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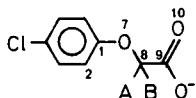
Letter to the Editor

“The influence of conformational factors on the metabolic conjugation of aryloxyacetates”—a comment

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The crystal structure of three aryloxyacetates have torsion angles significantly different from those forecast by van de Waterbeemd et al (1986) using quantum mechanical PCILO calculations. However, these torsion angles are near a minimum in their published three dimensional conformational maps.

In developing a model for the binding site of glucuronyltransferase, van de Waterbeemd et al (1986) used quantum mechanical calculations to explain the differences between *p*-chlorophenoxyacetic acid, **I**, 2-(*p*-chlorophenoxy)propionic acid, **II**, (inert towards metabolic conjugation) and 1-(*p*-chlorophenoxy)-2-methylpropionic acid, **III**, (undergoes extensive glucuronidation). The three variable torsion angles are defined in Scheme I. Keeping τ_3 constant, they plotted the conformational energy for varying values of τ_1 and τ_2 , and said that all compounds had similar regions of very low energy $0-8 \text{ kJ mol}^{-1}$ for $\tau_2 = 0 \pm 30^\circ$; $\tau_1 = 30-90$ and $210-300^\circ$.



Scheme I. τ_1 , 2-1-7-8; τ_2 , 1-7-8-9; τ_3 , 7-8-9-10.

In the region of low conformation energy ($8-21 \text{ kJ mol}^{-1}$), $\tau_2 = 0 \pm 90^\circ$ for compounds **I** and **II**, but $\tau_2 = 180 \pm 90^\circ$ for **III**. Although no suitable method is currently available to determine these values at the bonding site, their crystal structures are known (Kennard et al 1981, 1982), and they do differ from the values selected for these theoretical models (Table 1). Further-

more, the preferred solid state conformation for Type I unsubstituted and monosubstituted phenoxyacetic acids is planar and tional change), ca. 180° (Kennard & Smith 1979). A similar series of Type II (2-phenoxypropionic) and Type III (phenoxyisobutyric) acids are also extended with τ_2 ca. 90° . However, in the solid state, the acids are dimers about a centre of inversion, and for **II** and **III** τ_3 is not 0° . So far there is no evidence to suggest that the dimer formation in this type of acid has any influence on the torsion angles about τ_1 , τ_2 and τ_3 . It should be noted that the crystallographic results are included as near a minimum in their three dimensional conformational maps. Therefore these calculations do agree with the experimental evidence in the solid state, in spite of the fact that τ_3 was kept at 0° .

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Table 1. Comparison for the significant torsion angles (τ) in aryloxyacetates between quantum mechanical calculated values and those found from crystal structure determination.

			τ_1		τ_2		τ_3	
	A	B	Found	Calc	Found	Calc	Found	Assumed
			C(2)-C(1)-O(7)-C(8)	C(2)-C(1)-O(7)-C(8)	C(1)-O(7)-C(8)-C(9)	C(1)-O(7)-C(8)-C(9)	O(7)-C(8)-C(9)-O(10)	
I	H	H	+179.2	30-90 210-300	+178.5	0 ± 30 0 ± 90	-2.3	0
II	H	CH ₃	+171.1	30-90 210-300	+73.8	0 ± 30 0 ± 90	+25.7	0
III	CH ₃	CH ₃	+130.4	30-90 210-300	+79.0	0 ± 30 180 ± 90	+35.9	0

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