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# Understanding the Congener-Specific Toxicity in Polychlorinated Dibenzo-*p*-dioxins: Chlorination Pattern and Molecular Quadrupole Moment

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***Abstract:*** It is well known that the biological activities and toxicities of planar polychlorinated aromatic compounds are extremely sensitive to chlorination pattern. Although their toxic responses have been correlated with the relative affinity for the receptor, the origin of this congener specificity is not well understood. We present a general interpretation of the congener-specific activity in polychlorinated dibenzo-*p*-dioxins, which concludes that molecular electrostatics is the principal factor determining the structure−activity relationship in this highly controversial environmental pollutant even though this electrostatic interaction represents only a part of the total interaction energy. Through calculations of the molecular charge distribution in the complete set of 76 dioxin congeners, we show that all active congeners share a unique charge distribution pattern, which is quantitatively described in terms of the molecular quadrupole moment (QM). The QM of dioxins changes sensitively and systematically with chlorination pattern. The three-dimensional electrostatic interactions at the receptor-binding site, which are optimized at a specific QM pattern represented by that of 2,3,7,8-tetrachlorodibenzo-*p*-dioxin, could explain the congener specificity in the binding affinity and toxicity. Although the polarizability also changes systematically with chlorination, it can only account for the effect of the degree of chlorination, not the congener specificity.

## Introduction

Polyhalogenated aromatic compounds (PHAs) such as polychlorinated dibenzo-*p*-dioxins (PCDDs, or simply dioxins), dibenzofurans (PCDFs), and biphenyls (PCBs) are extremely persistent and toxic pollutants that are widespread in the environment.[1] The general theory for the toxic action of PHAs is based on a receptor-mediated response mechanism in which the various biological effects follow after binding to a signal-transducer protein, the aryl hydrocarbon receptor (AhR).[2−4] The ligand−receptor binding affinities are critically important in this receptor-based model: The stronger the binding affinity of a PHA for the AhR, the greater its toxicity. The most competitive ligand among PCDDs is 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD); the toxic activity drastically decreases on adding nonlateral chlorines or removing lateral chlorines from this structure.[2,3] The ring vibrational frequencies of PCDDs are also sensitive to the chlorination pattern.[5] In general, the toxicity of planar PHAs is extremely sensitive to both the number and position of halogen substituents;[1−3] however, the origin of this congener specificity is not well understood.

Studies[6−15] aimed at understanding the congener specificity in PCDDs have approached the problem indirectly because the molecular structure of the AhR is unknown. The approach commonly employed to elucidate the quantitative structure−activity relationship (QSAR) has been to seek common molecular properties among active congeners in order to gain insights into the nature of the ligand−receptor interactions. To date, two main theoretical models have been proposed for understanding the PCDD−AhR interaction: electrostatic[6−8] and dispersion-type[9−11] interaction models. The electrostatic model is based on the view that the effective interaction with the receptor depends on the molecular electrostatic potential (MEP) around the ligand.[6−8] The dispersion-type model considers the aromatic−

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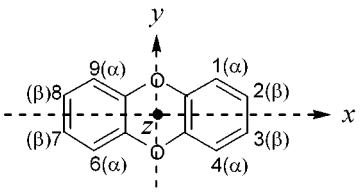
aromatic interaction, which is related to the molecular polarizability and the distance between the receptor and the ligand, to be of primary importance in the receptor−ligand affinity.[9] However, previous studies using these models have treated only a few dioxin congeners and have only partially described the molecular interactions without providing a comprehensive view. In this study, we describe the first comprehensive interpretation of the congener specificity of PCDDs. This interpretation is made using the molecular quadrupole moment (QM)[16] as a simple master parameter to describe the electrostatic interaction at the AhR active site.

## Computational Methods

Ab initio calculations were performed to quantitatively determine the electric multipole moments and polarizability of 76 dioxin congeners (75 PCDD congeners plus nonchlorinated dibenzo-*p*-dioxin (DD)) at the optimized geometry. These calculations were performed at the level of hybrid B3LYP density functional theory with a 6-31G** basis set using the Gaussian 98 suite of programs.[17] We confirmed that all the optimized geometries were in local minimums and planar.[5] In the results presented below, *x*, *y*, and *z* refer to the lateral direction, the nonlateral direction (parallel to the O−O axis), and the direction perpendicular to the molecular plane (the *xy* plane), respectively, as shown below.




The origin was placed at the molecule's center of nuclear charge, and the principal *X*, *Y*, and *Z* axes were taken according to the molecular symmetry. Then, we shifted the origin from the center of nuclear charge (CC) to the center of mass (CM). To compare molecular properties conveniently among PCDDs with different symmetry, we rotated the principal axes (*X*, *Y*, *Z*) of each congener to align with the common reference axes (*x*, *y*, *z*). We first defined the *y* axis parallel to the O−O axis, and then the *x* axis passed over CM perpendicular to the *y* axis. The *z* axis was perpendicular to the molecular plane (the *xy* plane). Accordingly, the calculated values were converted to those corresponding in the adjusted coordinate system. Upon shifting the origin from CC to CM, the values of second and quadrupole moments of PCDDs changed while the dipole moments and polarizabilities were invariant.[18] The multipole moments were calculated from the following equations.[19,20]

$$\mu_\alpha^{cc} = \sum_k Z_k r_{k\alpha} - 2\sum_i \langle\phi_i|r_\alpha|\phi_i\rangle \quad (\alpha, \beta, \gamma: X, Y, \text{or } Z) \tag{1}$$

$$S_{\alpha\beta}^{cm} = \sum_k Z_k (r_{k\alpha} - C_\alpha)(r_{k\beta} - C_\beta) - 2\sum_i \langle\phi_i|(r_\alpha - C_\alpha)(r_\beta - C_\beta)|\phi_i\rangle$$
$$= S_{\alpha\beta}^{cc} - C_\alpha \mu_\beta^{cc} - C_\beta \mu_\alpha^{cc} \tag{2}$$

$$Q_{\alpha\beta}^{cm} = \frac{1}{2}(3S_{\alpha\beta}^{cm} - \delta_{\alpha\beta} S^{cm}) \tag{3}$$

$$S^{cm} = (S_{\alpha\alpha}^{cm} + S_{\beta\beta}^{cm} + S_{\gamma\gamma}^{cm}) \tag{4}$$

where $\mu_\alpha^{cc}$ is the dipole moment at CC, $Z_k$ is the nucleus charge on atom *k*, $C_\alpha$ or $C_\beta$ is the position of CM, $\phi_i$ is the occupied molecular orbital, $S_{\alpha\beta}^{cc}$ is the second moment at CC, $S_{\alpha\beta}^{cm}$ is the second moment at CM, $\delta_{\alpha\beta}$ is the Kronecker delta (if $\alpha = \beta$, $\delta_{\alpha\beta} = 1$; $\alpha \neq \beta$, $\delta_{\alpha\beta} = 0$), and $Q_{\alpha\beta}^{cm}$ is the quadrupole moment at CM.

Dipole moments ($\mu$), polarizabilities ($\alpha$), second moments (*S*), and quadrupole moments (*Q*) are dependent on the rotation of internal coordinate. We take $\vec{s}$ to pass through two oxygen atoms in a dioxin molecule and $\theta$ to be the angle between $\vec{s}$ and the *Y* axis. Dioxin molecules are rotated by $\theta$ to make $\vec{s}$ parallel to the *Y* axis. When we take $\vec{n}$ as a unit vector along the *Y* axis, $\theta$ is expressed as

$$\theta = \mathrm{Cos}^{-1}\left(\frac{\vec{n}\cdot\vec{s}}{|\vec{n}| \times |\vec{s}|}\right) \tag{5}$$

We evaluated the dipole moment, quadrupole moment, and polarizability in the rotated internal coordinate. For example, quadrupole moments (*Q*) in the rotated coordinate system were evaluated from quadrupole moments ($Q^{cm}$) at CM by similarity transformation.[21]

$$[Q] = [TQ^{cm}T^{-1}] \tag{6}$$

$$\begin{pmatrix} Q_{xx} & Q_{xy} & Q_{zx} \\ Q_{xy} & Q_{yy} & Q_{yz} \\ Q_{zx} & Q_{yz} & Q_{zz} \end{pmatrix} = \begin{pmatrix} \cos(\theta) & -\sin(\theta) & 0 \\ \sin(\theta) & \cos(\theta) & 0 \\ 0 & 0 & 1 \end{pmatrix} \times \begin{pmatrix} Q_{XX}^{cm} & Q_{XY}^{cm} & Q_{ZX}^{cm} \\ Q_{XY}^{cm} & Q_{YY}^{cm} & Q_{YZ}^{cm} \\ Q_{ZX}^{cm} & Q_{YZ}^{cm} & Q_{ZZ}^{cm} \end{pmatrix} \begin{pmatrix} \cos(\theta) & \sin(\theta) & 0 \\ -\sin(\theta) & \cos(\theta) & 0 \\ 0 & 0 & 1 \end{pmatrix}$$

The numerical values of the molecular polarizability and QM tensor components for 76 congeners that were calculated in the above way are summarized in Supporting Information.

## Results and Discussion

Figure 1 displays the systematic variation of the polarizability tensors ($\alpha_{xx}$, $\alpha_{yy}$, $\alpha_{zz}$) along the reference axes for the 76 congeners. The successive substitution of lateral chlorines ($\beta$-Cl) preferentially increases $\alpha_{xx}$, whereas the substitution of nonlateral chlorines ($\alpha$-Cl) favorably raises the $\alpha_{yy}$. The $\alpha_{zz}$ values are dependent only on the total number of chlorines, which means both $\alpha$- and $\beta$-chlorines contribute equally to $\alpha_{zz}$. Thus, PCDD polarizabilities seem to vary in a clearly predictable way that is based on the additivity of chlorine substituents. It is noteworthy that the 2,3,7,8-substituted congeners carry the highest values of $\alpha_{xx}$ and the 1,4,6,9-substituted congeners have the highest values of $\alpha_{yy}$. The congeners with the same number of chlorines, however, are all similar in their average polarizabilities [$^1/_3(\alpha_{xx} + \alpha_{yy} + \alpha_{zz})$], which linearly increase with the total number of chlorines (Supporting Information, Figure 1S). The polarizability difference ($\alpha_{xx} - \alpha_{yy}$), which reflects the eccentricity in the polarizability ellipsoid of the molecular plane, also shows a simple linear correlation with the number difference

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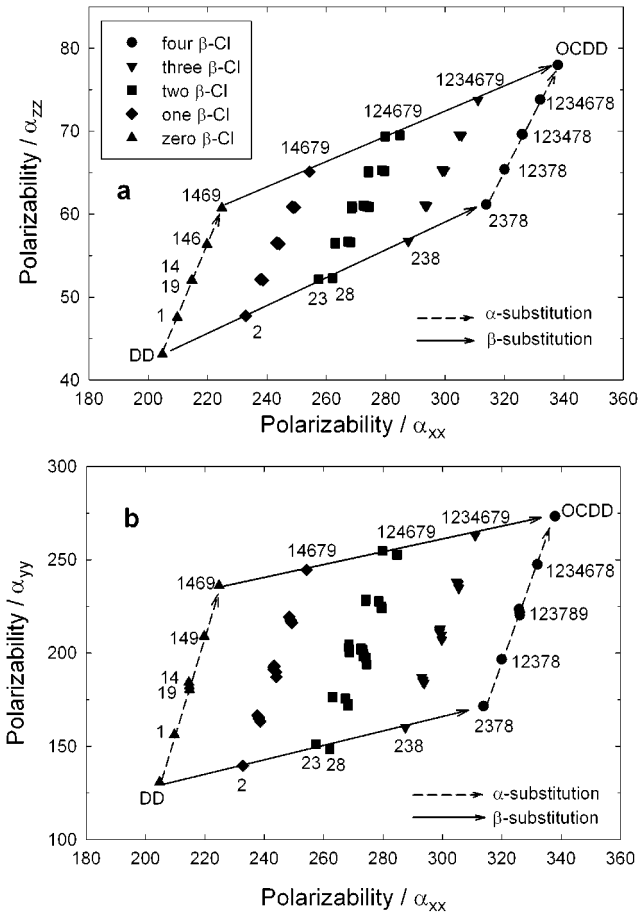


***Figure 1.*** Polarizability tensor components ($\alpha_{xx}$, $\alpha_{yy}$, $\alpha_{zz}$) along the reference axes for 76 dioxin congeners, plotted as (a) $\alpha_{zz}$ vs $\alpha_{xx}$ and (b) $\alpha_{yy}$ vs $\alpha_{xx}$. Polarizabilities are in atomic units (au) where 1 au = $0.165 \times 10^{-40}$ C m$^2$ V$^{-1}$. Congeners are classified into five groups according to the number of $\beta$-Cl; these groups are represented by different symbols. Selected congeners are labeled with numbers representing the positions of chlorine substitution (not all are labeled for clarity).

between the $\beta$- and α-chlorines (Supporting Information, Figure 2S). Since the polarizability in any direction monotonically increases with the number of chlorines (or the number of electrons), the binding affinity due to dispersion-type interactions would be expected to be highest at octachlorodibenzo-*p*-dioxin (OCDD). However, OCDD is known to be a weak ligand to the AhR.[3] There does not seem to be a simple relation between the polarizability and toxicity. McKinney[9] postulated a stacking model in which the molecular polarizability dominates the aromatic−aromatic (receptor−ligand) interaction. However, the polarization energy is mainly related to the size of the aromatic systems[22] and can only account for the effect of the degree of halogenation, not the congener specificity.

Alternative approaches have attempted to take electrostatic effects into account. The importance of the electrostatic component of the noncovalent intermolecular forces between aromatic compounds has been demonstrated theoretically and experimentally for various $\pi \rightarrow \pi$[23−30] and $\pi \rightarrow$ cation[31−36] systems in which the aromatic compounds are considered as hydrophobic anions[31] with large molecular QMs. The molecular QM characterizes the deviation of the overall charge distribution from spherical symmetry. The fact that the dioxin toxic activity is greatest in the symmetric, nondipolar 2,3,7,8-TCDD implies that the electrostatic interactions between the ligand−receptor pair should be described in terms of the higher electric moments. The molecular QMs of aromatic compounds are sensitive to the presence of electron-withdrawing substituents on the aromatic ring, which deplete the $\pi$-electron density and consequently change the QM polarity of the molecule. For example, the sign of the QM (out-of-plane direction) of hexafluorobenzene[27,28] is reversed from that of benzene, and this compound is viewed as a hydrophobic cation.

In Figure 2, the molecular QM tensor components ($Q_{xx}$, $Q_{yy}$, $Q_{zz}$) along the reference axes are plotted as $Q_{zz}$ versus $Q_{xx}$ for the 76 congeners. Since $Q_{xx} + Q_{yy} + Q_{zz} = 0$, $Q_{yy}$ is implicit in this plot and the diagonal line ($Q_{zz} = -Q_{xx}$) represents $Q_{yy} = 0$. The molecular charge distribution in the PCDDs sensitively varies according to the chlorination pattern. In particular, α- and $\beta$-substitution affects the molecular QM in quite different ways. Starting from the parent dibenzo-*p*-dioxin, successive addition of $\beta$-chlorines up to 2,3,7,8-TCDD drastically changes $Q_{xx}$ and $Q_{zz}$, reversing the sign of QMs, whereas addition of α-chlorines up to 1,4,6,9-TCDD changes $Q_{xx}$ and $Q_{zz}$ by a lesser degree. Thus, tetrachlorinated congeners are scattered over the plot, with 2,3,7,8-TCDD and 1,4,6,9-TCDD located at two extremes. This clearly shows the sensitivity of the molecular charge distribution to the substitution positions. The general trends are as follows: (1) $\beta$-substitution shifts $Q_{xx}$ to the negative and $Q_{yy}$ and $Q_{zz}$ to the positive direction, whereas α-substitution moves $Q_{xx}$ to the positive and $Q_{yy}$ to the negative direction; (2) the values of $Q_{zz}$ are stratified according to the number of $\beta$-Cl, whereas the effect of α-substitution on $Q_{zz}$ is unclear; (3) the congeners with more $\beta$-Cl than α-Cl have $Q_{yy} > 0$ (i.e., on the left side of the diagonal line), and those with more α-Cl than $\beta$-Cl have $Q_{yy} < 0$. The $\beta$-substitution not only changes the sign of the QMs ($\pi$-electron cloud above and below the aromatic rings) ($Q_{zz} > 0$) but also polarizes the electron density in the aromatic plane toward the lateral chlorines ($Q_{xx} < 0$) and weakens the negative charges around the oxygen atoms ($Q_{yy} > 0$). The molecular charge variation summarized in Figure 2 generalizes the previous MEP analysis of the specific electrostatic features found in selected highly active congeners.[6−8]

The three-dimensional molecular charge distribution patterns of the PCDDs can be classified into six groups (I−VI) in the $Q_{xx}-Q_{zz}$ plane (Figure 2) such that all congeners in the same group share the same polarity patterns (or three-dimensional

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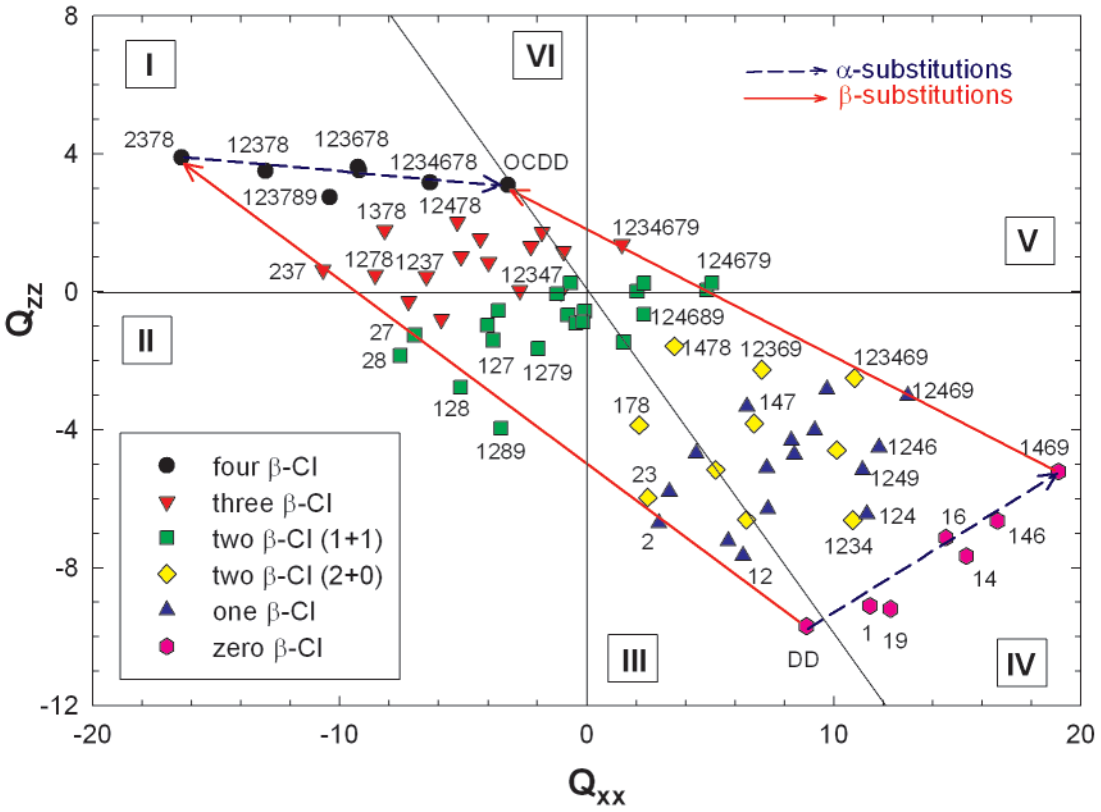


***Figure 2.*** Molecular QM tensor components ($Q_{xx}$, $Q_{yy}$, $Q_{zz}$) along the reference axes for 76 dioxin congeners, plotted as $Q_{zz}$ vs $Q_{xx}$. QMs are in atomic units (au), where 1 au = $4.49 \times 10^{-40}$ C m$^2$. Congeners with the same number of $\beta$-Cl are represented by the same symbol and congeners with two $\beta$-Cl are subdivided into two groups: one with one $\beta$-Cl on each benzene ring (1 + 1) and the other with two $\beta$-Cl on one benzene ring only (2 + 0). Selected congeners are labeled. The three-dimensional molecular polarity patterns are divided into six groups (I−VI) in the $Q_{xx}-Q_{zz}$ plane.

molecular charge distribution pattern) in the *x*, *y*, and *z* directions. The QM sign variations ($Q_{xx}$, $Q_{yy}$, $Q_{zz}$) in each group are group I (− + +), II (− + −), III (+ + −), IV (+ − −), V (+ − +), and VI (− − +). Using this grouping scheme, it is found that all congeners in group I have at least three lateral chlorines. This group contains the most toxic congener (2,3,7,8-TCDD), which gave the highest absolute values of $Q_{xx}$, $Q_{yy}$, and $Q_{zz}$. Group I therefore represents the molecular charge distribution pattern of the most active congeners. The three-dimensional molecular charge distribution around the receptor pocket site is thought to have polarities that are complementary to those of group I ligands. As a result, the unique electrostatic potentials generated around the receptor site selectively recognize group I ligands, which allows the use of the molecular QM of a ligand as a simple diagnostic parameter to determine whether the electrostatics are favorable for binding.

The QMs and the AhR binding affinities ($pEC_{50}$)[3] for selected congeners are compared in Table 1. Results are presented for the 14 dioxin congeners for which the homogeneous data sets of binding affinity to AhR ($pEC_{50} = -\log EC_{50}$) are available. These quantities are well correlated for group I congeners, as shown in Figure 3. Although congeners in other groups such as 1,7,8-TrCDD and 1,2,3,4-TCDD show moderate affinities, their binding seems to be associated with nonspecific interactions through higher dipole moments. Interestingly, we also obtained a good linear correlation between $pEC_{50}$ and the polarizability difference ($\alpha_{xx} - \alpha_{yy}$) for group I congeners (Supporting Information, Figure 3S), although it is hard to rationalize how ($\alpha_{xx} - \alpha_{yy}$) is related to the interaction energy or binding affinity. Since ($\alpha_{xx} - \alpha_{yy}$) values show little congener-specific variation

***Table 1.*** Tensor Components of the Molecular QM ($Q_{xx}$, $Q_{yy}$, $Q_{zz}$) and the Magnitude of the Dipole Moment ($|\mu|$) Compared with the Binding Affinity to AhR ($pEC_{50}$) for 14 Dioxin Congeners[a]

| congener | no. of $\beta$-Cl | QM group (Figure 2) | $Q_{xx}$ | $Q_{yy}$ | $Q_{zz}$ | $\|\mu\|$ | $pEC_{50}$[3] |
|---|---|---|---|---|---|---|---|
| 2378-TCDD | 4 | I | −16.40 | 12.51 | 3.89 | 0.00 | 8.00 |
| 12378-PCDD | 4 | I | −13.01 | 9.50 | 3.50 | 0.44 | 7.10 |
| 123478-HxCDD | 4 | I | −9.23 | 5.71 | 3.52 | 0.09 | 6.55 |
| OCDD | 4 | I | −3.19 | 0.09 | 3.10 | 0.00 | 5.00 |
| 237-TrCDD | 3 | I | −10.69 | 10.05 | 0.64 | 0.64 | 7.15 |
| 1378-TCDD | 3 | I | −8.19 | 6.39 | 1.79 | 0.44 | 6.10 |
| 1278-TCDD | 3 | I | −8.57 | 8.09 | 0.48 | 0.93 | 6.80 |
| 12478-PCDD | 3 | I | −5.25 | 3.23 | 2.03 | 0.36 | 5.96 |
| 12347-PCDD | 3 | I | −2.72 | 2.69 | 0.04 | 0.71 | 5.19 |
| 28-DCDD | 2 | II | −7.56 | 9.41 | −1.85 | 0.72 | 5.50 |
| 178-TrCDD | 2 | III | 2.11 | 1.75 | −3.87 | 1.26 | 6.66 |
| 1234-TCDD | 2 | IV | 10.75 | −4.13 | −6.62 | 1.38 | 5.89 |
| 124-TrCDD | 1 | IV | 11.32 | −4.87 | −6.45 | 1.01 | 4.89 |
| 1-MCDD | 0 | IV | 11.45 | −2.34 | −9.10 | 0.68 | 4.00 |

[a] The electric moments are in atomic unit (au).

within a congener group having the same number difference between the $\beta$- and $\alpha$-chlorines (Supporting Information, Figure 2S), its usefulness as a general molecular parameter to describe the congener-specific activity is questionable. Although the binding and subsequent activation steps could be also controlled by the dispersion interaction,[9] the degree to which the electrostatic interaction between dioxin and the receptor site is optimized seems to be the dominating factor in determining the biological activity. In particular, the electrostatic interaction perpendicular to the molecular plane seems to be critical, because the PCDD congeners are stratified according to the number of $\beta$-chlorines along the $Q_{zz}$ axis. Kim et al.[37] suggested

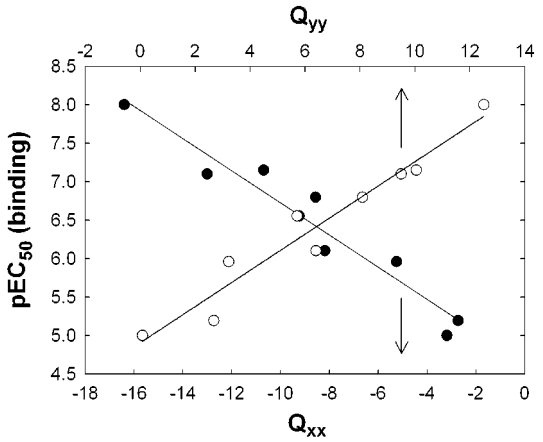


***Figure 3.*** Experimental binding affinities ($pEC_{50}$) for the AhR correlated with $Q_{xx}$ and $Q_{yy}$ for group I congeners, which satisfy the three-dimensional charge polarity requirement for optimum electrostatic interaction. Since $Q_{zz}$ varies within a narrow range (less than four units), the quantitative correlation was rather poor.

that repulsive interactions between the aromatics play a vital role in governing the geometry of the complex. The change in the polarity of $Q_{zz}$ with degree of $\beta$-Cl substitution seems to be related to the reduction of the repulsive interaction at the receptor site.

## Conclusions

In agreement with the high toxicity of laterally chlorinated congeners, these molecules carry a unique charge distribution pattern and the highest polarizabilities along the lateral ($x$) direction, which is consistent with the previous models.[6−11] In particular, the degree to which the electrostatics of the dioxin and receptor are in optimum spatial alignment is the main factor determining the biological specificity of a congener, even though this electrostatic interaction represents only a part of the total interaction energy. This implies that the dispersion-type interaction energy is relatively constant across a series of dioxin congeners with the same degree of chlorination.

Here we propose a hypothesis that our interpretation of the structure−activity relationship in PCDDs in terms of the molecular QM (i.e., electrostatics) as a new molecular descriptor could be generalized to other PHAs whose biological and toxic activity is based on a receptor-mediated mechanism. With this assumption, the use of the QM as an important molecular parameter could provide a simple theoretical tool for assessing the congener-specific toxicity of a wide range of PHAs, despite the unknown structure of the receptor-binding site. Furthermore, this method might be employed to understand the electrostatic interactions between ligands and proteins in general. Further studies are called for to confirm our hypothesis. Finally, with a more extensive homogeneous data set on biological activities of PCDDs available, one could employ statistical methods using multivariate regression (not just simple monovariate regression such as $pEC_{50}$ versus $Q_{xx}$) to get more quantitative understanding of the congener-specific toxicity.

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**Supporting Information Available:** Tables of the polarizability and the quadrupole, dipole, and second moments for 76 dioxin congeners and figures of average polarizability and polarizability differences (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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