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Note

Structure-Activity Relationship in BHC Stereoisomers

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The pharmacological action of BHC (benzene hexachloride, hexachloro*cyclo*hexane) depends on its stereochemistry. Of the isomers whose pharmacology has been studied, the α- and γ-isomers were found to be convulsant poisons, the β- and δ-isomers depressants, and the ϵ- and η-isomers are inactive.

In an attempt to account for these differences, Mullins[1] proposed a hypothesis relating the differences in pharmacological activity of the BHC isomers to the postulated size of the pores of the cell membrane (slightly larger than 8·5 Å) and to the molecular diameters of the BHC isomers. These diameters were measured on Stuart models, and 'insofar as the scale of the Stuart models is accurate, these measurements can be considered in angstrom units' (see footnote to the Table in Mullins' paper). Stuart models are not too accurate, however, and since Mullins' hypothesis rests entirely on the reliability of the models, it was thought desirable to obtain more accurate information on the dimensions of the various isomeric BHC molecules. The present writer, therefore, re-determined these dimensions with the help of models such as he had used in some earlier work.[2,3]*

Projections of the BHC isomers on the plane of the *cyclo*hexane

* These models are aluminium spheres, precision ground to the atomic radii listed by Wheland[4], on the scale of 1·27 cm to 1 Å, and connected by metal rods inserted into holes which were drilled into the aluminium spheres, at angles likewise taken from Wheland's listing. These models share one drawback of the Stuart models: they are rigid and thus do not allow for the compressibility of molecules and for the deformation of bond angles. However, as far as the dimensions of molecules with normal bond angles are concerned, the author's models are believed to give accurate information.

ring resemble the outline of more or less irregular hexagons. The first three figures in each row of Table I indicate the distance, measured in a projection on a plane laid through C_1, C_3, and C_5 of the *cyclo*hexane ring, between the outermost boundaries of the atoms attached to the two carbon atoms named in the column headings. The following three values show maximum distances measured in the same projection between opposite sides of the hexagon, the sides again being indicated by the numbers of carbon atoms in the column headings. Finally, the last figure represents the maximum thickness of each molecule.

The figures thus found are uniformly smaller than Mullins', and if we accept his value of 8·5 Å for the membrane pore size then every one of the BHC isomers fits into the pores of the membrane in either plane or on-end orientation. Even more is this true with the more generally accepted pore size of 50 Å.[5] This finding vitiates Mullins' hypothesis which is based on postulated differences in the ability of the several isomers to fit into the pores of the membrane. In terms of the relationship between molecular size and activity the data of Table I yield no more information than that generally only those BHC molecules are active which have diameters of at least 6·5 Å in all directions, and among these the thin molecules (thickness 3·3 and 4·6 Å) are depressant, thick molecules (thickness 6·1 Å) convulsant.

However, it may be more fruitful to consider the matter not from the point of view of diffusion through a sieve-like membrane, but from the more modern, and possibly more accurate, concept of an active transport through the cell wall. This would require consideration of factors such as electrostatic charge distribution, drug-receptor fit, etc. In this light, another correlation emerges from the data of Table I when attention is paid to the spatial arrangement of the chlorine atoms and therefore, the chlorine atoms being the negative ends of C–Cl dipoles, to the spatial arrangement of negative charges in the molecule. It is striking that among the BHC isomers which have been studied only those are active which have at least three chlorine atoms in contiguous equatorial positions. Thus ϵ- and η-BHC are inactive. It would seem that unless at least half of the BHC molecule has a flat shape with a slightly negatively charged rim, it does not fit into some receptor site essential for *any* pharmacological activity of BHC

Table I

Isomers	Position* of Cl at						Distances across the ring (in Å)						Thickness	Activity
	C_1	C_2	C_3	C_4	C_5	C_6	1–4	2–5	3–6	1,2–4,5	2,3–5,6	3,4–6,1		
α	a	a	e	e	e	e	6·8	6·8	8·2	6·5	7·0	7·0	6·1	weakly excitant
β	e	e	e	e	e	e	8·2	8·2	8·2	7·3	7·3	7·3	3·3	weakly depressant
γ	a	a	a	e	e	e	6·8	6·8	6·8	6·5	6·5	7·0	6·1	strongly excitant
δ	a	e	e	e	e	e	6·8	8·2	8·2	7·0	7·3	7·0	4·6	strongly depressant
ϵ	a	e	e	a	e	e	5·6	8·2	8·2	5·4	7·3	5·4	6·1	not insecticidal
η	a	e	a	a	e	e	5·6	8·2	6·8	5·4	7·0	6·1	6·1	not insecticidal

* In describing the position of the Cl atoms, e stands for equatorial and a for axial.

isomers. What this pharmacological activity is, is then determined by the shape of the other half of the molecule: if this, too, is either entirely flat (β) or almost entirely so (δ) it causes depression, but if it displays a negative charge cloud extending in both directions at right angles with the flat part of the molecule, as in α- and even more in γ-BHC, it is a convulsant.

All in all, the little that we can claim to know about structure–activity relationships in BHC stereoisomers seems to accord better with the concept of close fit of drug and receptor than with Mullins' postulated relationship of molecular size and membrane pore size.

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