

A Structure-Mutagenicity Relationship for α,β -Unsaturated Carbonyl Compounds and a Comparison with Acute Toxicity

Yana K. Koleva, Judith C. Madden, Mark T.D. Cronin*



School of Pharmacy and Chemistry, Liverpool John Moores University, Byrom Street, Liverpool, L3 3AF, England. Corresponding author: Mark Cronin, e-mail: m.t.cronin@ljmu.ac.uk

Introduction

Modelling toxicity of aliphatic compounds exemplifies a problem in developing QSARs i.e. to achieve accurate prediction of toxicity it is essential to establish the domain of the model.

Certain α,β -unsaturated carbonyl compounds are electrophilic and fall into the Michael-type acceptor reaction mechanistic domain as shown in Figure 1¹.

Protein binding reaction Modified protein



Double or triple bond with electron-withdrawing substituent X, such as -CHO, -COR, -CO₂R, -CN, -SO₂R, -NO₂ etc

Figure 1. Michael acceptor domain

Enhanced toxicity of reactive electrophiles is assumed to be caused by reactions with biological nucleophiles, such as proteins and DNA, either directly or after metabolic activation. The hardness of these electrophiles can define their classification in terms of their reactivity.

Aims

To model a 'category' of α,β -unsaturated aldehydes and ketones, believed to act by Michael-type addition, using data from *Salmonella typhimurium* (strain TA100 -S9)

To build a simple QSAR model for mutagenicity, enabling further interpretation of possible mechanisms of action, and to compare this with acute aquatic toxicity to *Tetrahymena pyriformis*.

Methods

Mutagenicity: Mutagenicity data (*Salmonella typhimurium* TA100 strain) were retrieved from the literature²⁻⁴. *Salmonella* results without S9 activation were utilised as these chemicals are direct-acting agents and S9 reduces their activity by providing non-specific targets.

Acute aquatic toxicity: Data for toxicity to *Tetrahymena pyriformis* of 32 aliphatic polarised α,β -unsaturated aldehydes and ketones were obtained from the literature⁵.

No	CAS	NAME	Mutagenicity - <i>Salmonella typhimurium</i> TA100 [revertants/ μ mole]	logKow [mol.L ⁻¹ mol ⁻¹ L _w]	Q _{βC-atom} [au]	Acute aquatic toxicity - <i>Tetrahymena pyriformis</i> Log(IC50) ⁻¹ [mmol/l]
1.	107-02-8	Acrolein	2400	0.1888	-0.2354	1.87
2.	4170-30-3	Crotonaldehyde	1952	0.6013	-0.0861	0.7
3.	31424-04-1	Pentalenal	1409	1.0924	-0.0837	0.66
4.	1335-39-3	Hexenal	980	1.5835	-0.0837	0.76
5.	29381-66-6	Heptenal	475	2.0746	-0.0838	
6.	3913-81-3	trans-2-decen-1-al				1.85
7.	142-83-6	2,4-hexadienal	1863	1.3685	-0.0567	0.75
8.	4313-03-5	trans,trans-2,4-heptadienal				0.86
9.	6750-03-4	2,4-Nonadienal	0			1.225
10.	557-48-2	trans-2,cis-6-nonadienal				1.335
11.	107-86-8	3,3-Dimethylacrolein	43-78 (Not significant)			0.088
12.	5362-56-1	4-Methyl-2-pentalenal				0.819
13.	5392-40-5	2,6-Octadienal, 3,7-dimethyl	0			
14.	78-85-3	Methacrolein	460	0.7361	-0.1335	
15.	922-63-4	Alpha-E	240	1.2272	-0.134	0.911
16.	1070-13-9	2-Propylacrolein	180	1.7183	-0.1354	
17.	1070-66-2	2-Methylenehexenal	460	2.2094	-0.1352	1.07
18.	497-03-0	2-Butenal,2-methyl-, (2E)-	16			-0.139
19.	623-36-9	2-Methyl-2-pentalenal				-0.022
20.	80192-48-9	2,4-Dimethyl-2,6-heptadienal				0.083
21.	78-94-4	Methyl vinyl ketone	472	0.4083	-0.1753	1.506
22.	1423-60-5	But-3-yn-2-one				1.412
23.	1119-44-4	3-hepten-2-one				0.698
24.	1669-44-9	3-Octen-2-one				0.74
25.	14309-57-0	3-nonen-2-one				0.983
26.	1629-58-9	1-Pentene-3-one	1293	0.8994	-0.1316	1.527
27.	1629-60-3	1-Hexen-3-one				1.656
28.	4312-99-6	1-Octen-3-one				1.914
29.	2497-21-4	4-Hexen-3-one	7 (Not significance)			0.93
30.	625-33-2	3-Penten-2-one				0.538
31.	1679-36-3	3-Hexyn-2-one				1.319
32.	141-79-7	4-Methyl-3-penten-2-one				-0.644
33.	565-62-8	3-Methyl-3-penten-2-one				-0.345
34.	930-30-3	2-Cyclopenten-1-one	0			0.638
35.	2758-18-1	3-Methyl-2-cyclopenten-1-one				-1.323
36.	1120-73-6	2-Methyl-2-cyclopenten-1-one				-0.826

Table 1. Acute aquatic toxicity and mutagenicity data for α,β -Unsaturated carbonyl compounds

Descriptors. 3D structures and relevant descriptors were obtained from TSAR 3.3 (Accelrys Inc, Oxford, UK) following input as Simplified Molecular Input Line Entry System (SMILES) notations.

Statistical Analyses. QSARs were developed using regression analysis in MINITAB. Log(TA100⁻¹) values reported in revertants/ μ mole units were used as the independent variable. Resulting model fit was assessed by the coefficient of determination adjusted for the degrees of freedom (R²), the square root of the mean square error (s), Q² determined by the leave-one-out method in addition to the Fisher's criterion (F).

Results & Discussion

Regression analysis of the mutagenicity of α,β -unsaturated aldehydes and ketones gives:

$$\text{Log}(1/\text{TA}100) = 1.79 (\pm 0.3585) + 0.417 (\pm 0.1271) \log\text{Kow} - 7.30 (\pm 2.306) Q_{\beta\text{C}}$$

$$n = 12 \quad R^2 = 0.627 \quad R^2 (\text{adj.}) = 0.544 \quad Q^2 = 0.251 \quad s = 0.251 \quad F = 7.57$$

The relationship between mutagenicity and hydrophobicity (logKow) with charge on β -carbon atom (Q _{β C}) of compounds is shown in Figure 2.

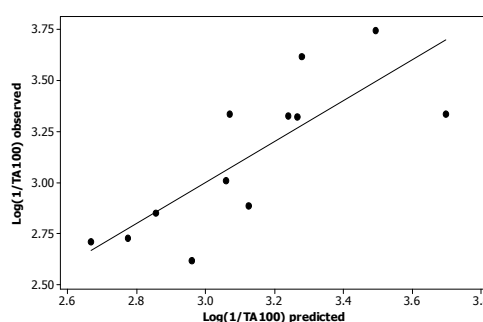


Figure 2.

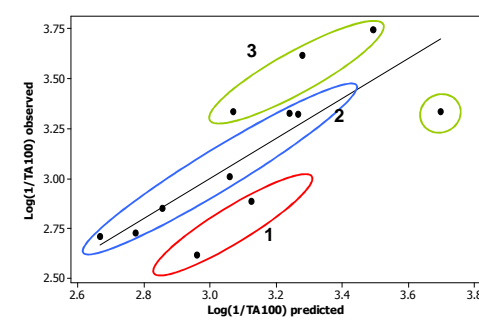


Figure 3.

Examination of Figure 2 shows that α,β -unsaturated carbonyl compounds demonstrate different reactivity; sub-groups are shown in Figure 3.

The training set for mutagenicity contains 10 unsaturated aldehydes and 2 unsaturated ketones. The second group (α,β -unsaturated aldehydes and ketones) has different reactivity, but are considered together. The compounds of subgroup 2 (with substituents in the β -position) are less mutagenic than the first group (acrolein etc) and subgroup 3 is the least mutagenic (with substituents in α -position).

For the comparison of the acute toxicity with mutagenicity α,β -unsaturated aldehydes were separated from α,β -unsaturated ketones. For aldehydes the following sub-groups were defined:

- ✓ A1) acrolein (sole member of its subgroup)
- ✓ A2) monosubstituted acroleins, which includes RCH=CHCHO (i.e., vinylenes aldehydes)
- ✓ A3) disubstituted acroleins represented by RCH=CRCHO and R₂C=CHCHO

For the α,β -unsaturated ketones the following subgroups were defined:

- ✓ B1) monosubstituted ketones, which includes RCOCH=CH₂
- ✓ B2) disubstituted ketones of the form RCOCH=CHR
- ✓ B3) trisubstituted ketones consisting of either RCOCH=CR₂ or RCOCR=CHR.

For a given Y group (e.g. carbonyl group (C=O)) the ranking order of reactivity is R₂C=CRCO < R₂C=CHCO, RCH=CRCO < CH₂=CRCO, and RCH=CHCO < CH₂=CHCO.

The degree and pattern of alkyl substitution on the α,β -carbons has a strong impact on the reactivity and toxicity of α,β -unsaturated carbonyl compounds. The activation energy for nucleophilic addition to the electrophile is increased by alkyl groups on either the α - or β -carbons. The effect of α -substituted alkyl groups is mainly to increase the energy of the intermediate, whereas, the effect of β -substituted alkyl groups mainly lowers the energy of the electrophile.

Comparison of these classifications between the two endpoints indicates that α,β -unsaturated aldehydes and ketones have different reactivity for acute aquatic toxicity and mutagenicity. This can be explained by the differences between the reactions with the nucleophiles centres (proteins and DNA) and the hardness of the electrophiles:

For carbonyl compounds the following order for mutagenicity was found:

α -substituted unsaturated < β -substituted unsaturated < non-substituted unsaturated

There are some restraints for molecular weight, geometric hindrances, and the hardness of electrophiles

For carbonyl compounds the following order for acute toxicity was found:

R₂C=CRCO < R₂C=CHCO, RCH=CRCO < CH₂=CRCO, and RCH=CHCO < CH₂=CHCO

Conclusions

α,β -unsaturated carbonyl compounds can be grouped to allow predictions for mutagenicity and acute aquatic toxicity

The different classification of α - and β -substituted aldehydes for mutagenicity and acute aquatic toxicity can be explained by the type of nucleophilic centre (proteins and/or DNA) and the hardness of the electrophiles

References

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