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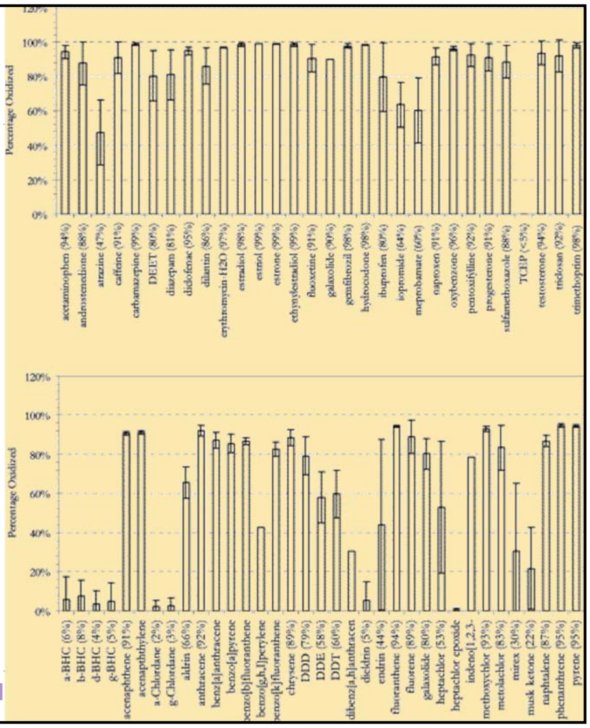
CEE 697z
Organic Compounds in Water and Wastewater

Structure – Activity Models for PPCPs

Lecture #26

TOrCs

- A few PPCPs
  - Removal by ozone
- Problem
  - ~9,000,000 organic compounds known
  - About 80,000 in common use
  - Many more are present as unwanted byproducts



Westerhoff et al., 2005 [EST 39:17:6649]

Kinetic Prediction Methods

- Types
  - Based on properties
    - QPAR: Quantitative Property-Activity Relationships
      - ☐ e.g., predicting bioaccumulation from K_{ow}
    - QPPR: Quantitative Property-Property Relationships
      - ☐ e.g., predicting K_{ow} from chromatographic retention time (k')
  - Based on structure
    - QSAR: Quantitative Structure-Activity Relationships
      - ☐ e.g., rate constants from ring substituents
    - QSPR: Quantitative Structure-Property Relationships
      - ☐ e.g., solubility from ionic radius

EPA Suite: http://www.ecs.umass.edu/eve/background/chemicals/properties.html

LFERs

- Linear Free Energy Relationships
  - Theoretical Basis
    - Kinetics are correlated to thermodynamics for a given "type" of reaction

$$\frac{\Delta G^{\neq}}{\Delta G^{o}} \approx const.$$

  - Types
    - Bronsted: acid/base catalyzed reactions
    - Hammett: aromatic and alkene reactions
    - Taft: aliphatic reactions
    - Marcus: metal redox reactions

Hammett Equation I

- Developed in 1930s to explain substituent effects on rates of meta and para substituted benzene compounds
- Reaction rates depend on substituent and position and effect is similar from one reaction to another

Reaction rate of a particular substituted benzoic acid

Acid ionization constant for a particular substituted benzoic acid

$$\log\left(\frac{k_i}{k_o}\right) = \rho \log\left(\frac{K_i}{K_o}\right)$$

Reaction rate of unsubstituted benzoic acid

Acid ionization constant for unsubstituted benzoic acid

- And $$\sigma_i \equiv \log\left(\frac{K_i}{K_o}\right)$$
- So: $$\log\left(\frac{k_i}{k_o}\right) = \rho\sigma$$

Because the ion recombinations (benzoate + proton) are diffusion controlled, they all occur at about the same rate. This makes k_f directly proportional to K, and results in ρ =1.0 for benzoic acid dissociation.

Hammett Equation II

- Substituent & Reaction Constants
  - Meaning
    - Substituent constants are a measure of changes in electron density at the reactive site as a result of the presence of the substituent
      - ☐ As σ ↑, e^- density ↓
  - Source of Constants
    - Table 7-3A for substituent constants (σ)
    - Table 7-3B for reaction constants (ρ)
  - Effects of meta and para substituents are additive
  - Not applicable to ortho substituents due to large steric affects
- Reactions which Hammett Equation applies
  - Hydrolysis
  - Aromatic substitution
  - Oxidation
  - Enzyme catalyzed reactions

Brezonik, P.L. Chemical Kinetics and Process Dynamics in Aquatic Systems, 1994

Substituent Constants

- Values from Brezonik
  - Table 7-3a
    - (pg. 563)
- Meaning
  - $\sigma > 0$
    - Electron withdrawing
  - $\sigma < 0$
    - Electron donating

Substituent	σ_p	σ_m	$\sigma_p{+}$	$\sigma{+}_m$	σ^*
$-NH_2$	-0.66	-0.15			0.1
-OH	-0.35	0.08			0.25
$-OCH_3$	-0.26	0.08	-0.76	0.05	0.25
$-CH_3$	-0.16	-0.07	-0.31	-0.06	-0.05
$-C_6H_5$	-0.01	0.06	-0.18	0.11	0.1
-H	0	0	0	0	0
-F	0.08	0.35	-0.07	0.35	0.52
-Cl	0.23	0.37	0.11	0.4	0.47
-Br	0.23	0.39	0.15	0.41	0.45
-I	0.28	0.35	0.14	0.36	0.39
-CN	0.68	0.62	0.66	0.56	0.58
$-CH_3SO_2$	0.71	0.65			0.59
$-NO_2$	0.79	0.71	0.79	0.67	0.63

$$\log\left(\frac{k_i}{k_o}\right) = \rho\sigma$$

Reaction Constants

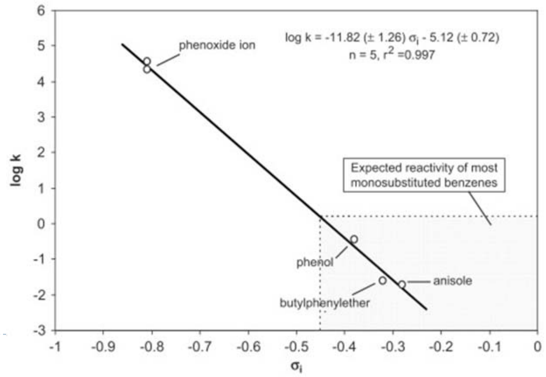
- Values from Brezonik
  - Table 7-3b
    - (pg. 563)
- Meaning
  - $\rho > 0$
    - Nucleophilic reaction
    - Hindered by high electron density
  - $\rho < 0$
    - Electrophilic reaction
    - Accelerated by high electron density

Reactions	ρ	ρ^*	δ
ionization of benzoic acids	1.00		
OH- catalyzed hydrolysis of ethylbenzoates	2.55		
Methlation of benzoic acids	-0.58		
Ionization of carboxylic acids		1.72	
Alkaline hydrolysis of $Co(NH_3)_5O_2CR^{+2}$ in water		0.79	
Catalysis of nitraminde decomposition by RCOO-		-1.43	
Acid hydrolysis of formals, $CH_2(OR)_2$		-4.17	
Alkaline hydrolysis of primary amides		1.60	
ionization of orthobenzoic acids		1.79	
Hydrolysis of bromoalkanes		-11.9	
Acid dissociation constants of aldehyde-bisfulites		-1.29	
Alkaline hydrolysis of diphthalate esters		4.59	1.52
Acid hydrolysis of orthobenzamides			0.81
Acid methanolysis of 2-naphthyl esters			1.38
Methyl iodide reaction with alkylpyridines			2.07

$$\log\left(\frac{k_i}{k_o}\right) = \rho\sigma$$

Hammett Relationship

- Mono-substituted aromatics and HOCl
  - Assumed $\sigma_i \approx \sigma_{ortho} \approx \sigma_{para}$
  - second-order rate constants for the reaction of phenoxide ion, phenol, anisole and butylphenylether with HOCl versus the estimated Hammett constants of the substituents on benzene (O^-, OH, OCH_3 and OC_4H_9) (*T* 22–25 °C).

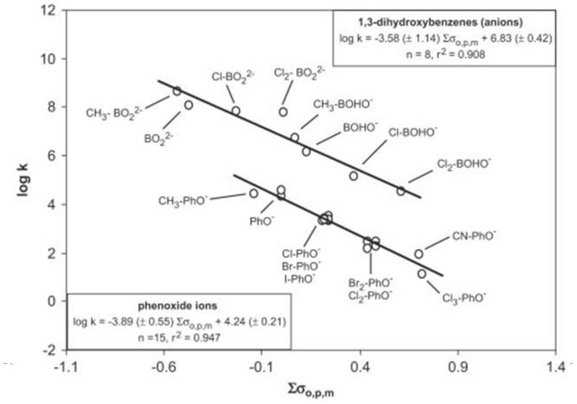


From: Deborde & von Gunten, 2008 **[Wat. Res. 42(1)13]**

Hammett Relationship

- Poly-substituted aromatics and HOCl
  - Cross-linear correlation between the second-order rate constants for the reactions of substituted phenoxide ions (PhO^-) and 1,3-dihydroxybenzene anions ($BOHO^-$ and BO_2^{2-}) with HOCl and the Hammett constants (T 22–25 °C).
  - Assumed $\sigma_{ortho} \approx \sigma_{para}$

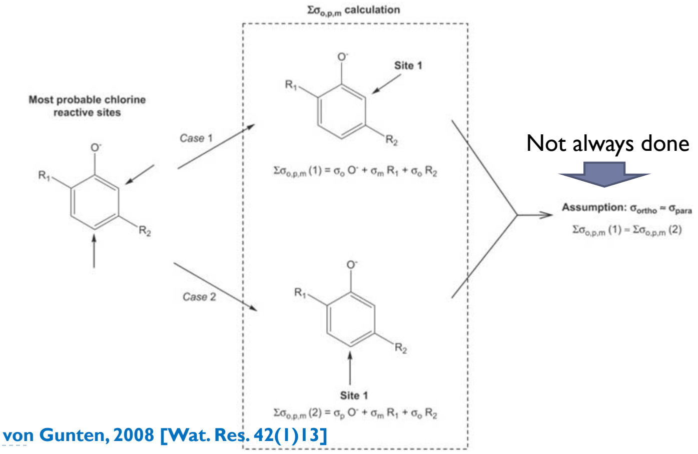
Large negative slope (-3.6 to -3.9) indicates electrophilic nature of this reaction



From: Deborde & von Gunten, 2008 **[Wat. Res. 42(1)13]**

Calculation of sigma

- Example of $\sum\sigma_{o,p,m}$ calculation for the corrected Hammett-type correlation

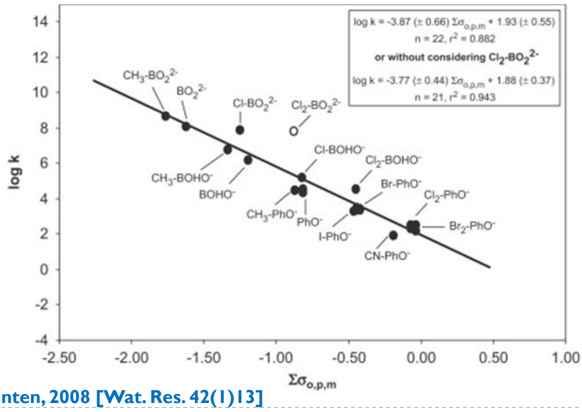


Not always done

From: Deborde & von Gunten, 2008 [Wat. Res. 42(1)13]

Combined Hammett plot

- Corrected Hammett-type correlation of log *k* versus $\sum\sigma_{o,p,m}$ (determined from substituent position to the most probable chlorine reactive site) for the reaction of HOCl with phenoxide ions (PhO^-), 1,3-dihydroxybenzene anions ($BOHO^-$ and BO_2^{2-}) (*T* 22–25 °C).



From: Deborde & von Gunten, 2008 [Wat. Res. 42(1)13]

Components

- Composition
  - Resonance (R)
  - Field (F) or Inductive
- Relationship

$$\sigma_p \approx R + F$$

$$\sigma_m \approx 0.3R + 1.1F - 0.03$$

Substituent	σ_p	σ_m	σ_p+	$\sigma+_m$	σ^*	R	F
$-N(CH_3)_2$	-0.83	-0.16	-1.70			-0.98	0.15
$-NH_2$	-0.66	-0.15			0.10	-0.74	0.08
-OH	-0.35	0.08			0.25	-0.70	0.33
$-OCH_3$	-0.26	0.08	-0.76	0.05	0.25	-0.56	0.29
$-C(CH_3)_3$	-0.20	-0.10	-0.26			-0.18	-0.02
$-CH_3$	-0.16	-0.07	-0.31	-0.06	-0.05	-0.18	0.01
$-CH(CH_3)_2$	-0.15	-0.04	-0.28			-0.19	0.04
$-CH_2C_6H_5$	-0.09	-0.08	-0.28			-0.05	-0.04
$-CH{=}CHC_6H_5$	-0.07	0.03	-1.00			-0.17	0.10
$-CH{=}CH_2$	-0.04	0.06	-0.16			-0.17	0.13
$-OC_6H_5$	-0.03	0.25	-0.50			-0.40	0.37
$-C_6H_5$	-0.01	0.06	-0.18	0.11	0.10	-0.13	0.12
-H	0	0	0	0	0	0	0
$-NHCOCH_3$	0.00	0.21	-0.60			-0.31	0.31
-F	0.08	0.35	-0.07	0.35	0.52	-0.39	0.45
-Cl	0.23	0.37	0.11	0.40	0.47	-0.19	0.42
-Br	0.23	0.39	0.15	0.41	0.45	-0.22	0.45
-I	0.28	0.35	0.14	0.36	0.39	-0.24	0.42
$-CONH_2$	0.36	0.28				0.10	0.26
-CHO	0.42	0.35	0.73			0.09	0.33
$-COC_6H_5$	0.43	0.34	0.51			0.12	0.31
$-COOCH_3$	0.45	0.36	0.49			0.11	0.34
$-COCH_3$	0.50	0.38				0.17	0.33
-CN	0.68	0.62	0.66	0.56	0.58	0.15	0.51
$-CH_3SO_2$	0.71	0.65			0.59		
$-NO_2$	0.79	0.71	0.79	0.67	0.63	0.13	0.65

Other types of reactions

- Reactions involving carbonium ions or carbanion intermediates
  - Need to use $\sigma+$ values (σ_p+, σ_m+)
  - These were determined from hydrolysis of m- and p-substituted 2-chloro-phenylpropanones

Others

- Taft relationship
  - Includes electronic and steric effects
  - Applied mostly to aliphatics
    - Therefore resonance isn't important

Taft Substituent Constants

- From Schwarzenbach et al., 1993
  - Environmental Organic Chemistry

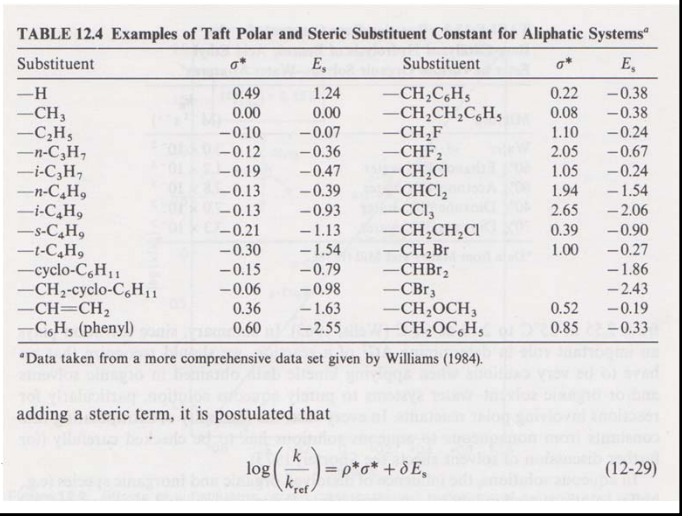


TABLE 12.4 Examples of Taft Polar and Steric Substituent Constant for Aliphatic Systems[a]

Substituent	σ^*	E_s	Substituent	σ^*	E_s
—H	0.49	1.24	—$CH_2C_6H_5$	0.22	−0.38
—CH_3	0.00	0.00	—$CH_2CH_2C_6H_5$	0.08	−0.38
—C_2H_5	−0.10	−0.07	—CH_2F	1.10	−0.24
—n-C_3H_7	−0.12	−0.36	—CHF_2	2.05	−0.67
—i-C_3H_7	−0.19	−0.47	—CH_2Cl	1.05	−0.24
—n-C_4H_9	−0.13	−0.39	—$CHCl_2$	1.94	−1.54
—i-C_4H_9	−0.13	−0.93	—CCl_3	2.65	−2.06
—s-C_4H_9	−0.21	−1.13	—CH_2CH_2Cl	0.39	−0.90
—t-C_4H_9	−0.30	−1.54	—CH_2Br	1.00	−0.27
—cyclo-C_6H_{11}	−0.15	−0.79	—$CHBr_2$		−1.86
—CH_2-cyclo-C_6H_{11}	−0.06	−0.98	—CBr_3		−2.43
—$CH{=}CH_2$	0.36	−1.63	—CH_2OCH_3	0.52	−0.19
—C_6H_5 (phenyl)	0.60	−2.55	—$CH_2OC_6H_5$	0.85	−0.33

[a] Data taken from a more comprehensive data set given by Williams (1984).

adding a steric term, it is postulated that

$$\log\left(\frac{k}{k_{\text{ref}}}\right) = \rho^*\sigma^* + \delta E_s \qquad (12\text{-}29)$$

N-chloro-organics

- Reactions of chlorine with organic amines
  - Primary amines

$$R-NH_2 \xrightarrow{HOCl} R-NHCl \xrightarrow{HOCl} R-NCl_2$$

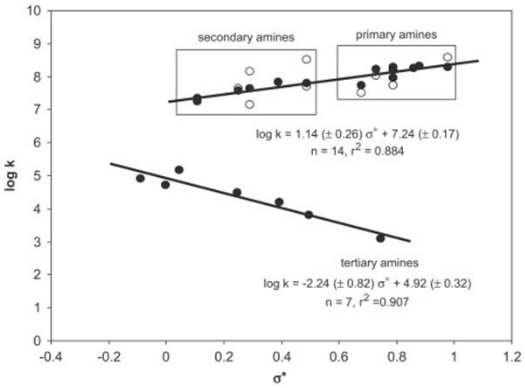
  - Secondary amines

$$R_2-NH \xrightarrow{HOCl} R_2-NCl$$

- Inorganic chloramines can transfer their active chlorine in a similar fashion

Taft Plot

- Formation of organic chloramines

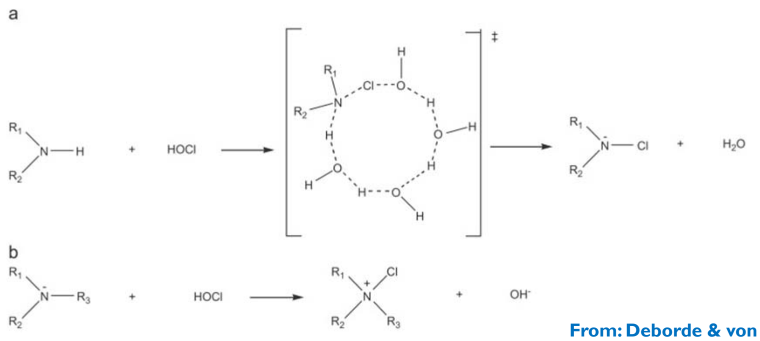


Taft's correlation for chlorination of basic aliphatic amines at 25 °C: Full symbols (●) represent rate constant values used by Abia et al. (1998) and were used for calculation of correlation coefficients and Taft's plot equations; open circles (○) represent other rate constants reported in literature

From: Deborde & von Gunten, 2008 [Wat. Res. 42(1)13]

Interpretation

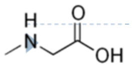
- Reaction schemes proposed by Abia et al. (1998) for the chlorination of organic aliphatic amines: (a) primary and secondary amines; (b) tertiary amines.



From: Deborde & von Gunten, 2008 [Wat. Res. 42(1)13]

Degradation of Organic Chloramines

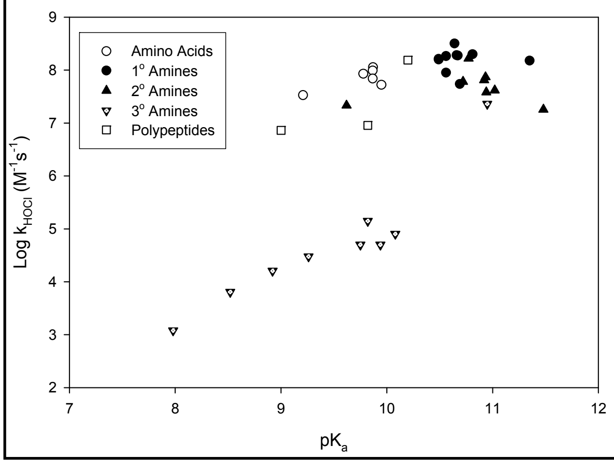
Parent Amine	k_{obs} (s^{-1})	$t_{½}$ (min)
Alanine	1.3E-04	86
Glycine	1.4E-06	8400
Histidine	2.7E-04	43
Leucine	1.6E-04	72
Phenylalanine	2.2E-04	52
Serine	2.4E-04	49
Creatinine	3.5E-06	3300
Glycine N acetyl	6.0E-07	19000
Glycine ethyl ester	2.3E-04	50
Glycylglycine	1.0E-05	1100
Sarcosine	5.3E-05	210



QSPRs

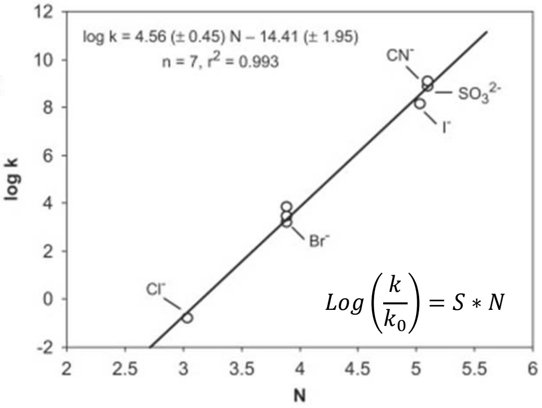
- **Relationship between basicity and 2nd order rate constants for reaction of HOCl with N-compounds**

Data Sources: Friend, 1956; Hussain et al., 1972; Isaac et al., 1983; Armesto et al., 1993; Armesto et al., 1994; Antelo et al., 1995; Abia et al., 1998



QPAR: Rate Constants vs Nucleophilicty

- Nucleophilicity
  - Tendency to donate a pai
    of electrons
  - Closely aligned with Basicity
    - Tendency to donate a pair of electrons to an H atom/ion



$$Log\left(\frac{k}{k_0}\right) = S * N$$

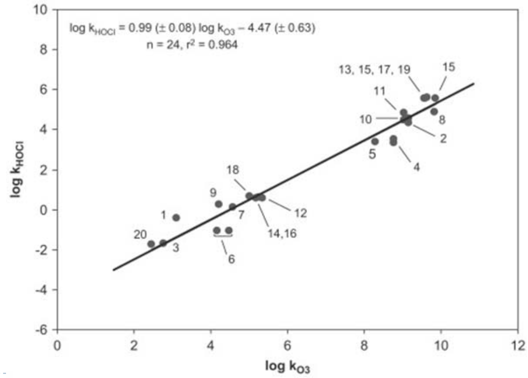
Swain–Scott plot of log *k* for the reaction of HOCl with Cl^-, Br^-, I^-, SO_3^{2-} and CN^- versus the nucleophilicity (N) of the anions at 25 °C. Adapted from Gerritsen and Margerum (1990).

From: Deborde & von Gunten, 2008 [Wat. Res. 42(1)13]

QAAR I

From: Deborde & von Gunten, 2008 [Wat. Res. 42(1)13]

- Linear correlation between the log k_{HOCl} and log k_{O3} for selected aromatic compounds (mostly phenols) for which electrophilic chlorine and ozone attack is expected..



No.	Compounds
1	Phenol
2	Phenoxide ion
3	4-chlorophenol
4	4-chlorophenoxide ion
5	2-chlorophenoxide ion
6	4-methylphenol
7	4-*n*-nonylphenol
8	4-*n*-nonylphenol (ionized)
9	Bisphenol A
10	Bisphenol A (ionized 1)
11	Bisphenol A (ionized 2)
12	Estradiol
13	Estradiol (ionized)
14	17-ethinylestradiol
15	17-ethinylestradiol (ionized)
16	Estrone
17	Estrone (ionized)
18	Estriol
19	Estriol (ionized)
20	Anisole

QAAR II

- Decarboxylation and metal complexation
  - Malonic acid's reaction with various metals

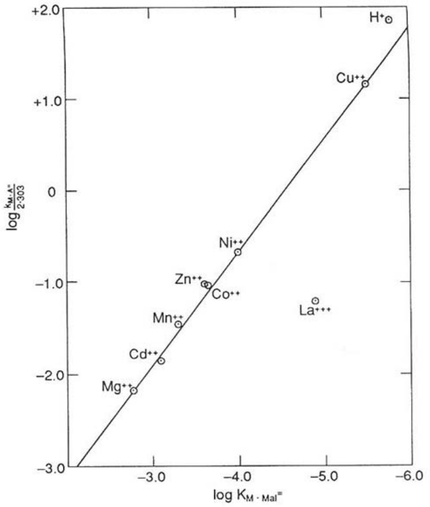


Figure 4-2. The rate constant, k, for metal-catalyzed decarboxylation of malonic acid (acetonedicarboxylic acid) is correlated with K_{MMa}, the dissociation constant for corresponding metal-malonate complex — a linear free-energy relationship. [From Prue, J.E., *J. Chem. Soc.*, II, 2331 (1952). With permission.]

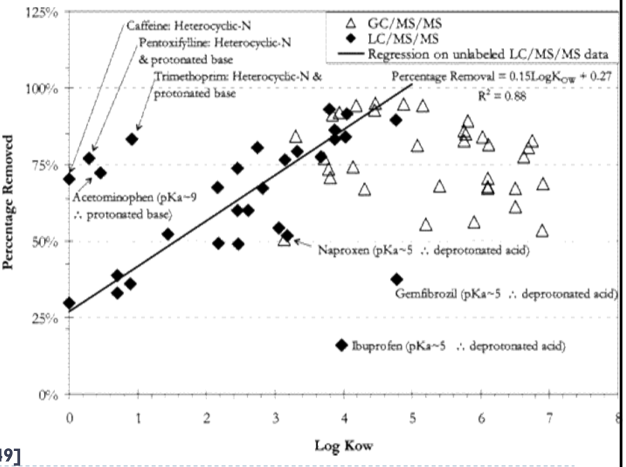
Ozonation

- Removal by ozone

Westerhoff et al., 2005 [EST 39:17:6649]

QPAR: GAC adsorption of PPCPs

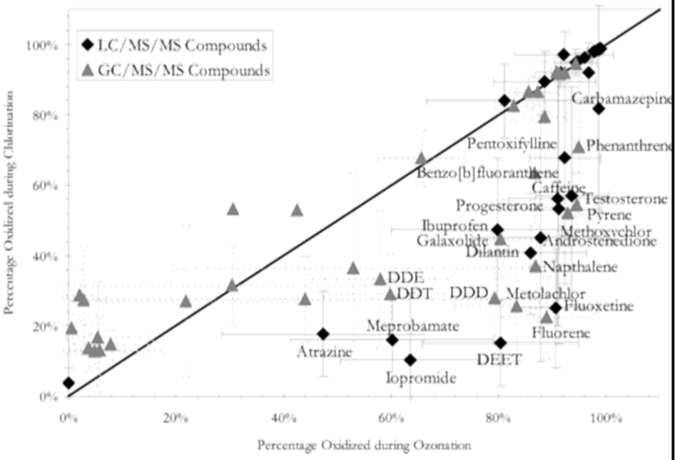
- EDC/PPCP removal as a function of predicted log K_{ow} based upon average removal data from all four source water experiments (5 mg/L WPM; 4-h contact time). Selected LC/MS/MS compounds are identified



Westerhoff et al., 2005 [ES&T, 39:6649]

QAAR – Oxidation of PPCPs

- Average percentage removal of LC/MS/MS and GC/MS/MS compounds by ozone and chlorine across four waters spiked with EDC/PPCPs (PVW, ORW, SRW, CRW).
  - Solid line represents 1:1 removal between ozonation and chlorination experiments. Error bars represent one standard deviation in percentage removal based on experiments in the four waters.



Westerhoff et al., 2005 [ES&T, 39:6649]

Other approaches

- Extending estimations to more robust & empirical approximations

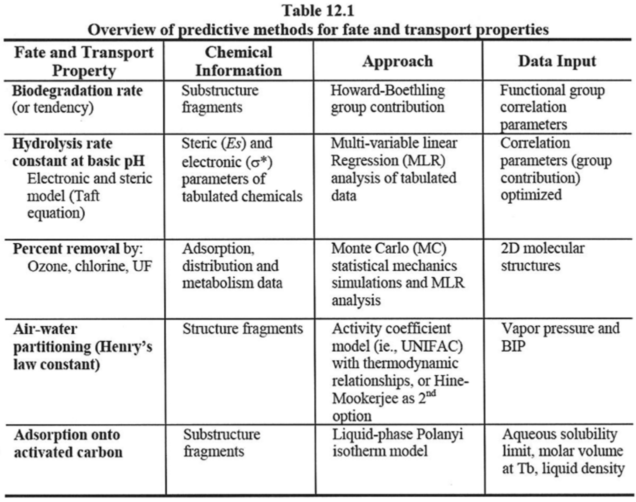


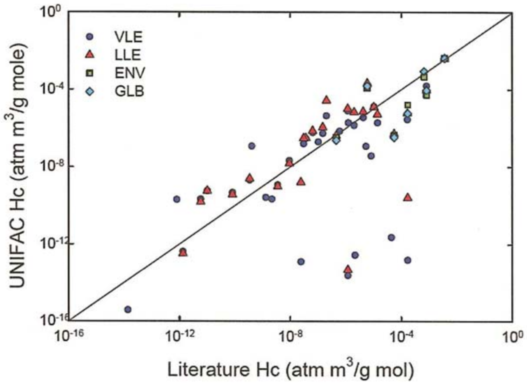
Table 12.1
Overview of predictive methods for fate and transport properties

Fate and Transport Property	Chemical Information	Approach	Data Input
Biodegradation rate (or tendency)	Substructure fragments	Howard-Boethling group contribution	Functional group correlation parameters
Hydrolysis rate constant at basic pH Electronic and steric model (Taft equation)	Steric (*Es*) and electronic (σ^*) parameters of tabulated chemicals	Multi-variable linear Regression (MLR) analysis of tabulated data	Correlation parameters (group contribution) optimized
Percent removal by: Ozone, chlorine, UF	Adsorption, distribution and metabolism data	Monte Carlo (MC) statistical mechanics simulations and MLR analysis	2D molecular structures
Air-water partitioning (Henry's law constant)	Structure fragments	Activity coefficient model (ie., UNIFAC) with thermodynamic relationships, or Hine-Mookerjee as 2nd option	Vapor pressure and BIP
Adsorption onto activated carbon	Substructure fragments	Liquid-phase Polanyi isotherm model	Aqueous solubility limit, molar volume at Tb, liquid density

Snyder et al., 2007
"Removal of EDCs and Pharmaceuticals in Drinking and Reuse Treatment Processes"
[AWWARF final report]

Volatilization

- Henry's law constants by UNIFAC



Snyder et al., 2007
"Removal of EDCs and Pharmaceuticals in Drinking and Reuse Treatment Processes"
[AWWARF final report]

Figure 12.3 Comparison of predicted and experimental Henry's constants

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Hydrolysis I

- Returning to more fundamental LFERs

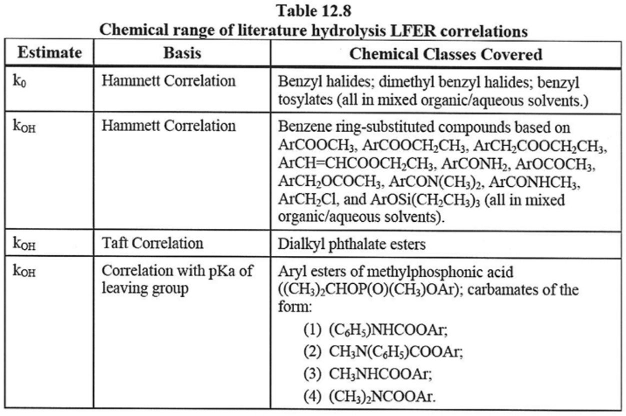

Table 12.8
Chemical range of literature hydrolysis LFER correlations

Estimate	Basis	Chemical Classes Covered
k_0	Hammett Correlation	Benzyl halides; dimethyl benzyl halides; benzyl tosylates (all in mixed organic/aqueous solvents.)
k_{OH}	Hammett Correlation	Benzene ring-substituted compounds based on $ArCOOCH_3$, $ArCOOCH_2CH_3$, $ArCH_2COOCH_2CH_3$, $ArCH{=}CHCOOCH_2CH_3$, $ArCONH_2$, $ArOCOCH_3$, $ArCH_2OCOCH_3$, $ArCON(CH_3)_2$, $ArCONHCH_3$, $ArCH_2Cl$, and $ArOSi(CH_2CH_3)_3$ (all in mixed organic/aqueous solvents).
k_{OH}	Taft Correlation	Dialkyl phthalate esters
k_{OH}	Correlation with pKa of leaving group	Aryl esters of methylphosphonic acid ($(CH_3)_2CHOP(O)(CH_3)OAr$); carbamates of the form: (1) $(C_6H_5)NHCOOAr$; (2) $CH_3N(C_6H_5)COOAr$; (3) $CH_3NHCOOAr$; (4) $(CH_3)_2NCOOAr$.

Snyder et al., 2007
"Removal of EDCs and Pharmaceuticals in Drinking and Reuse Treatment Processes"
[AWWARF final report]

Hydrolysis II

- Applied to PPCPs

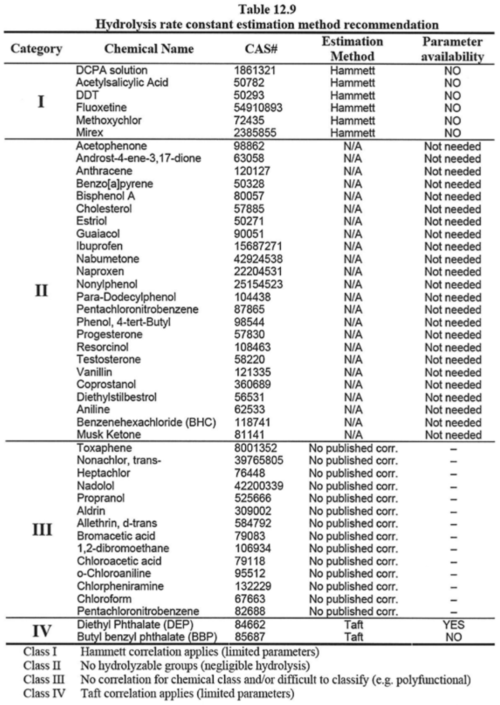

Table 12.9
Hydrolysis rate constant estimation method recommendation

Category	Chemical Name	CAS#	Estimation Method	Parameter availability
I	DCPA solution	1861321	Hammett	NO
	Acetylsalicylic Acid	50782	Hammett	NO
	DDT	50293	Hammett	NO
	Fluoxetine	54910893	Hammett	NO
	Methoxychlor	72435	Hammett	NO
	Mirex	2385855	Hammett	NO
II	Acetophenone	98862	N/A	Not needed
	Androst-4-ene-3,17-dione	63058	N/A	Not needed
	Anthracene	120127	N/A	Not needed
	Benzo[a]pyrene	50328	N/A	Not needed
	Bisphenol A	80057	N/A	Not needed
	Cholesterol	57885	N/A	Not needed
	Estriol	50271	N/A	Not needed
	Guaiacol	90051	N/A	Not needed
	Ibuprofen	15687271	N/A	Not needed
	Nabumetone	42924538	N/A	Not needed
	Naproxen	22204531	N/A	Not needed
	Nonylphenol	25154523	N/A	Not needed
	Para-Dodecylphenol	104438	N/A	Not needed
	Pentachloronitrobenzene	87865	N/A	Not needed
	Phenol, 4-tert-Butyl	98544	N/A	Not needed
	Progesterone	57830	N/A	Not needed
	Resorcinol	108463	N/A	Not needed
	Testosterone	58220	N/A	Not needed
	Vanillin	121335	N/A	Not needed
	Coprostanol	360689	N/A	Not needed
	Diethylstilbestrol	56531	N/A	Not needed
	Aniline	62533	N/A	Not needed
	Benzenehexachloride (BHC)	118741	N/A	Not needed
	Musk Ketone	81141	N/A	Not needed
III	Toxaphene	8001352	No published corr.	–
	Nonachlor, trans-	39765805	No published corr.	–
	Heptachlor	76448	No published corr.	–
	Nadolol	42200339	No published corr.	–
	Propranol	525666	No published corr.	–
	Aldrin	309002	No published corr.	–
	Allethrin, d-trans	584792	No published corr.	–
	Bromacetic acid	79083	No published corr.	–
	1,2-dibromoethane	106934	No published corr.	–
	Chloroacetic acid	79118	No published corr.	–
	o-Chloroaniline	95512	No published corr.	–
	Chlorpheniramine	132229	No published corr.	–
	Chloroform	67663	No published corr.	–
	Pentachloronitrobenzene	82688	No published corr.	–
IV	Diethyl Phthalate (DEP)	84662	Taft	YES
	Butyl benzyl phthalate (BBP)	85687	Taft	NO

Class I	Hammett correlation applies (limited parameters)
Class II	No hydrolyzable groups (negligible hydrolysis)
Class III	No correlation for chemical class and/or difficult to classify (e.g. polyfunctional)
Class IV	Taft correlation applies (limited parameters)

Snyder et al., 2007
"Removal of EDCs and Pharmaceuticals in Drinking and Reuse Treatment Processes"
[AWWARF final report]

- To next lecture