conformation and compare the results with the corresponding solid state data.

2. Experimental

2.1. Synthesis of PCB quinones

The structure and nomenclature of the six PCB quinones investigated is shown in Fig. 1. They were synthesized as previously described (Amaro et al., 1996; Song et al., 2008a). Briefly, 2-(2-chloro-phenyl)-[1,4]benzoquinone (2′-Cl-2,5-Q), 2-(3-chloro-phenyl)-[1,4]benzoquinone (3′-Cl-2,5-Q), 2-(4-chloro-phenyl)-[1,4]benzoquinone (4′-Cl-2,5-Q), 2-(2,5-dichloro-phenyl)-[1,4]benzoquinone (2′,5′-Cl-2,5-Q) and 2-(3,4-dichloro-phenyl)-[1,4]benzoquinone (3′,4′-Cl-2,5-Q) were synthesized from 1,4-benzoquinone and the corresponding chloroanilines using the Meerwein arylation. 2,5-Dichloro-3-(4-chloro-phenyl)-[1,4]benzoquinone (3,4′,6-Cl-2,5-Q) was synthesized using the Suzuki cross-coupling reaction from 3-bromo-2,5-dichloro-1,4-dimethoxy-benzene and 4-chloro-phenylboronic acid, followed by oxidation with cerium ammonium nitrate. The analytical data for the PCB quinones were in agreement with the proposed structure. All PCB quinones were >99% pure according to gas chromatographic analysis (based on relative peak area).

2.2. X-ray crystal structure analysis

Crystals of the PCB benzoquinones were obtained by slow crystallization from acetone. Diffraction data for crystals of 4′-Cl-2,5-Q, 2′,5′-Cl-2,5-Q and 3′,4′-Cl-2,5-Q were collected on a Nonius KappaCCD diffractometer system, but crystals of 2′-Cl-2,5-Q, 3′-Cl-2,5-Q and 3,4′,6-Cl-2,5-Q proved too small for analysis on conventional small-molecule diffraction equipment. For these, diffraction data were collected using Cu Kα x-rays on a specially configured hybrid small/macromolecule diffraction system based on the Bruker-Nonius X8 Proteum (Nonius FR-591 rotating anode x-ray generator, Bruker Helios graded multilayer optics, Nonius Kappa goniometer, Bruker SMART 6000 CCD detector). All data were collected at 90 K using a CryoCool LN2 low temperature device from CryoIndustries of America.

For each crystal, initial unit cell parameters were obtained using either Denzo_SMN or APEX2 software (Bruker-Nonius, 2004). Final cell parameters were obtained either with Scalepack in DenzoSMN or SaintPlus in APEX2 (Bruker-Nonius, 2004) using spot positions from all data collection frames. Correction of Lorentz and polarization effects, data reduction, merging and an empirical absorption correction for each dataset were performed within either Denzo_SMN or APEX2 packages. The structures were solved by direct methods using SHELXS97 (Sheldrick, 2008) and refined by full-matrix least-squares against F^2 using SHELXL97 (Sheldrick, 2008). All non-hydrogen atoms in both structures were refined with anisotropic displacement parameters (ADPs).

Crystallographic data (excluding structure factors) for the structures in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication nos. CCDC 806858 - 806863. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK, (fax:+44 (0)1223 336033 or e-mail: deposit@ccdc.cam.ac.uk).

2.3. Calculations

The PCB quinone structures were built in ArgusLab 4.0 (Thompson). After the initial geometry optimization using the AM1 method in ArgusLab, these structures were re-optimized at HF/3-21G, B3LYP/6-31G** and UB3LYP/6-311G** levels of theory using Gaussian 03 (Frisch, 2004). These approaches have been used previously to predict the conformation, chemical properties and a range of other descriptors of a variety of environmental contaminants