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Structural Influences and Mechanisms of Toxic Effects of Alcohols and Their Derivatives*

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A large amount of data is available in the literature on the toxic effects of alcohols. This has provided useful information for structure-activity analyses, from which predictions may be made. A study by CHVAPIL et al. (1962) provides toxic data on alcohols influencing several biological processes, and in addition data on the corresponding alcohol derivatives xanthogenates. From this data, it should be possible to gain information on the structural influence on several activities in both series, and also to analyse the inter-relation of alcohol and xanthogenate within each biological study. From this it may be possible to draw certain conclusions about biological conversion of the derivative to the alcohol and to propose a general method to predict the extent of such an event.

Biological Data

CHVAPIL et al. (1962) have reported on the biological effects of several alcohols and their corresponding xanthogenates for four biological processes: haemolysis of erythrocytes, inhibition of the Tubifex worm, change of position of the fish Lebistes reticulatus, and the LD_{50} from i.v. injection in white mice. The log of the concentrations producing a constant response for each effect and for both series of molecules is summarized in Table I.

The haemolysis of the erythrocytes was the observation of the instantaneous effect of the compound introduced into an isotonic medium with the cells. The worm study was based upon the observation of the inhibition of all worm movement within 2 minutes after immersion in a solution of the compound. The effect on the fish was the observation that all fish assumed a side position or inverted position after 9-10 minutes of exposure to the compound under study. The toxicity in mice was the LD_{50} from i.v. injection into females.

Structural Description

The method used in this study to quantitate the structure of the compounds is the method known as molecular connectivity (KIER and HALL 1976, 1977, 1979). Molecular connectivity is a non-

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empirical quantitation of molecular structure which encodes information about molecule size, branching, cyclization, unsaturation and heteroatom content. The molecular connectivity indexes arise from the assignment of delta values to atoms, other than hydrogen, in a molecule. The simple delta value, δ, is a count of the number of sigma bonds (other than to hydrogen) emanating from that atom and is equal to the number of skeletal bonds: $\delta = \sigma - h$, where σ is the number of sigma bonds and h is the number of hydrogen atoms bonded to the atom.

The molecule is dissected into substructures of one, two or more contiguous bonds (paths). Each path is defined by the delta values describing each atom in the substructure. A term for each path (substructure of one bond) is calculated according to the algorithm $S_k = (\delta_i \delta_j)^{-\frac{1}{2}}$, where δ_i and δ_j are values assigned to the two atoms of a bond or path of the first order. The molecular connectivity index of the first order,

$$^1\chi = \Sigma S_k \text{ for all bonds,}$$

is computed as the sum of all the first order path terms. This simple first order index has been shown to rank molecules according to their size and branching and to be closely related to many of their physical properties (KIER and HALL 1976). Higher order indexes, based on larger substructures, encode more complex aspects of structure and often appear in multivariate regression analyses of molecules for physical and biological properties (KIER and HALL 1978, 1981; HALL and KIER 1978a, 1978b, 1981).

A second class of molecular connectivity indexes arise from the assignment of atom delta values based upon a count of all atom valence electrons other than those bonding to hydrogen, $\delta^V = \sigma + p + \ell - h$ where p is number of pi bonds and ℓ is number of lone pair electrons. These valence delta values, δ^V, are employed just like the simple delta values to compute a family of valence molecular connectivity indexes, $^m\chi^V$, of different orders, m. Electronic information about the molecule has been shown to encode in these valence molecular connectivity indexes (KIER and HALL 1981).

Results of Structure-Activity Relationship Studies

a) Haemolysis of Erythrocytes

A single variable, the $^1\chi$ molecular connectivity index is capable of correlating with the log concentration to produce instantaneous hemolysis of erythrocytes:

$$\text{Log C (R-OH)} = 1.55 - 0.78\ ^1\chi,\ r = 0.987,\ s = 0.13,\ n = 16$$

$$\text{Log C (R-OX)} = 1.69 - 0.64\ ^1\chi,\ r = 0.971,\ s = 0.18,\ n = 9$$

The log C values for both series of molecules in the haemolysis study can be found in Table I. The $^1\chi$ values for both series are found in Table II.

The two equations explain 98% and 94% of the variation in the biological data. This is probably the upper limit that can be expected from such an equation since no better than 5% variation in this kind of biological data is to be expected.

b) Inhibition of movement of the Tubifex worm

Table 1

Biological Effects of Alcohols (R-OH) and their Xanthogenate Derivatives (R-OX), X = $-CS_2^-$

R Group		Hemolysis		Worm Inhibition		Fish Inhibition		Mice LD50	
1	Me	.87	.14	.39	-.69	.60	-.50	2.25	.22
2	ET	.61	-.20	.20	-.73	.01	-.51	1.73	.09
3	iPr	.32	-.24	-.07	-.76	-.36	-.49	1.49	.08
4	tBu	-.06		-.38		-.62		1.32	
5	nPr	-.10	-.54	-.33	-.76	-.72	-.57	1.26	.01
6	iBu	-.36	-.59	-.77	.80	-1.24	-.68	.91	-.08
7	neoPen				-.66				
8	sBu	-.26		-.79	-.80	-1.09		1.01	.01
9	tAm	-.34		-1.04				.84	
10	nBu	-.36	-.70	-1.01	-.80		-.68	.71	-.08
11	iAm	-.76	-.59	-1.49	-.87			.42	
12	nAm	-.75		-1.73	-.88	-2.12	-.82	.32	-.31
13	nHex	-1.28	-1.34	-2.23	-1.09		-1.04	.00	-.51
14	iHex	-1.12		-1.80		-2.92		.07	
15	tHex	-.80		-1.56				.38	
16	tHep			-1.76				.13	
17	nOcT	-1.70	-2.22		-1.51		-1.92	-.28	-.66
18	sOcT	-1.70		-2.61	-1.21			-.29	
19	nDec				-2.08				-.21
20	cyHex			-1.32	-.85			.43	-.05

The concentration at which the movement of all Tubifex worms was arrested within 2 minutes was found to be well correlated with $^1\chi$ for alcohols and moderately well for the xanthates.

Log C (R-OH) = 1.51 - 1.00 $^1\chi$, r = 0.980, s = 0.17, n = 17; Log C (R-OX) = 0.21 - 0.29 $^1\chi$, r = 0.913, s = 0.16, n = 15

An inspection of the data for ROH and ROX in Table I and the equations above, reveals that the xanthates are more potent than the corresponding alcohols up to the butyl analogs. For compounds with larger R groups, the alcohols are more potent than the corresponding xanthates.

c) Fish Position Change

This toxic effect on fish is well correlated for the alcohols with the $^1\chi$ molecular connectivity index. The correlation with the xanthates is moderate. Log C (ROH) = 2.23 - 1.52 $^1\chi$, r = 0.994, s = 0.12, n = 10; Log C (ROX) = 0.65 - 0.39 $^1\chi$, r = 0.912, s = 0.20, n = 9.

Table I reveals and these equations quantify the observation that the xanthates are more potent than the corresponding alcohols through the series up to the butyl moieties. Larger R groups result in the alcohols being more potent.

d) LD_{50} in Mice

The i.v. induced death of female white mice was recorded as the concentration causing death in 50% of the animals. This LD_{50} was correlated well with $^1\chi$ in the case of the alcohols. A modest correlation was found with the xanthates.

LD_{50} (ROH) = 2.71 - 0.75 $^1\chi$, r = 0.972, s = 0.17, n = 18

LD_{50} (ROX) = 0.86 - 0.25 $^1\chi$, r = 0.909, s = 0.12, n = 11

All of the xanthates are more potent than the corresponding alcohols.

Discussion

The relationships developed for each activity for the two series permits certain conclusions to be drawn concerning the relationship between structure and activity and the interrelation of the two series.

a) Hemolysis Study

In the hemolysis study, the two equations relating Log effective concentration and $^1\chi$ are quite similar. The equations indicate an increasing potency as R increases in molecular size. Branching in the R group reduces the potency relative to the unbranched isomer. The high degree of linearity of both equations indicates the alkyl moiety is influencing the relative potency in an additive way through each series. This is characteristic of dispersion interaction of alkyl groups in biologically active molecules. It is also characteristic of a molecular mechanism in which partitioning of the molecule through a membrane or into a lipid depot, is not a limiting factor in the potency.

The two equations from the hemolysis study have comparable slopes and intercepts. From this we can infer that the R groups in each series are likely playing a comparable role in the potency of each molecule in each series. The finding that the intercepts of both equations are very close, suggests that the two series might be involking hemolysis through a common

mechanism. The observation that the potency of the xanthates is uniformly greater than the alcohols is explainable by assuming that the hydroxy group and the xanthate group contribute to the potency in a non-specific but quantitatively different way.

Table 2
Molecular Connectivity Indexes for Alcohols and Xanthates

R Group	$^1\chi$(ROH)	$^1\chi(ROCS_2^-)$	R Group	$^1\chi$(ROH)	$^1\chi(ROCS_2^-)$
1. Methyl	1.000	2.270	11. iAmyl	2.770	4.126
2. Ethyl	1.414	2.770	12. nAmyl	2.914	4.270
3. iPropyl	1.732	3.126	13. nHexyl	3.414	4.770
4. tButyl	2.000		14. iHexyl	3.270	
5. nPropyl	1.914	3.270	15. tHexyl	3.061	
6. iButyl	2.270	3.626	16. tHeptyl	3.561	
7. ntPentyl		3.417	17. nOctyl	4.414	5.770
8. sButyl	2.270	3.664	18. sOctyl	4.270	5.664
9. tSmyl	2.561		19. nDecyl		6.770
10. nButyl	2.414	3.770	20. cycHexyl	2.894	4.288

b) Worm Inhibition Study

The equation relating $^1\chi$ for alcohols with the log effective concentration inhibiting worms is markedly linear. The relationship reflects a uniform contribution to potency with the addition of each carbon to the R moiety.

In contrast, a single linear equation in $^1\chi$ correlates only moderately with the effective concentration of xanthates. The low value of the slope of this equation characterizes a very modest influence of R on potency up to about $^1\chi = 4.5$. Thus when R is larger than 5 carbons, the influence of R on potency increases significantly.

The ionic character of the xanthates appreciably alters the relationship of R moiety to the potency, in comparison with the non-ionic alcohols. The contrasting behavior reflects a non-linear absorption of the xanthates into the worm. Thus for lower homologs of xanthates, partitioning into the lipoidal membrane of the worm is not favored. When the R moiety is large enough, beyond five carbons, there is appreciable absorption and the xanthates can exhibit the effect of significant in vivo concentrations.

c) Fish Narcosis

The structure activity analyses of both series of molecules in this test resembles closely the results from the worm narcosis study. The alcohols exhibit markedly linear behavior relative to the $^1\chi$ index. The curve or bilinear relationship of the xanthate potency versus $^1\chi$ is very similar to the xanthate behavior in worms. Homologs larges than four carbons begin a significant increase in potency relative to the size of the R moiety. Again, we hypothesize that this effect is due to the ionic character of the xanthates and the favorable absorption behavior of homologs beyond four carbons.

d) Mouse LD_{50}

This response correlates well with $^1\chi$ for the alcohols.

The xanthates exhibit a fairly linear response with $^1\chi$ although there are enough ontlyers to produce only a modest correlation. In this study, there is sufficient time for the lower xanthates to be absorbed so that the increase in R parallels the potency. Thus there is sufficient time between injection and absorption at the active sight to permit a toxic concentration of the more polar lower homologs to be present to exert their effect.

Conclusion

The simple connectivity index $^1\chi$ gives a reasonable account of the variation of potency with molecular structure for each of the cases presented here. The behavior of the alcohols is described better by the simple linear relationship than is the behavior of the xanthates, especially for inhibition of Tubifex worms and fish narcosis. Although a bilinear or nonlinear relationship may give improved description in these cases, lack of data in the region of higher monologs makes such equations difficult to justify on statistical grounds.

The fact that the simple (nonvalence) index gives good correlation suggests that the heteroatoms (alcohol or xanthate group) plays a constant role in the biological processes. Variation in potency arises from variation in alkyl group structure.

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