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Chloro-substituent sites and probability of co-planarity in polychlorinated biphenyls in determining uroporphyrin formation in cultured liver cells

We agree with McKinney & Pedersen [1] in that MNDO, a semi-empirical molecular orbital method, may not give the perfect solution for calculating the conformational energy of polychlorinated biphenyls (PCBs). It is clear that appropriate precautions are necessary for the use of a semi-empirical method.

McKinney & Pedersen [1] raised a question about the use of MNDO (modified neglect of diatomic overlap) for calculating the conformational energy of PCBs. The two main points of their criticism are (i) calculated results by MNDO in an sp^2 - sp^2 system do not agree with experimental data obtained by X-ray crystallography or gaseous phase, and (ii) although MNDO may be applicable to *ortho*-substituted congeners, it is not suitable for calculating the conformational energy of non-*ortho*-substituted molecules. They also compared the minimum energy structures of several related stilbenes with X-ray structures using (i) molecular mechanics (MM2p), (ii) MNDO and (iii) *ab initio* (STO-3G) and report that the MNDO gave large average absolute errors in estimating torsional angles found in the X-ray structures. Based on these findings, McKinney & Pedersen [1] caution against the use of MNDO for quantitative structure-activity relationship studies on PCBs.

Perhaps it is necessary to discuss why we chose MNDO for the calculation of the conformational energy of PCBs to seek for a possible structure-activity relationship of PCBs and uroporphyrin formation in PCB-treated cultured liver cells [2]. It is reasonable to expect, using MNDO, that a certain trend can be resolved for the structure-activity relationship of PCBs if the method is applied to a group of several related congeners. For example, Kaminsky *et al.* [3] made molecular orbital calculations on dichlorobiphenyls by using MNDO for the structure-activity relationship of their metabolism by purified rat liver cytochrome *P*-450 species and were able to make certain predictions of the necessary structure for metabolism. For these reasons, we chose MNDO for the molecular orbital calculation of PCBs for the study of the structure-activity relationships of PCBs on uroporphyrin formation.

Our results demonstrated that, based on the conformational energy, which is calculated as a function of the dihedral angle between the two phenyl rings, biphenyl congeners can be classified into four groups with different conformations. The conformation of active PCBs was relatively flexible, whereas inactive species had

Fig. 1. Relationship between cumulative probability index for congener co-planarity and uroporphyrin formation

●, 3,4,3',4'-tetrachlorobiphenyl; ○, 2,4,3',4'-tetrachlorobiphenyl; ▲, 2,3,2',3'-tetrachlorobiphenyl; △, 2,6,2',6'-tetrachlorobiphenyl.

a rigidly angulated conformation. Furthermore, the calculated probability of the conformation distribution for each congener indicated that the probability of co-planarity was higher for active biphenyls than for inactive congeners. This is one of our two important conclusions which distinguish the active PCBs from the inactive congeners. The other is that at least two halogens must be present at lateral adjacent sites in both phenyl rings. Based on these findings, we suggested that both the chloro-substituent sites and the probability of co-planarity are important in determining the inhibitory effect of PCBs on uroporphyrinogen decarboxylase activity.

The model proposed by McKinney & Pedersen [1] stresses the importance of the polarizability of PCBs and the receptor-PCB separation distance. On the other hand, we introduced the concept that the cumulative probability index for congener co-planarity is critical in determining uroporphyrin formation in cultured chick embryo hepatocytes with PCBs. Our data clearly showed that the cumulative probability index for co-planarity for the four representative PCB groups was closely correlated ($r = 0.99$) with uroporphyrin accumulating activity (Fig. 1). It was not our intention to conclude that the use of MNDO yields an absolutely exact figure; instead we demonstrated that the data obtained by using MNDO were in excellent agreement with our experimental data, i.e. uroporphyrin formation in PCB-treated liver cultures.

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