Theor Chim Acta (1987) 72:507-517

Theoretica Chimica Acta

Electrostatic potentials of some dibenzo-*p*-dioxins in relation to their biological activities*

Jane S. Murray and Peter Politzer

Department of Chemistry, University of New Orleans, New Orleans, LA 70148, USA

(Received May 19/Accepted June 11, 1987)

A computational analysis of the electrostatic potentials of eight halogenated dibenzo-*p*-dioxins has been carried out at the *ab initio* SCF STO-5G level. It focuses upon the relationships between these potentials and the biological activities of the molecules, including toxicity, aryl hydrocarbon hydroxylase induction and receptor binding. In general, regions of negative potential are found to be associated with the oxygens and with the halogen substituents. Biological activity appears to be related to the presence of an optimum range of negative potentials above the lateral portions of the molecules in conjunction with a weakening of those near the oxygens.

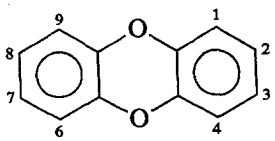
Key words: Dibenzo-*p*-dioxins — *ab initio* SCF — Electrostatic potentials

1. Introduction

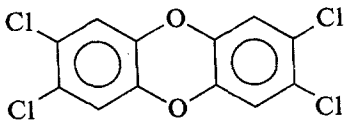
In the initial phase of this continuing computational study of the properties and behavior of substituted dibenzo-*p*-dioxins [1], we compared the electrostatic potentials of the parent molecule, dibenzo-*p*-dioxin (I), and three of its derivatives, among them the highly toxic and notorious 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD, II). We now extend our analysis to the systems III–X, again focusing upon the relationship between their electrostic potentials and their biological activities. The latter include varying degrees of toxicity, aryl hydrocarbon hydroxylase induction, and receptor binding.

The toxic responses elicited by some halogenated dibenzo-*p*-dioxins include carcinogenesis, gastric lesions, hepatotoxicity, loss of lymphoid tissue, acute loss of weight, and chloracne [2–4]. These compounds also induce aryl hydrocarbon hydroxylase (AHH) activity to differing extents [5, 6]; this is a microsomal enzyme

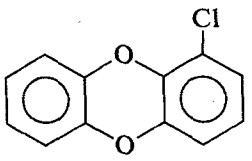
* Dedicated to Professor J. Koutecký on the occasion of his 65th birthday



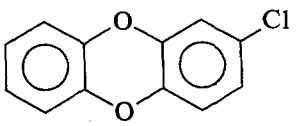
I



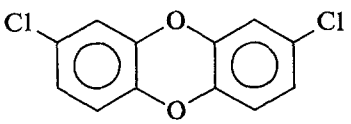
II



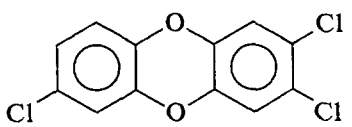
III



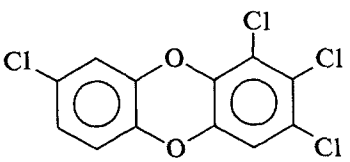
IV



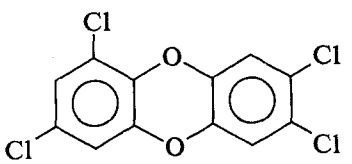
V



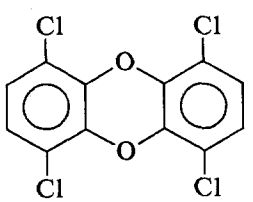
VI



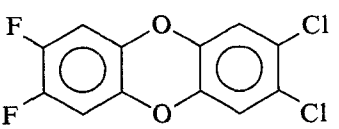
VII



VIII



IX



X

system that is involved in the metabolic oxidation of aromatic hydrocarbons, producing metabolites that are in some instances carcinogenic [7, 8]. Laboratory studies have revealed a good correlation, for a series of dibenzo-*p*-dioxins, between toxicity and AHH induction [4, 5, 6, 9]. Certain structural features have also been identified as being associated with both types of activities [3, 6]: (a) At least three of the four lateral positions (2, 3, 7 and 8) must be halogenated (especially with chlorines or bromines). A greater degree of activity is observed if all four of these positions bear halogens. (b) The effectiveness of the halogens

in inducing toxicity and AHH activity decreases in the order Br > Cl > F. (c) At least one ring position must be unsubstituted.

Another study has demonstrated a very good correlation between AHH induction and binding to a cytosolic receptor, for a group of 23 halogenated dibenzo-*p*-dioxins and dibenzofurans [3]. It is believed that the toxicities of these compounds are also receptor-mediated, via an initial recognition step [10, 11].

In such a recognition process, the receptor "recognizes" that an approaching molecule possesses certain features that would promote their mutual interaction. This recognition is believed to occur when the molecule and receptor are at a relatively large separation, prior to any charge polarization or covalent bond formation. It has been shown that an effective means of identifying key features that will lead to such recognition is through the analysis of the electrostatic potential that is created in the space around a molecule by its nuclei and electrons [12–17]; it is this potential that initially affects the receptor. We accordingly focus our efforts upon determining the patterns of positive and negative potentials, among the substituted dibenzo-*p*-dioxins, that are associated with varying degrees of receptor interaction, toxicity and AHH induction.

While there are certainly good correlations between these different types of activities, there do exist some discrepancies. For example, 2,3,7-trichlorodibenzo-*p*-dioxin (VI) and 2,3,7,9-tetrachlorodibenzo-*p*-dioxin (VIII) have nearly the same receptor binding affinities but the latter is 10 times more toxic [6]. The analysis of such discrepancies should lead eventually to the elucidation of the factors involved in the various types of activities.

2. Methods and procedure

The molecular electrostatic potential at any point $\hat{r}$ is given rigorously by Eq. (1):

$$V(\boldsymbol{r}) = \sum_A \frac{Z_A}{|\boldsymbol{R}_A - \boldsymbol{r}|} - \int \frac{\rho(\boldsymbol{r}')\, d\boldsymbol{r}'}{|\boldsymbol{r}' - \boldsymbol{r}|} \tag{1}$$

Z_A is the charge on nucleus A, located at $\boldsymbol{R}_A$, and $\rho(\boldsymbol{r})$ is the electronic density function of the molecule, which we obtain by an *ab initio* self-consistent-field molecular orbital procedure. The first term on the right side of Eq. (1) represents the contribution of the nuclei, which is positive; the second term brings in the effect of the electrons, which is negative.

The electrostatic potential is a well-established analytical tool for interpreting and predicting biological recognition processes (e.g. drug-receptor and enzyme-substrate interactions), as well as other aspects of molecular reactivity [17–20]. An important feature of $V(\boldsymbol{r})$ is the fact that it is a real physical property, which can be determined experimentally by diffraction techniques as well as computationally [20].

We have computed the electrostatic potentials of molecules III–X at the STO-5G level, using the GAUSSIAN 82 system of programs [21]. We modeled the

geometries after the crystallographically-determined structure of TCDD (II) [22]. C–H and C–F bond lengths were taken to be 1.08 Å and 1.35 Å, respectively [23, 24]. For each molecule, we calculated the electrostatic potentials at 1.75 Å above the molecular plane, since this is what a receptor would encounter; 1.75 Å is the van der Waals radius of the largest atom (chlorine) that these molecules contain [25]. We also computed $V(r)$ in the perpendicular plane through the oxygens, in order to examine the effects of varying degrees of substitution upon the negative regions near the oxygens.

3. Results and discussion

In Table 1 are listed the most negative values (the minima) of the calculated electrostatic potential in the plane 1.75 Å above each molecule I–X. Also included in this table are the minima near the oxygens, as obtained from the perpendicular plots.

It is seen that only the parent molecule, dibenzo-*p*-dioxin (I), has negative regions above the aromatic rings; these can be attributed to the pi electrons. (A plot of the electrostatic potential of I at 1.75 Å above its molecular plane is given in Ref. 1.) The inductive electron-withdrawing effect of just one chlorine substituent, however, is enough to eliminate these negative potentials; it is particularly noteworthy that this occurs even for the ring that does not bear the chlorine (see results for III and IV in Table 1.)

The strong inductive power of chlorine is seen again in examining the negative regions associated with the oxygens. These show a general weakening as more

Table 1. Calculated electrostatic potential minima (kcal/mole)

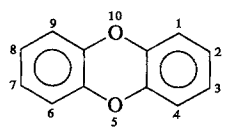
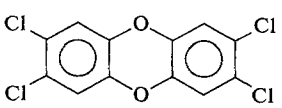
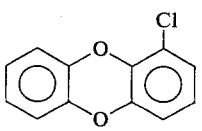
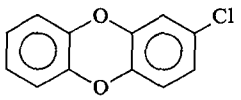
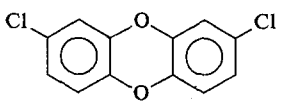
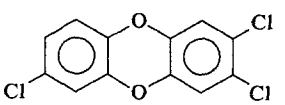
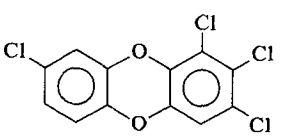
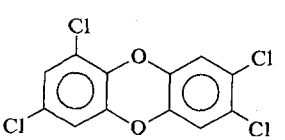
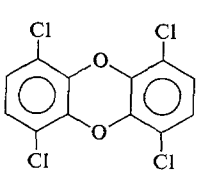
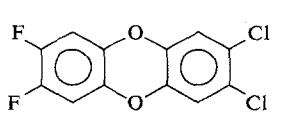
Molecule	$V(r)$ minima at 1.75 Å above molecular plane	$V(r)$ minima near oxygens, in perpendicular plane
 I	−11.6 (0)[a] −5.8 (aromatic rings)[a]	−50.7[a]
 II	−12.9 (Cl)[a]	−28.9[a]
 III	−20.5 (Cl) −7.2 [O(5)]	−50.5 [O(10)] −45.5 [O(5)]

Table 1.—*continued*

Molecule	$V(r)$ minima at 1.75 Å above molecular plane	$V(r)$ minima near oxygens, in perpendicular plane
 IV	−18.6 (Cl) −7.3 [O(10)] −6.8 [O(5)]	−45.5 [O(10)] −44.0 [O(5)]
 V	−16.4 (Cl) −3.3 [O(10)] −2.1 [O(5)]	−39.4 [O(10)] −38.7 [O(5)]
 VI	−14.9 [Cl(2)] −14.8 [Cl(3)] −14.4 [Cl(7)]	−34.2 [O(10)] −35.5 [O(5)]
 VII	−12.5 [Cl(1)] −13.5 [Cl(2)] −11.4 [Cl(3)] −13.4 [Cl(8)]	−34.6 [O(10)] −29.6 [O(5)]
 VIII	−13.7 [Cl(2)] −13.3 [Cl(3)] −10.5 [Cl(7)] −11.3 [Cl(9)]	−34.5 [O(10)] −29.6 [O(5)]
 IX	−14.8 (Cl)	−40.1
 X	−15.1 (Cl) −3.2 (F)	−34.7

[a] Data for II and III are taken from [1]

chlorines are introduced, going from −50.7 kcal/mole for the unsubstituted dibenzo-*p*-dioxin, I, to −28.9 kcal/mole for 2,3,7,8-tetrachlorodibenzo-*p*-dioxin, II. There is a parallel decrease in the sizes of these negative regions. For example, whereas in *V*, which has two chlorines, the negative oxygen potentials extend beyond 1.75 Å above the molecular plane (Figure 1), the substitution of a third chlorine, as in VI, reduces their sizes to such an extent that no negative values remain at 1.75 Å (Figure 2). The apparent exceptions to these observations—such as IX, in which the oxygen potentials are more negative than might be anticipated with four chlorines—can be explained on the basis of the proximity of the substituents to the oxygens; the negative regions of the chlorines overlap those of the oxygens, and the latter are consequently reinforced.

Table 1 and Figs. 1-6 show that there are invariably negative potentials at 1.75 Å above the chlorine and fluorine substituents. These become weaker and less negative as the number of halogens increases (again taking into account overlapping with oxygen negative regions). This is consistent with earlier observations that as the number of electron-withdrawing substituents increases, each of them becomes less negative, since it is receiving a smaller share of the polarizable electronic charge [1, 26].

In this context it is interesting to compare the halogen potentials (at 1.75 Å) in X with those in II and VI (Table 1 and Figs. 2 and 3). The chlorines in the 2 and 3 positions of *X* are more negative than their counterparts in either II or VI, indicating that they are more successful in competing for the polarizable electronic charge against two fluorines than against even only one chlorine (as in VI). This reflects the fact that the capacity of fluorine for accommodating additional electronic charge diminishes rather rapidly, despite its high intrinsic electronegativity [27-31].

Of the molecules that we have studied, the ones that are biologically relatively inactive are I, III-V, and IX [3, 5]. We observe in Table 1 and Figs. 1, 4 and 5, that these are also the molecules that have the largest and strongest negative potentials associated with the oxygens; they all extend to at least 1.75 Å above the molecular plane and they have the most negative oxygen minima that have been found in this work. We have suggested earlier that biological activity on the part of the substituted dibenzo-*p*-dioxins may require that the negative potentials of the oxygens be rather weak [1]. Our results in this work are consistent with this speculation.

A second factor that we have tentatively linked to biological activity is the presence of relatively strong negative potentials above the two lateral regions of the molecule (positions 2, 3 and 7, 8) [1]. This can be achieved, for example, by having halogen substituents at these positions. Again, our present results support this hypothesis. Thus, Figs. 2 and 6 show that molecules VI and VII have negative potentials above one lateral region and half of the other. The same is true of VIII (see Table 1). All three of these molecules do show some degrees of activity, although less than TCDD (II), which has both lateral regions completely negative. On the other hand, none of the five inactive molecules (I, III-V, and IX) has even one lateral region that is completely negative (Table 1 and Figs. 1, 4 and 5).

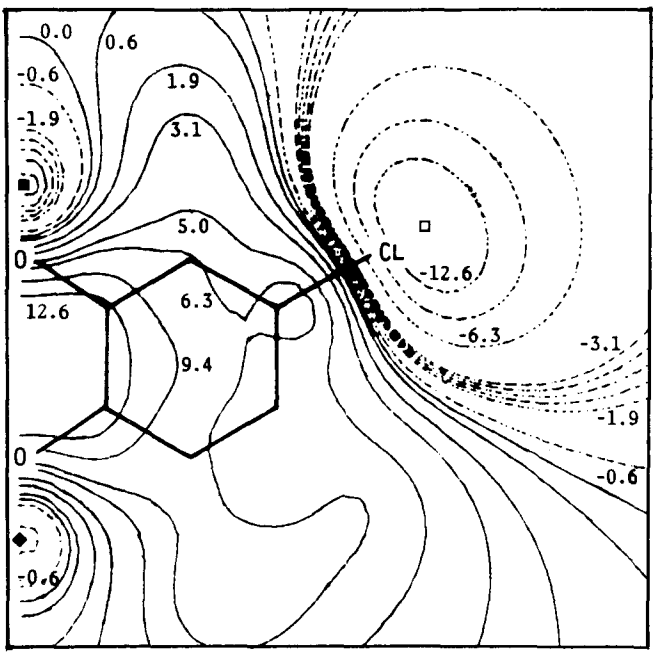


Fig. 1. Calculated electrostatic potential of 2,8-dichlorodibenzo-*p*-dioxin (V), in kcal/mole, at 1.75 Å above molecular plane. Half of plane is shown. *Dashed contours* correspond to negative potentials. Positions of most negative potentials are indicated; the values are: □ −16.4; ■ −3.3; ◆ −2.1 kcal/mole

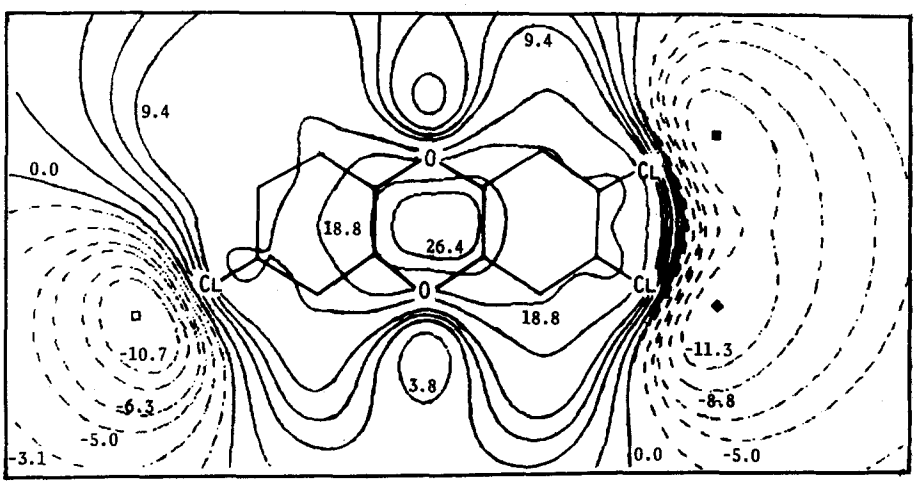


Fig. 2. Calculated electrostatic potential of 2,3,7-trichlorodibenzo-*p*-dioxin (VI), in kcal/mole, at 1.75 Å above molecular plane. *Dashed contours* correspond to negative potentials. Positions of most negative potentials are indicated; the values are: ■ −14.9; ◆ −14.8; □ −14.4 kcal/mole

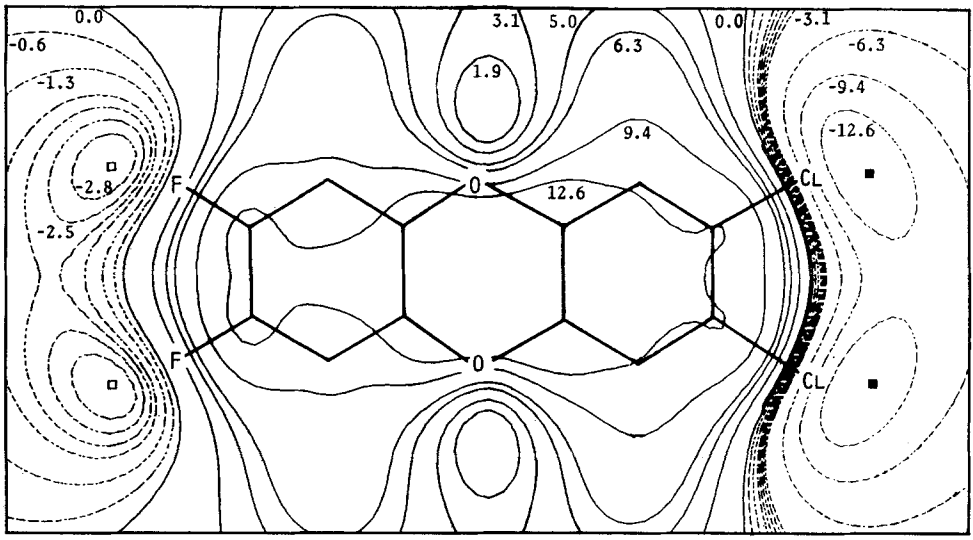


Fig. 3. Calculated electrostatic potential of 2,3-dichloro-7,8-difluorodibenzo-*p*-dioxin (X), in kcal/mole, at 1.75 Å above molecular plane. *Dashed contours* correspond to negative potentials. Positions of most negative potentials are indicated; the values are: ■ −15.1; □ −3.2 kcal/mole

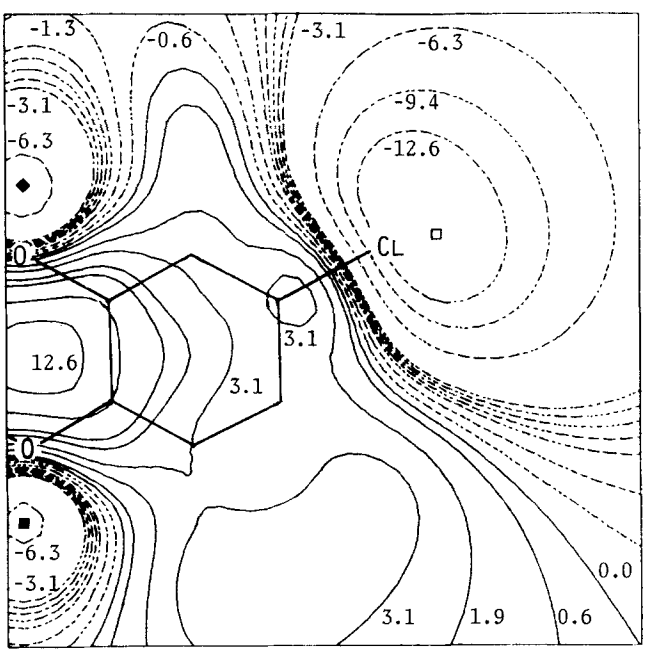


Fig. 4. Calculated electrostatic potential of 2-chlorodibenzo-*p*-dioxin (IV), in kcal/mole, at 1.75 Å above molecular plane. The side with the oxygen is shown. *Dashed contours* correspond to negative potentials. Positions of most negative potentials are indicated; the values are: □ −18.6; ◆ −7.3; ■ −6.8 kcal/mole

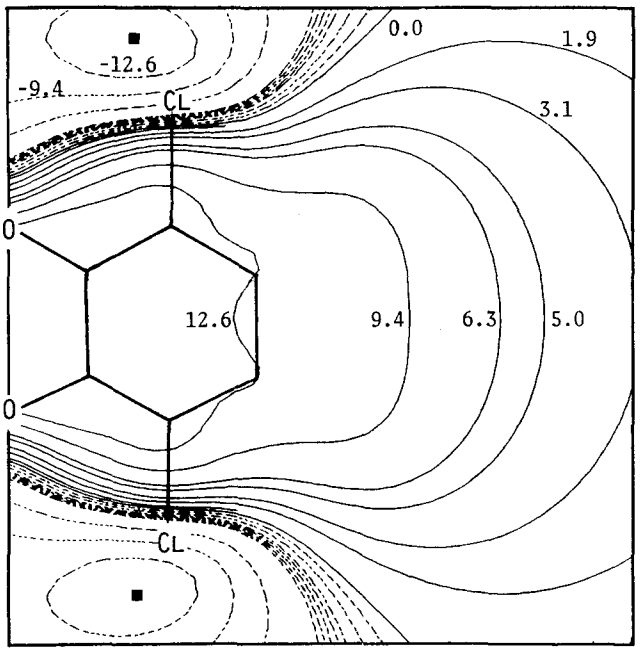


Fig. 5. Calculated electrostatic potential of 1,4,6,9-tetrachlorodibenzo-*p*-dioxin (IX), in kcal/mole, at 1.75 Å above molecular plane. Half of plane is shown. *Dashed contours* correspond to negative potentials. Positions of most negative potentials are indicated; the values are: ■ −14.8 kcal/mole

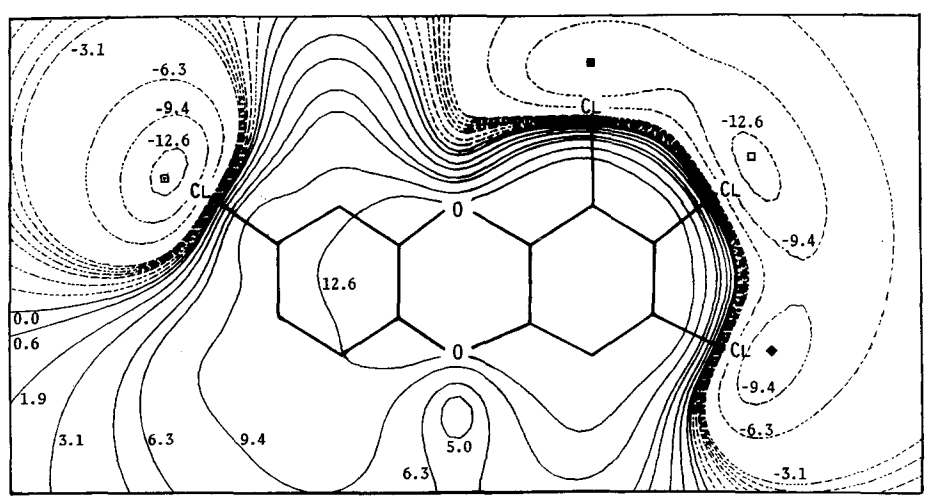


Fig. 6. Calculated electrostatic potential of 1,2,3,8-tetrachlorodibenzo-*p*-dioxin (VII), in kcal/mole, at 1.75 Å above molecular plane. *Dashed contours* correspond to negative potentials. Positions of most negative potentials are indicated; the values are: □ −13.5; ⊡ −13.4; ■ −12.5; ◆ −11.4 kcal/mole

It should be noted, however, that while both lateral regions are completely negative in the highly active TCDD, the magnitudes of these potentials are relatively low (Table 1). Indeed, in the group II, VI and VIII, biological activity increases as the lateral potentials become less negative [6, 32]. It may be, therefore, that there is some optimum intermediate magnitude for the potentials in these regions. Accordingly, the low activity of X [32] may be either because the chlorine side is too negative or the fluorine side not negative enough, or both.

Up to this point, we have carried out electrostatic potential analyses for a relatively small number of dibenzo-*p*-dioxin derivatives. We have accordingly limited ourselves to relating these results only to the general biological activities of the molecules. As more systems are studied, however, it should become possible to be more specific, and to identify qualitative and/or quantitative features of their electrostatic potentials that correlate with particular types of activities. This will eventually permit a better understanding of such situations as molecules VI and VIII having similar receptor binding affinities but differing significantly in AHH induction and toxicity.

4. Summary and conclusions

Our results in this work, as in our earlier study [1], focus attention upon the electrostatic potentials above the lateral regions and the oxygens of the substituted dibenzo-*p*-dioxins. Biological activity appears to be associated with the presence of negative potentials above all or most of the lateral regions; our present findings indicate that there may be a certain optimum range of magnitudes (in the neighborhood of −13 kcal/mole when computed with the STO-5G basis set). Above the oxygens, the need seems to be for considerably weaker negative potentials than those in the unsubstituted parent molecule. Our further studies will seek to determine specifically how these factors, separately or in combination, are related to each of the several forms of biological activity—receptor binding, AHH induction, and toxicity.

Acknowledgements. We express our appreciation to the U.S. Environmental Protection Agency for partial funding of this work under cooperative agreement number CR-813013-01-0 to Peter Politzer. The contents do not necessarily reflect the views and policies of the Environmental Protection Agency, nor does mention of trade names or commercial products constitute endorsement or recommendation for use. We are also grateful for the financial support provided by the University of New Orleans Computer Research Center.

References

1. Murray JS, Zilles BA, Jayasuriya K, Politzer P (1986) J Am Chem Soc 108:915
2. Pitot HC, Goldsworthy T, Campbell HA, Poland A (1980) Cancer Res 40:3616
3. Poland A, Knutson JC (1982) Annu Rev Pharmacol Toxicol 22:517
4. Windholz ME (1983) The merck index, 10th edn. Merck, Rahway, NJ, p 8957
5. Poland A, Glover E (1973) Mol Pharmacol 9:736
6. Kende AS, Wade J, Ridge D, Poland A (1974) J Org Chem 39:931

7. Harvey RG (1981) Acc Chem Res 14:218
8. Guengerich FP, Macdonald TL (1984) Acc Chem Res 17:9
9. McKinney JD, Chae K, Gupta BN, Moore JA, Goldstein JA (1976) Toxicol Appl Pharmacol 36:65
10. Poland A, Glover E, Kende AS (1976) J Biol Chem 251:4936
11. Goldstein JA (1980). In: Kimbrough RD (ed) Halogenated biphenyls, terphenyls, naphthalenes, dibenzodioxins and related products. Elsevier, North Holland, New York, p 151
12. Loew GH, Berkowitz, DS (1975) J Med Chem 18:656
13. Petrongolo C, Tomasi J (1975) Int J Quantum Chem Quantum Biol Symp 2:181
14. Osman R, Weinstein H, Topiol S 1981 Ann NY Acad Sci 367:356
15. Weinstein H, Osman R, Green JP, Topiol S (1981). In: Politzer P, Truhlar DG (eds) Chemical applications of atomic and molecular electrostatic potentials. Plenum Press, New York, pp 309–334
16. Thomson C, Brandt R (1983) Int J Quantum Chem Quantum Biol Symp 10:357
17. Politzer P, Laurence PR, Jayasuriya K (1985) Environ Health Perspect 61:191
18. Politzer P, Daiker KC (1981). In: Deb BM (ed) The force concept in chemistry. Van Nostrand Reinhold, New York, p. 294
19. Scrocco E, Tomasi J (1978) Adv Quantum Chem 11:116
20. Politzer P, Truhlar, DG (1981) Chemical applications of atomic and molecular electrostatic potentials. Plenum Press, New York
21. Binkley JS, Frisch M, Raghavachari K, DeFrees D, Schlegel HB, Whiteside R, Fluder E, Seeger R, Pople JA: GAUSSIAN 82, Release A, Carnegie-Mellon University, Pittsburgh, Pa
22. Boer FB, Van Remoortere FP, North PP, Newman MA (1972) Acta Crystallogr Sect B Crystallogr Cryst Chem 28:1023
23. Huheey JE (1972) Inorganic chemistry: Principles of structure and reactivity. Harper and Row, New York, p 699
24. Harmony MD, Laurie VW, Kuczkowshi RL, Schwendeman RH, Ramsay DA, Lovas FJ, Lafferty WJ, Maki AG (1979) J Phys Chem Ref Data 8:619
25. Bondi A (1964) J Phys Chem 68:441
26. Politzer P, Hedges WL (1982) Int J Quantum Chem, Quantum Biol Symp 9:307
27. Huheey JE (1965) J Phys Chem 69:3284
28. Politzer P (1969) J Am Chem Soc 91:6235
29. Politzer P, Timberlake JW (1972) J Org Chem 37:3557
30. Evans RS, Huheey JE (1973) Chem Phys Lett 19:114
31. Politzer P, Laurence PR (1984) Int J Quantum Chem Quantum Biol Symp 11:155.
32. Cheney BV, Tolly T (1979) Int J Quantum Chem 16:87