Quantitative Structure/Activity Relationships for Laterally Chlorinated Dibenzo-p-Dioxins Using Spectroscopically Generated Molecular Geometry Parameters, Valence-Bond Approximations and Hydrophobicity Parameters

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ABSTRACT
Evaluation of molecular geometry parameters from Fourier transform infrared (FTIR), carbon-13 nuclear magnetic resonance (^{13}C NMR) and animal toxicity data exhibit good structure/activity correlations among the toxic laterally tetrachlorinated dibenzo-p-dioxin congeners for which data is available. COC bond angles, oxonium ion «s» character, and hydrophobicity parameters from cyclodextrin-modified micellar electrokinetic chromato-graphy (CD/MEKC), and from octanol/water partitioning data were correlated with toxicity.

INTRODUCTION

Quantitative structure/activity relationships for chlorinated dibenzo-p-dioxins (CDD) have been have been investigated (1-10) with results indicating enhanced toxicity for congeners containing four lateral chlorine substituents and at least one hydrogen atom (2). Toxicity and induction responses for CDD congeners are both considered to involve binding to cytosolic (Ah) receptors although structure /induction and structure/toxicity responses have been determined to be different (11, 12). Correlations of both interactions with the polarizability properties of chlorinated hydrocarbon-receptor charge transfer complexes have been noted (5) with the results of CNDO/2 calculations on dibenzo-p-dioxin and 2,3,7,8-TCDD (6) indicating that electronic withdrawal by chlorine substituents establishes a potential for 2,3,7,8-TCDD to assume the role of an electron acceptor in a charge transfer complex where the binding strength of the complex is directly proportional to substituent electronegativity. Ab initio calculations (7) conclude that charge stabilization of the ligand-receptor complex is enhanced by lateral chlorine substitution that lowers the effective acceptor energy. Longitudinal chlorine substitution also lowers the effective acceptor energy, with steric blocking interactions between the CDD congener and the receptor reducing toxicity through a lower binding affinity. A recent QSAR investigation(9) also concluded that the most active conformers exhibit the highest electron acceptor properties and reactivities as expressed by the lowest values of E_{LUMO} and $E_{HOMO\text{-}LUMO}$, respectively. Although these computational determinations assumed planar molecular geometries based on limited x-ray crystallography results on 6 congeners, molecular geometry approximations from FTIR (14) data indicate CDD COC bond angles ranging from near- tetrahedral for longitudinally substituted congeners to near-planar for laterally substituted congeners. In this work, correlations between structure and toxicity are examined in terms of spectroscopically generated molecular geometry parameters such as valence-bond charge density differences, COC bond angles and oxonium ion s character, and in terms of hydrophobicity parameters such as cyclodextrin-modified micellar electrokinetic

chromatography (CD/MEKC) capacity factors and octanol/water coefficients.

THEORY

Resonance theory derives from a qualitative treatment of the quantum mechanical description of a system by a wave equation. One approximate valence-bond method for solution of the wave equation is based on the assumption that the wave function can be expressed as a linear combination of known functions:

$$Yo = c_1f_1 + c_2f_2 + ... + c_nf_n = Sc_if_i \qquad (1)$$

where Yo represents a wavefunction for a specific canonical form, and c represents a weighting coefficient. Each wave function corresponds to some definite value E for the energy of the system and can be correlated with delocalization parameters at a specific site. The wavefunction for the nth state of a system can be expanded as:

$$Y_n = Y_n^{(o)} + lY_n^{(1)} + l^2Y_n^{(2)} + ... \qquad (2)$$

where l is a perturbation parameter(0 £ l £ 1)chosen such that as l -> 0, Y_n -> $Y_n^{(0)}$ and equation (2) can be used for the unperturbed state. From infrared data, substitution patterns for dibenzo-p-dioxins can be determined from characteristic model ring aromatic skeletal stretching [Vcc(arom)] frequencies and the most intense aromatic skeletal stretching frequency band [Vcc(arom)MAX]. The degree of chlorine substitution can be determined from the [Vcoc(asym)/Vcc(arom)] ratio. The identities of specific synthetic isomer pair components may be determined from:

$$Vcoc(asym) = V^ococ(asym) + SnS + F + Q \qquad (3)$$

where $V^ococ(asym)$ is the value (cm^{-1}) of the dominant model ring, SnS represents the number (n) of laterally stabilized delocalizations (S) among chlorine substituents on the two aromatic rings in the system that affect the partial double bond character of the ether linkage, and F and Q are steric interaction terms that respectively describe nonbonded interaction effects. For NMR, the magnetic shielding constant [s] derives from three additive shield-ing parameters representing diamagnetic, paramagnetic, and neighboring group anisotropy contributions, respectively. For 13C, the paramagnetic shielding term ($s_{[para]}$) dominates, and may be expressed as

$$s_{[para]} = [C(DE^{-1})(r^{-3})][Q_{aa} - SQ_{ax}] \qquad (4)$$

where [Q_{aa} -SQ_{ax}] represents the charge density/bond order matrix for the 2p electrons. Steric repulsion and extended HMO calculations both predict upfield shifts from small charge density increases at sterically perturbed nuclei.

RESULTS AND DISCUSSION

Molecular geometry parameters, toxicity values and hydrophobicity parameters for laterally chlorinated dibenzo-p-dioxins are presented in Table 1. The a values for FTIR and x-ray

Table 1. Spectroscopically derived molecular geometry parameters, partitioning parameters and toxicity parameters for laterally chlorinated dibenzo-p-dioxins

CDD	COC bond angle(a) FTIR/X-ray[12]	13C $C_{a/b}$ chemical shift(d)	« s» character Oxonium ion	log P_{ow} [15]	CD/MEKC capacity factor (k')	LD-50(mg/kg) Guinea pigs[14]	Mice[3]
DPD	117.0/116.3	141.7	0.307/0.302	5.47/5.00«	1.44		
27	116.8/116.3	141.9b	0.306/0.302	6.23/5.75«	1.32		
28	114.1/114.7	141.7b	0.285/0.290		1.32	300	
23	120.8	140.8	0.336	6.23/5.60«	0.49		
237	116.3	140.6a	0.302	6.97	0.91	29	
2378	115.1/115.7	139.6	0.293/0297	7.70/7.20«	1.49	0.001	0.284
12378	114.7	137.2a	0.290	8.41/7.40«	2.55	0.003	0.338
123678	111.3		0.263	9.13	5.53	0.1	1.250
123789	112.3/117.5		0.272/0.311			0.1	1.440
123478	110.0	136.7a	0.254	7.80«	5.19	0.073	1.250
1234678				8.00«		7.2	
r^2 toxicity correlation	0.830G 0.871M		0.830G 0.876M	0.736G 0.960M	0.968G 0.981M		

« experimental values

crystallography generated COC bond angles are averages for a specific congener. Correlations with toxicity were calculated for laterally tetrachlorinated dibenzo-p-dioxins. The FTIR COC bond angles were calculated using mass approximations for the terminal atom in a nonlinear XY_2 model while neglecting the valence force equation symmetric bending term (12). The «s» character values for the oxonium ion (representing hybridization and the degree of partial double bond character) were calculated from a values. The highest degree of s character(and the highest degree of partial double bond character) in the laterally tetrachlorinated dibenzo-p-dioxin (LTCDD) congener group is exhibited by 2,3,7,8 - TCDD. This maximum value for 2,3,7,8-TCDD as a function of model ring electron-withdrawing capacities, steric and delocalization parameters is consistent with calculated Vcoc(asym values) from Equation 3. The heterocyclic carbon atoms located para to carbon 2 and carbon 3 are designated c_b and c_a , respectively. According to Equation 4, charge density/bond order correlations with paramagnetic shielding result in shifts to higher field. The higher field chemical shift value of 2,8- DCDD relative to 2,7-DCDD results from each of 2 canonical forms for the former isomer exhibiting one laterally stabilized delocalization. The higher field c_a values of 1,2,3,7,8-PnCDD and 1,2,3,4,7,8-HxCDD (relative to 2,3,7,8-TCDD) are generated by the steric sheilding effects of one and two longitudinal chlorine substituents, respectively. In spite of the larger charge density values, increasing degrees of longitudinal substitution have been shown to distort planarity and to decrease the transmission of delocalization effects through the aromatic system, resulting in a decrease in acceptor/receptor complex binding. Until empirically determined values for steric, inductive and delocalization effects are defined for ^{13}C NMR chemical shifts, infrared oxonium ion «s» character values exhibit reasonable correlations for molecular geometry parameters that contribute to LTCDD frontier

orbital electron acceptor properties in the ligand/receptor complex. The k' values represent partitioning ratios between g-cyclodextrin and SDS micelles in a borate buffer. Partitioning in octanol/water systems has been quantitatively correlated with physicochemical properties and biological activity where contributions from several parameters can be expressed through application of multiple linear regression. In this context, biological activity can be manifested as a summation of specific interactions that a compound experiences during transport through membranes and reaction at the active site. For CDD congeners, k' values from CD/MEKC determinations exhibit a higher linear correlation with toxicity than log P_{ow} . This may be attributed to steric and electronic interactions of the CDD congeners with g-CD active sites that more closely approximate receptor interactions than solvent partitioning coefficients.

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