On the possibility of coplanar conformations of tetrachlorobenzyltoluenes (TCBTs) and their toxicity.

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Abstract

Semi-empirical molecular modelling calculations of ring rotation energy barriers are carried out for TCBTs and PCBs. Comparison with PCBs reveals that 2 out of the 69 TCBT isomers investigated may have a planar conformation as required for 3-MC- or dioxintype enzyme induction.

Introduction

Tetrachlorobenzyltoluenes (TCBTs), known under the trade name Ugilec 141, have been used as a substitute for PCBs in hydraulic liquids resistant to inflammation, especially by mining industry, as a dielectric fluid in capacitors, and as a cooling and isolation fluid in transformers[1]. Like PCBs, Ugilec 141 consist of a complex mixture of TCBT-isomers. Theoretically 96 isomers of this type are possible (Fig. 1).

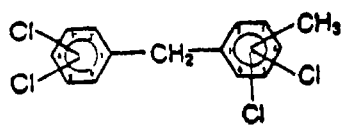


Fig. 1. Molecular structure of TCBT

Still little is known about the toxicological and biological activity of TCBTs. Because of the large similarities in the molecular structure and physico chemical properties of PCBs and TCBTs, comparable toxicological and biological activities of both compounds may be expected.
On account of toxicological data there is sufficient evidence for a weak 3-MC-type induction activity for Ugilec 141[2]. A similar spectrum of toxicological alterations were induced by the technical TCBT mixture, Ugilec 141, Aroclor 1254 and PCB 77, respectively, in Ah-responsive and Ah nonresponsive mouse strains. In relation to the 3-MC-type induction activity, the Ah mediated biochemical changes, such as induction of cytochrome P4501A1 measured as EROD activity were induced by both Ugilec 141 and PCBs. The EROD induction potency of Ugilec 141 however, was considerably less than that of PCB-77 and Aroclor-1254[2].

One of the conditions for a 3-MC-type induction, AHH/EROD-induction and a high toxicity is the possibility of a molecule to get a planar conformation. The possibility of a PCB congener to become coplanar is restricted by the amount of ortho-chloro substituents. An additional criterion for 3-MC-type induction and a high toxicity is the presence of at least 3 to 4 lateral chlorine atoms in such a way that the molecule fits into the 3*10 Å geometry of the 2,3,7,8-TCDD molecule (Fig. 2).

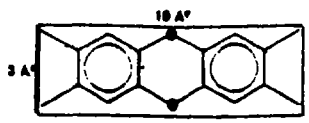


Fig. 2. 3*10 Å geometry of 2,3,7,8-TCDD.

In this paper semi-empirical molecular modeling energy calculations are carried out for TCBTs, diphenylethers (DPEs) and PCBs, in order to test whether coplanarity may be expected. Contrary to PCBs the coplanarity of TCBTs has not yet been investigated. In addition, we evaluate which of the possible coplanar structures fit into a 3*10 Å rectangle and meet the 3-MC-type induction criteria.

Method

The semi-empirical molecular modelling energy calculations were performed using the program PC-MODEL (SERENA SOFTWARE, Bloomington, USA) on a 386 personal computer with coprocessor. PC-MODEL does not involve ab initio quantum mechanical calculations, but uses semi empirical quantum mechanical theories (π-VESCF and Hückel). The atomic positions determining the circumscribed rectangle of a TCBT isomer which has to fit within the 3*10 Å rectangle are displayed using the same program PC-MODEL.

The classification of PCBs into three groups of congeners is given according to the literature[3]. To verify the energy barriers (the difference between the conformation with minimal energy and the coplanar conformation) found for TCBTs, calculations are carried out for PCBs, DPEs and TCBTs. In addition the calculated PCB data are compared with ab initio calculations from literature[4].

Results and discussion

69 TCBT isomers are investigated, among which 44 isomers show an energy barrier, corresponding to that of the mono-ortho coplanar PCBs (group I, see Table 1). These are the coplanar, the mono-ortho and the 2,2' di-ortho TCBTs. The energy barriers of the 22 2,6-di-ortho and tri-ortho TCBTs are similar to those of the di-ortho coplanar

PCBs (group II). Theoretically, the 3 tetra-ortho TCBTs investigated cannot adopt a coplanar conformation on account of the large energy barrier (group III). To verify our calculations, we compared the PC-MODEL results for PCBs with ab initio calculations from the literature[4]. PC-MODEL results differed between 8 and 45 % from the ab initio results, which we consider satisfactory.

Table 1. Energy barriers calculated for TCBTs and PCBs with PC-MODEL and classification into three groups.

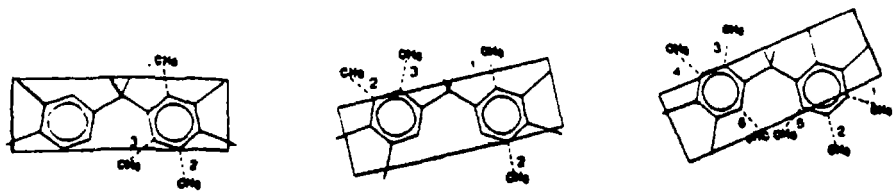
Group	TCBT isomers	Energy barrier kcal/mol	Number[a] of isomers	PCB group	Energy barrier PCB group kcal/mol
I	Coplanar TCBTs Mono-ortho-chloro TCBTs Mono-ortho-Me TCBTs 2,2'-di-ortho-Cl/Me TCBTs 2,2'-di-ortho-chloro TCBTs	11.6 12.2 12.4 12.2 13.0	2 13 3 9 17	Mono-ortho-chloro derivatives of coplanar PCBs	10.1-12.4
II	2,6-di-ortho-chloro-TCBTs 2,6-di-ortho-Cl/Me TCBTs Tri-ortho-chloro-TCBTs Tri-chloro-Cl/Me TCBTs	24.1 24.0 24.4 25.2	2 2 9 9	Di-ortho-chloro derivatives of coplanar isomers	20.0-26.0
III	Tetra-ortho-chloro TCBTs Tetra-chloro-Cl/Me TCBTs	44.1 50.0	1 2	Tri-ortho-chloro PCBs	41.7-55.9

a: Only the 69 isomers which occur in the technical mixture Ugilec 141.

We investigated the planar conformations of the 66 TCBTs from group I and II with regard to the criterion of having four Cl atoms fitting in the 3*10 Å geometry. Nine TCBT isomers can adopt a planar conformation that meets the above criterion. This is illustrated in Fig. 3. As can be seen from Fig. 3, three possible 3*10 Å geometries exist for TCBTs.

Fig. 3 also shows that the three 3,3',4,4'-Cl-2,5,6-Me-TCBT isomers fit into two possible 3*10 Å geometries, whereas the six 2,3,3',4'-Cl-4,5,6-Me/2',3,3',4-Cl-2,5,6-Me TCBT isomers fit into one possible TCDD geometry. Hence the three 3,3',4,4'-TCBT isomers are favourable from an entropic point of view. The calculated energies required for the three 3,3',4,4'-TCBT isomers to adopt the first geometry fall within the 10-12 kcal.mol^{-1} range. However, the energies required to adopt the second geometry is 10-12 kcal.mol^{-1} for 3,3',4,4'-Cl-2-Me TCBT and 3,3',4,4'-Cl-5-Me TCBT, whereas it takes around 20 kcal.mol^{-1} for 3,3',4,4'-Cl-6-Me TCBT to adopt that conformation. We therefore conclude that 3,3',4,4'-Cl-2-Me TCBT and 3,3',4,4'-Cl-5-Me are most likely the TCBT isomers, which may exert 3-MC- or dioxin-type enzyme induction.

Fig. 3. The three possible 3*10 Å geometries for TCBTs.



1 3,3',4,4'-Cl-2-MeTCBT	1 3,3',4,4'-Cl-2-MeTCBT	1 2,3,3',4'-Cl-4-MeTCBT
2 3,3',4,4'-Cl-5-MeTCBT	2 3,3',4,4'-CL-5-MeTCBT	2 2,3,3',4'-Cl-5-MeTCBT
3 3,3',4,4'-Cl-6-MeTCBT	3 3,3',4,4'-Cl-6-MeTCBT	3 2',3,3',4-Cl-6-MeTCBT
		4 2',3,3',4-Cl-5-MeTCBT
		5 2,3,3',4'-Cl-6-MeTCBT
		6 2',3,3',4-Cl-2-MeTCBT

The above conclusion is supported by our findings for DPEs (not shown here) which show that the 2 criteria used here apply also to 2 toxic DPE congeners.
Since TCBTs have a tetraedric angle between the phenyl rings, the effect of the ortho atom of this molecule is not comparable with the effect of the ortho substituent in PCBs. This can be seen from the energy barrier of the 2,2'-di-ortho TCBTs which corresponds to that of group I (Table 1).
Although the results obtained by PC-MODEL are quite satisfying, PC-MODEL is only a semi-emperical molecular modelling technique. In future research more extensive quantum mechanical molecular modelling techniques will be used.
The results of this study suggest that future research should be directed to Ah-mediated enzyme induction of 3,3',4,4'-TCBT isomers.
Finally, the classification of TCBTs into the three classes can be of importance for other physico chemical properties like partition coefficients.

References

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