Electron-Acceptor Properties of Chlorinated Dibenzo-*p*-Dioxins

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The chemical and biological properties of 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD, Structure I) are becoming well-documented. TCDD is virtually insoluble in water and most organic solvents (CRUMMETT et al., 1973), has a high affinity for cytosol protein (POLAND and GLOVER, 1976), binds tightly to soil (HELLING 1970), is rapidly photoreduced (CROSBY et al., 1971), and is exceptionally toxic (SCHWETZ et al., 1973), teratogenic (NEUBERT et al., 1973), and mutagenic (HUSSAIN et al., 1972), intercalating between base pairs in DNA (HUSSAIN et al., 1972). The binding characteristics suggest that complexation may be important in the unusual properties of TCDD; charge-transfer would seem the most reasonable, as TCDD has six electronegative atoms available to stabilize added charge.

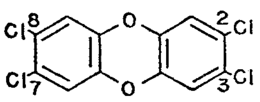
Charge-transfer complexes can be described (MULLIKEN and PERSON, 1969) in terms of a total wave function ψN:

$$\psi N(AD) = a\psi_o(A,D) + b\psi_1(A^+D^-)$$

where A and D are the acceptor and donor molecules, respectively. The wave function $\psi_o(A,D)$ representa a non-bonded resonance structure of separate molecules, while $\psi_1(A^+D^-)$ represents a resonance structure where an electron has been completely transferred from donor to acceptor. Factors which tend to increase this second species increase the extent of charge-transfer interaction (complexation); for example, the more electron-deficient the atoms to receive charge in the acceptor, the stronger the binding of the resulting complex.

Our purpose in performing molecular orbital calculations was to analyze the electron distribution in both the unchlorinated dibenzo-p-dioxin (II) and TCDD, particularly their first unoccupied orbitals which would receive the greatest proportion of added charge in any charge-transfer interaction (MULLIKEN and PERSON, 1969). In this way, we hope to demonstrate that neutral TCDD can be viewed as an electron acceptor; rationalize the necessity of halogenation for toxicity; and explain the chlorination pattern required for toxicity [i.e., 2,3,7,8-TCDD is toxic, while 1,2,3,4-TCDD is not (KHERA and RUDDICK, 1973)].

Bulletin of Environmental Contamination & Toxicology,
Vol. 18, No. 5 © 1977 by Springer-Verlag New York Inc.



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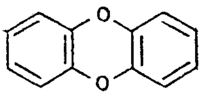

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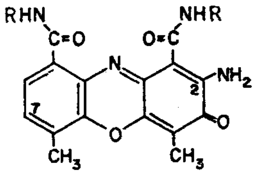

III

METHODS

Molecular orbital calculations were performed with the CNDO/2 and Parsier-Parr-Pople (PPP) computer programs. Both programs represent semi-empirical methods which have received extensive parameterization to fit the vacuum properties of test molecules. The CNDO/2 is a valence-electron calculation based on the parameterization of POPLE and BEVERIDGE (1969) and has been shown to provide satisfactory electron-density predictions for both paired and unpaired electrons. The PPP program is a pi-electron calculation, with a charge iteration developed by GRABE and SKANCKE (1972) to take into account polarization of the sigma core electrons and parameterization by ROSS and SKANCKE (1967), HÖJER (1969), and GRABE (1968); coupled with the open-shell techniques of Roothan, it has given satisfactory results for charge-transfer complexes between chloranil and tyrosine (WALAH and INGRAHAM 1976).

The maximum deviation in the largest density-matrix element was less than 0.001 electron units and maximum charge deviation on any atomic center was 0.01 electron units. The bond angles and bond lengths were taken from x-ray diffraction data of BOER et al., (1973). Both TCDD and unsubstituted dibenzo-*p*-dioxin have been shown to be virtually planar (BOER et al., 1973; CORDES and FAIR 1974), and our calculations assumed planarity.

RESULTS AND DISCUSSION

Valence-shell (CNDO-2) and radical-anion unpaired (PPP) electron densities were calculated for the ground states of TCDD and unchlorinated dibenzo-p-dioxin (Tables I-III) to determine which atoms are electron-deficient; if stabilized complexation does occur, the added charge should be distributed primarily on these. For simplicity, the carbon positions are relabelled A, B, and C as shown in Table I. Examination of the valence-shell population of dibenzo-p-dioxin (Table I) shows that the hydrogen atoms weakly donate electrons into the carbon skeleton, the A and B carbons are almost neutral and have approximately the same populations, and each C carbon adjacent to an oxygen is deficient by 0.13 electrons. When the ring is chlorine-substituted (TCDD), an electron-withdrawing element replaces the electron-donating one, and re-examination of the B and C positions now shows them both to be electron-deficient; in fact, the carbon skeleton has a total deficiency of 0.84 electron. The chlorines and oxygens obviously are the recipients (0.42 and 0.56 electrons, respectively). TCDD is seen to be a charge-transfer acceptor.

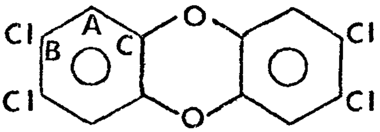

TABLE I. CNDO/2 Gross Atomic Population (Valence Shell) of TCDD and Dibenzo-p-dioxin

Atom	Position	Valence Shell Population[a]	
		TCDD	Dibenzo-p-dioxin
C	A	4.02	4.03
C	B	3.91	4.01
C	C	3.86	3.87
O	O	6.21	6.22
Cl	Cl	7.14	----
H	H_A	----	0.98
H	H_B	0.96	0.99

[a] Values ± 0.01 electrons.

When the acceptor in a charge-transfer complex receives electrons, it must do so primarily into an unfilled orbital the characteristics of which can be calculated with the PPP program. It is of interest to determine which chlorination pattern would most stabilize a radical anion--the extreme case of complete donation of an electron to a tetrachlorodibenzo-p-dioxin--and to ascertain which atoms would be expected to receive the greatest proportion of the donated charge. In the unchlorinated dioxin (Table II), nearly all of the charge is distributed to the B and C positions; one can predict that chlorination at the B position would increasingly stabilize added charge, while chlorination at the A position would have a much smaller effect. Indeed, the

TABLE II. PPP Unpaired Electron Densities of Radical Anions of TCDD and Dibenzo-p-dioxin

Atom	Position	Densities[a]	
		TCDD	Dibenzo-p-dioxin
C	A	0.027	0.025
C	B	0.143	0.136
C	C	0.131	0.141
O	O	0.004	0.004
Cl	Cl	0.004	-----

[a] Values ± 0.001 electrons

calculation shows that the B and C positions in TCDD receive nearly all of the added electron, while chlorines and carbons at the A positions participate very little.

The effects of the chlorine atoms on complex-stability is apparent when the CNDO/2 and PPP contributions are combined for these radical-anions (Table III). Each B position of dibenzo-*p*-dioxin now is decidedly negative, contributing to a total carbon-skeleton charge of 0.92 electron, while the TCDD carbon-skeleton is closer to electroneutrality (more stable) by 0.52 electron. The oxygens and chlorines once more are the electron recipients.

TABLE III. Summation of CNDO and PPP Densities for Radical Anions

Atom	Position	Total Density	
		TCDD	Dibenzo-*p*-dioxin
C	A	4.05	4.06
C	B	4.06	4.15
C	C	3.99	4.02
O	O	6.21	6.22
Cl	Cl	7.14	----

These calculations indicate that halogenation of dibenzo-*p*-dioxins at the B-positions offer considerable structural stabilization to added charge; the greater the degree of chlorination at these positions, the stronger the charge-transfer complex would be. Chlorination at A positions provides much poorer acceptors--precisely the observed chlorination requirement for dioxin toxicity. Analogous patterns in other chlorinated compounds (biphenyls, dibenzofurans, anthracenes, etc.) should confer similar but less pronounced acceptor (and toxic) activity.

The calculations also may provide a rationale for the unusually firm binding of TCDD to soil and protein, both of which tend to be electron-rich or to contain electron-donors. Other chlorinated compounds, such as DDT (O'BRIEN and MATSUMURA 1964), are considered to be charge-transfer acceptors and exhibit similar binding properties. This suggests that TCDD might be solubilized by the presence of suitable electron-donors, displaced from its complexes by stronger electron-acceptors, or bound preferentially by a specific electronegative protein in target organs such as the liver. Charge-transfer binding to bases such as guanine (SLIFKIN 1972) may help to explain TCDD mutagenicity.

The electropositivity of the rings is further reflected in the very slow metabolic decomposition of TCDD (VINOPAL and CASIDA 1973), as the electron-seeking oxygenation reactions normally dominate the metabolism of aromatic compounds. On the other hand, the absorption of a photon by this electropositive system could facilitate the release of a chlorine radical from a B position and contribute to the observed propensity of TCDD toward hydrogen-abstraction from surrounding solvent (photoreduction) (CROSBY et al., 1971).

The combination of DNA-intercalation, charge-transfer complexation, and diminished oxidative degradation may be a dangerous one. For example, the highly toxic actinomycin D (III), R = pentapeptide) is, like TCDD, a good charge-transfer acceptor (SLIFKIN 1972); it, too, intercalates in DNA (MÜLLER and CROTHERS, 1968) and is very teratogenic (TUCHMANN-DUPLESSIS and MERCIER-PAROT 1960). One can conceive of chlorinated ethers, acridine dyes, coumarins, and other substances which could share these properties. However, that TCDD does in fact serve as a stable biological electron-acceptor must await experimental verification.

ACKNOWLEDGMENT

This research was supported in part by training grant ES-00125 (to G.M.) from the National Institute of Environmental Health Sciences and by USDA Regional Research Project W-45.

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