QSPRs FOR THE PREDICTION OF EXPERIMENTAL HALF-LIVES OF BFRs, THEIR METABOLITES AND CHLORO/BROMOPHENOLS

Harju Mikael[1], **Bastos Patricia**[2], **Bergman Åke**[2] and **Heimstad Eldbjørg Sofie**[1]

[1] NILU, Polar Environmental Centre, 9296 Tromsø, Norway; [2] Department of Environmental Chemistry, Stockholm University, 10691 Stockholm, Sweden

Introduction

To evaluate the persistency of a chemical in the environment one should take into account the major degradation routes in different environmental compartments such as oxidation, radical reactions and UV degradation in air and water, reduction in soil and sediments. In this work we have focused on oxidation and if the use of the linear solvation energy relationship (LSER and TLSER) could be valuable as a relatively simple means for multimedia modelers to evaluate the reactivity of different chemicals.

We aim at developing user-friendly quantitiative structure-property relationship (QSPR) models where molecular descriptors are easily accessible and be interpreted and understood on a chemical basis and have a relevance for multimedia modellers. Applying this predictive methodology based on experimental reactivity and *in silico* methods should lead to improvements in risk assessments of chemicals.

QSPR data-base with temperature normalized experimental data[a] containing logarithmically transformed oxidation half-lives, calculated physicochemical data for all variables included in MLR models and predicted results for the regressions based on all variables[b] and TLSER[c] variables.

		Physicochemical variables								Oxidation half-lives (log(1/t½))				
Chemical	Abbreviation	pKa	B	Vm	Ea	Qh+	TotDip	H_{charge}	ΔE_{OH}	Exp.[a]	MLR[b]	PLS[b]	MLR[c]	PLS[c]
Training set														
2-bromophenol	2-BP	8.1	0.31	1.03	0.12	0.10	6.19	0.08	-8.0	-1.96	-1.80	-2.02	-1.87	-1.88
2,4-dibromophenol	24-DBP	8	0.23	1.27	0.18	0.23	4.65	0.10	-8.5	-2.36	-2.55	-2.68	-2.62	-2.69
2,6-dibromophenol	26-DBP	6.8	0.22	1.24	0.13	0.10	6.43	0.10	-8.4	-1.96	-2.59	-2.57	-2.57	-2.75
2,4,6-tribromophenol	246-TBP	6.7	0.15	1.45	0.13	0.12	6.77	0.12	-8.8	-2.79	-3.31	-3.16	-2.41	-3.06
2,3,4,6-tetrabromophenol	2346-TeBP	6.3	0.07	1.69	0.18	0.24	5.21	0.12	-9.0	-4.14	-3.54	-3.45	-2.96	-3.68
2,3,4-trichlorophenol	234-TCP	8.1	0.15	1.24	0.13	0.12	5.53	0.10	-8.5	-2.96	-2.71	-3.00	-2.45	-2.39
Bisphenol-A	BPA	10.1	0.91	2.08	0.17	0.22	9.35	0.08	-13.7	-1.96	-2.00	-1.63	-2.29	-1.99
2,2',4-trichlorobisphenol-A	TCBPA	6.5	0.4	2.64	0.15	0.22	10.6	0.05	-8.6	-1.15	-1.07	-1.17	-2.02	-1.81
3,3'-dibromodipheyl ether	bde11	14	0.31	1.98	0.18	0.17	5.18	0.14	-14.2	-5.38	-4.69	-4.85	-4.90	-4.40
2,4,4'-tribromodiphenyl ether	bde28	14	0.32	2.18	0.18	0.17	6.54	0.15	-14.3	-5.22	-4.94	-5.05	-4.81	-4.87
2,2',4,5'-tetrabromodiphenyl ether	bde49	14	0.25	2.38	0.18	0.17	6.32	0.16	-14.3	-4.96	-5.33	-5.25	-5.22	-5.34
2,3',4,4'-tetrabromodiphenyl ether	bde66	14	0.25	2.37	0.18	0.17	6.40	0.16	-14.3	-4.87	-5.32	-5.29	-5.17	-5.23
2,2',4,4',5-pentabromodiphenyl ether	bde99	14	0.18	2.61	0.19	0.18	6.95	0.16	-14.4	-5.33	-5.48	-5.48	-5.62	-5.72
2,2',4,4',5,5'-hexabromodiphenyl ether	bde153	14	0.11	2.76	0.19	0.18	6.80	0.17	-14.5	-5.70	-5.89	-5.90	-5.93	-6.09
6-OH-2,2',4-tribromodiphenyl ether	6-OH-bde17	7.7	0.38	2.24	0.15	0.17	8.26	0.12	-9.0	-2.51	-2.89	-2.76	-3.10	-2.64
6-OH-2,2',4,4'-tetrabromodiphenyl ether	6OH-BDE47	7.6	0.37	2.43	0.15	0.18	11.4	0.13	-9.1	-3.51	-3.19	-3.14	-2.21	-2.75
6'-OH-2,2',4,5'-tetrabromodiphenyl ether	6'-OH-BDE49	6.8	0.25	2.38	0.15	0.15	9.06	0.11	-8.9	-3.18	-2.90	-2.77	-3.49	-3.23
2'-OH-2,3',4,4'-tetrabromodiphenyl ether	2'-OH-BDE66	6.7	0.25	2.4	0.15	0.18	9.34	0.12	-9.1	-1.87	-3.20	-2.95	-2.82	-2.78
6-OH-2,2',3,4,4'-pentabromodiphenyl ether	6-OH-BDE85	7.6	0.23	2.62	0.15	0.17	9.15	0.14	-9.4	-4.21	-3.77	-3.58	-3.46	-3.45
6-OH-2,2',3,4,4',5-hexabromodiphenyl ether	6-OH-BDE137	6.3	0.04	2.81	0.15	0.17	9.47	0.14	-9.6	-4.53	-4.23	-3.94	-3.68	-3.88
Prediction set														
2,4,6-trichlorophenol	246-TCP	6.3	0.15	1.24	0.13	0.12	4.71	0.12	-8.48	-2.88	-3.24	-3.07	-2.71	-2.32
2,2',4,4'-tetrabromobisphenol-A	TBBPA	6.9	0.40	2.95	0.15	0.23	13.43	0.05	-8.83	-1.26	-1.12	-1.26	-1.42	-1.91
2,2',4-tribromodiphenyl ether	bde17	14	0.32	2.23	0.18	0.16	6.51	0.14	-14.2	-5.46	-4.67	-4.83	-5.11	-4.95
2,2',4,4'-tetrabromodiphenyl ether	bde47	14	0.26	2.41	0.18	0.17	7.01	0.16	-14.3	-4.92	-5.30	-5.25	-5.05	-5.33
4'-OH-2,2',4-tribromodiphenyl ether	4'-OH-BDE17	8.9	0.53	2.24	0.15	0.16	11.07	0.10	-8.75	-1.84	-2.02	-2.23	-2.41	-2.89
6-OH-2,2',3,4',5-pentabromodiphenyl ether	6-OH-BDE90	6.7	0.14	2.67	0.15	0.17	9.65	0.13	-9.38	-4.07	-3.73	-3.44	-3.38	-3.48

pKa = Acidic equlibrium constant; B = hydrogen bonding basicity parameter; Vm = McGowan's molecular volume; Ea = Covalent acidity; Qh+ = Electrostatic acidity

Totdip = Total dipolar momentum; H_{charge} = hydrogen with the lowest positive charge; ΔE_{OH} = Energy difference of HOMO (substrate) and LUMO (OH radical)

The **experimental data**[1,2], was created by a single laboratory with the same method of oxidation using $KMnO_4$ as an oxidation agent at a pH of 7.6. The temperature and solvent mixture (methanol and water) were changed due to differences in reaction rates and solubility of these compounds. To normalize the data set we extrapolated the data to the same temperature (298K) using the Arrhenius equation.

Molecular structures were generated in **Cache WorkSystem pro** (Fujitsu Limited) and geometry optimised by energy minimisation using MOPAC AM1 method.

Three main methods were applied to calculate molecular descriptors;

1) **Cache MOPAC AM1**; properties such as polarity, reactivity (E_{HOMO} and E_{LUMO}), charges, electron density and electrophilic/nucleophilic/radical susceptibility.
2) **ADME boxes v. 3.5** (Pharma Algorithms, Inc.); Properties based on LSER[3] such as molar refraction, polarizability, H-bond acidity/basicity and McGowan's volume.
3) **MADCAP**[4]; Properties based on the theoretical TLSER[4] describing polarity, covalent/electrostatic acidity and basicity, dipole moments and molecular volume.

$$y_i = \beta_0 + \beta_1 x_{1i} + \cdots + \beta_p x_{pi} + \varepsilon_i,$$

For the creation of QSPR models we used two software suites;

1) **ADME works model builder** (Fujitsu Ltd); used for variable selection with an genetic algorithm and for the creation of multiple linear regression equations (MLR).
2) **Simca P** (Umetrics, Inc); used for the creation of regression models based on the partial least square projection to latent structures (PLS).

Summary

We have here calculated a large suit of different physicochemical properties using multiple linear regression methods (**MLR**) (**see Figure**) to find correlations between physicochemical properties and the oxidation half-lives.

Models suggests that molecular modelling could be used to make some fair estimates of the oxidation potential of compounds when experimental data is unavailable.

Results show that quantum mechanical **TLSER** gives better correlation to degradation rates than **LSER** parameters.

The most important **TLSER** physicochemical properties being, in falling order of magnitude, the molecular volume (Vm), covalent acidity (Ea) and electrostatic acidity (Qh+).

Results for the modelling on **ALL VARIABLES** show an decrease in oxidation half-times strongly correlated to the proton charge (H_{charge}) and reactivity properties (DE_{OH}).

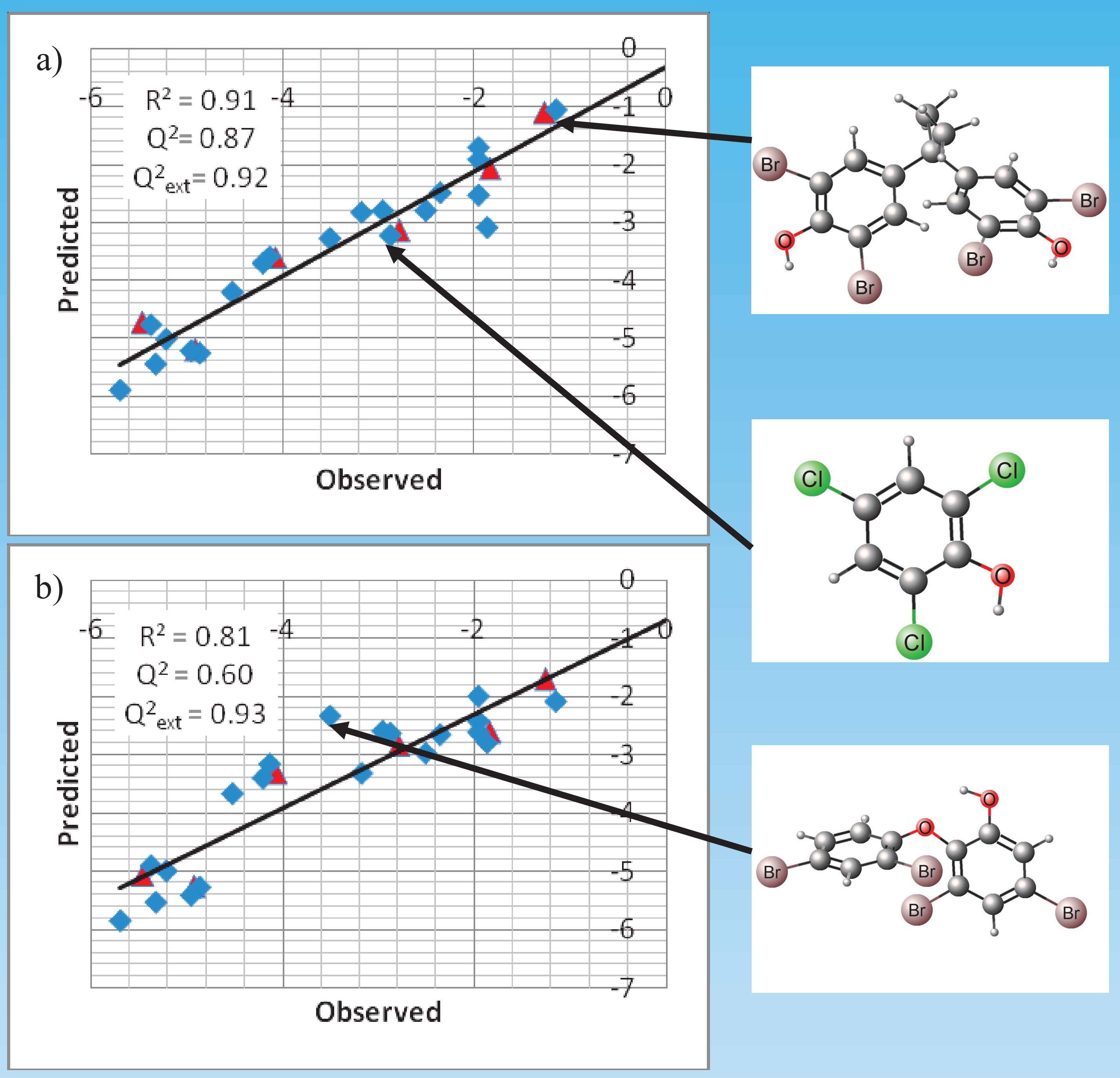

Figure. Observed and predicted oxidation half-lives (log $1/t_{1/2}$) and the correlation coefficients for the compounds in the training set (◆) R^2, the goodness of prediction Q^2 and Q^2_{ext} for the prediction set (▲). **a)** MLR model using all calculated variables, **b)** MLR model using only TLSER variables

MLR model based on ALL VARIABLES

$$\text{Log}(1/t_{1/2}) = 1.3871 - 24.4328 \times \mathbf{H_{charge}} + 0.2517 \times \mathbf{DE_{OH}} + 1.9741 \times \mathbf{B} + 0.0221 \times \mathbf{pKa}$$

$(n = 20, R^2 = 0.91, F = 36.5, p < 1.2E\text{-}7, S^2 = 0.49, R^2ext = 0.86)$

MLR model based on the TLSER variables

$$\text{Log}(1/t_{1/2}) = 0.9060 - 1.7016 \times \mathbf{Vm} - 42.1222 \times \mathbf{Ea} + 20.5695 \times \mathbf{Qh+} \, 0.3186 \times \mathbf{Totdip}$$

$(n = 20, R^2 = 0.81, F = 16.2, p < 2.6E\text{-}5, S^2 = 0.70, R^2ext = 0.88)$

Referenses

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