Slide 1

4。结构与活性的线性自由能关系
Correlation of structure with reactivity

（5 学时）

Slide 2

前 章 回 顾
（3。有机反应及试剂分类）

3.1 极性与自由基途径
　　极性反应；自由基反应；亲核试剂；亲电试剂；活性
3.2 基本有机反应分类
　　键的形成与断裂；转移反应；消除与加成；周环反应；氧化与还原
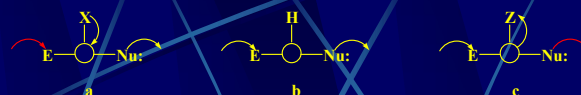3.3 协同反应的优势
3.4 电子的供与求（'推与拉'）
3.5 过渡态性质与结构变化

Slide 3

4.1 取代基的电子效应

电子效应 ⟨ 诱导效应　I
　　　　　 共轭效应　R
　　　　　 场效应　　S

Examples		Effects
-O⁻	+R, +I	electron-donating
-NR₂, -OR, -SR	+R > -I	electron-donating
-R	+R	electron-donating
-Hal	+R < -I	electron-withdrawing
>C=O, >SO₂, -NO₂	-R, -I	electron-withdrawing
-N⁺R₃, -P⁺R3	-I	electron-withdrawing

Slide 4

Model expressing the effect on reactivities of nucleophilic(-Nu:) and electrophilic centres(-E).

-X: electron-donating subsituents;

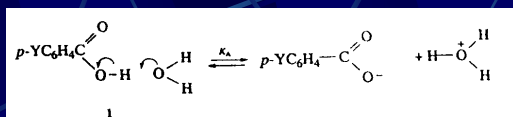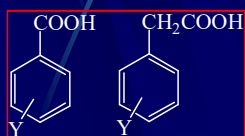-Z: electron-withdrawing subsituents.

-X: 提高HOMO能级，增强亲核性（碱性），亲电性降低

-Z: 降低LUMO能级，增强亲电性（酸性），亲核性降低

Slide 5

Y:	-NO₂	-CN	-Cl	-H	-Me	-OMe	
log K_A	-3·45	-3·56	-4·00	-4·20	-4·37	-4·47	($pK_A = -\log K_A$)
σ:	+0·75	+0·64	+0·2	0·00	-0·17	-0·27	

Slide 6

4.2 Hammett方程

1. Hammett方程

$$lgK_Y/K_0 = lgK_Y'/K_0' = C$$

K_0, K_0'—苯甲酸，苯乙酸

K_Y, K_Y'—取代苯甲酸,取代苯乙酸

令 $lgK_Y/K_0 = \sigma$ (25°C)

$$lgK_Y/K_0 = \rho\sigma \qquad or \qquad lg\,k_Y/k_0 = \rho\sigma$$

上式为Hammett方程一般形式。

σ - 取代基常数

ρ - 反应常数

Slide 7:

$$p\text{-}YC_6H_4COOEt \xrightarrow{OH^-, k} p\text{-}YC_6H_4COO^- + EtOH$$

Y:	-NO₂	-CN	-Cl	-H	-Me	-OMe
$k/M^{-1}S^{-1}$	32.9	15.7	2.10	0.289	0.172	0.143

Slide 8:

Fig. 4.2. a, Log-log plot of relative rates of hydrolysis of substituted ethyl benzoates (ordinate) against acid dissociation constants of benzoic acids (abscissa). b, The same, plotting values of σ on the abscissa.

Slide 9:
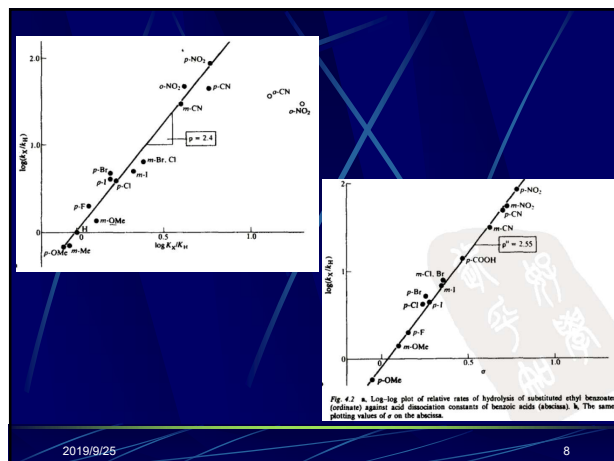
K_Y，k_Y分别为Y-C₆H₄-X的平衡常数、速率常数

K_0，k_0分别为C₆H₄-X的平衡常数、速率常数

由$\Delta G = -2.3RT \lg K$, 代入Hammett方程

$$-\Delta G_Y/2.3RT + \Delta G_0/2.3RT = \rho\sigma$$

即， $-\Delta G_Y = 2.3RT\rho\sigma - \Delta G_0$

对于一组特定条件下的反应，ρ为常数，因此σ与ΔG成线性关系，称为线性自由能关系(linear free energy relationship, LFER)。

LFER

Slide 10:

2. 取代基常数 (Substituent constants, σ)

　　用于表征结构因素，是度量其对环境电子扰动能力的。对于不同的取代基，σ值不同；对于一个给定的基团，不论由此基团的化合物涉及什么反应，其值不变。

以H为参照(σ =0)，σ > 0时，为吸电子的取代基

σ < 0时，为供电子的取代基

Unshared-pair substituents, –X:	+R, –I
Alkyl group, –R	+R
Acceptor groups, –Z	–R, –I
Cationic centres with no vacant orbitals	–I

Slide 11:

Examples	Effects		Sign of σ
-O⁻	+R, +I	electron-donating	-(large)
-NR₂, -OR, -SR	+R > –I	electron-donating	-(large)
-R	+R	electron-donating	-(small)
-Hal	+R < –I	electron-withdrawing	+(small)
>C=O, >SO₂, -NO₂	–R, –I	electron-withdrawing	+(large)
-N⁺R₃, -P⁺R3	–I	electron-withdrawing	+(large)

See P₁₅₉, Fig. 4.4

Slide 12:

Fig. 4.4. Analysis of total electronic substituent effect, σ, as a resultant of I and R components. a, +R groups; b, –R groups.

Slide 13
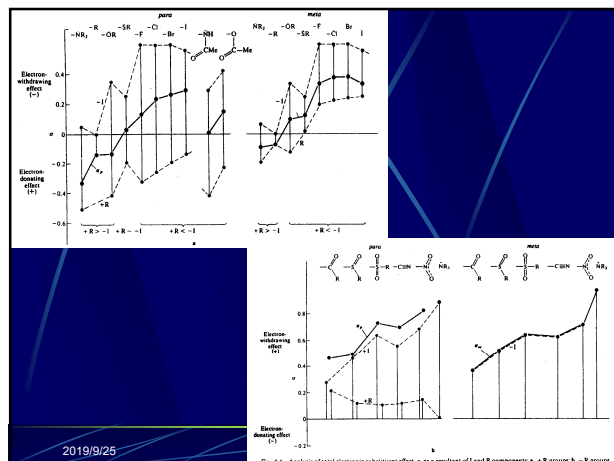
3. 反应常数 ρ

　　用于度量反应对取代基电子效应敏感性的大小。在给定的反应条件下进行反应时，无论涉及什么取代基，反应常数 ρ 值是一定的。不同的反应条件，有不同的 ρ 值。ρ = +3 ～ -3. ρ 值越大，表明反应对取代基效应的敏感度越高。

ρ 值：反应中心与取代基之间的"核"传递电子效应的能力

The acid ionization of the compounds (K_A)

K_A of:	ArCOOH	$ArCH_2COOH$	$ArCH_2CH_2COOH$	ArCH=CHCOOH	$ArC≡CCOOH$
ρ	1.000	0.562	0.212	0.466	1.1

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Sign of ρ	Rate increased by:
+	electron withdrawal
−	electron donation

　　ρ > 0，表明总反应中慢步骤的过渡态出现负电荷（或正电荷减少），可被吸电子取代基所促进(σ >0)，被供电子基抑制；
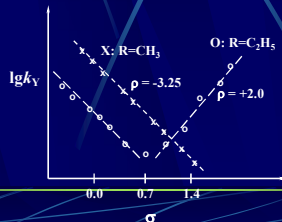
　　ρ < 0，表明总反应中慢步骤的过渡态出现正电荷（或负电荷减少），可被供电子取代基所促进(σ <0)，被吸电子基抑制

Slide 15

4.3 Hammett 方程的偏离与修正

1. 机理改变引起偏离

$$\text{ArCOOR} + H_2O \xrightarrow[k_Y]{99.9\% H_2SO_4, 25^\circ C} \text{ArCOOH} + ROH \quad (R = Me, Et)$$

X: R=CH₃　O: R=C₂H₅　ρ = -3.25　ρ = +2.0

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A. 反应途径的改变

X: R=CH₃　O: R=C₂H₅　ρ = -3.25　ρ = +2.0

(i) $Ar-\overset{OR}{\underset{}{C}}=\overset{+}{O}H \xrightarrow{Slow} \overset{H_2O:}{}\ Ar-C=O + ROH \rightleftharpoons Ar-\overset{+}{O}H_2 \longrightarrow Ar-\overset{OH}{C}=O$
R = Me, Et

(ii) $Ar-\overset{HO-Et}{\underset{}{C}}=\overset{+}{O}H \xrightarrow{Slow} Ar-\overset{OH}{C}=O + \overset{+}{C}H_2CH_3$　CH_3^+ 极不稳定，不能生成

正电荷减少　$\xrightarrow{H_2O} HOCH_2CH_3 + H^+$

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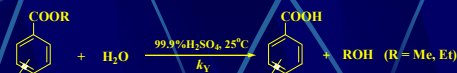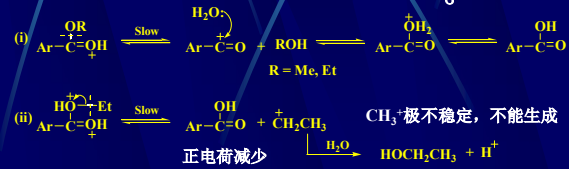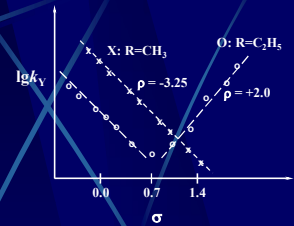
B. 决速步骤的改变
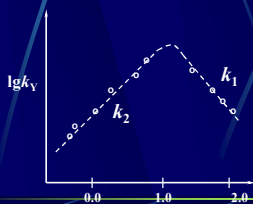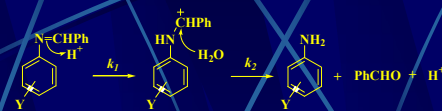
决速步骤：

k_2　供电子取代基　$k_1\uparrow$, $k_2\downarrow$

k_1　吸电子取代基　$k_1\downarrow$, $k_2\uparrow\uparrow$

$\sigma\uparrow$(供电子→吸电子)：

当 $k_2 > k_1$, $k_2 \rightarrow k_1$

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P164 Fig. 4.5

A nonlinear hammett relationship as evidence for a change-over in mechanism in the alkaline hydrolysis of methyl carbanilates

Tetrahedron Letter 1981, 22, 977-940.

A nonlinear Hammett relationship could be used as evidence for a change-over in mechanism in the alkaline hydrolysis of methyl carbanilates. The electron-withdrawing substituted compounds hydrolyse via an A–E pathway (ρ 1.06) whereas the hydrolysis of the electron-donating substituted compounds involves an E-A scheme.

?　开口向上　反应途径改变；
　　开口向下　决速步骤改变

Slide 19
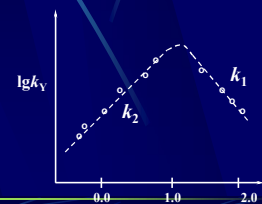
在取代基变化过程中，具有**活化能相似的二条反应途径的**或者**有多个步骤的**反应发生相应的变化：（途径变化）or（决速步的变化），且变化的二者具有**相反的电子需求**，这类反应将呈现背离Hammett线性关系，在Hammett关系图上前者为"∨"（开口向上）；后者为"∧"（开口向下）

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2.增强共轭(Enhanced resonance)

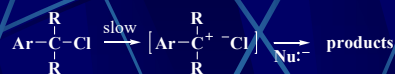$$Ar\underset{R}{\overset{R}{-}}C-Cl \xrightarrow{slow} [Ar\underset{R}{\overset{R}{-}}C^+ \ ^-Cl] \longrightarrow products$$

这里，Hamett方程仅适用于那些-R,-I的*p*-、*m*-取代基的反应物

$$H_3CO-\overset{+}{\underset{}{\bigcirc}}=C\overset{Ph}{\underset{Ph}{}}$$ $$H_3CO-\bigcirc-C\overset{O}{\underset{O}{}}$$

三苯氯甲烷的溶剂解反应   **对甲氧基苯甲酸**

$$lgK_{p\text{-CH3O}}/K_H \gg \quad \sigma = lgK'_{p\text{-CH3O}}/K'_H$$

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反应中心与取代基直接共轭，使其速率增大比由σ值计算值大很多。

$$O\overset{O}{\underset{O}{}}N-\bigcirc-\bar{O}$$ $$O\overset{O}{\underset{O}{}}N-\bigcirc-C\overset{O}{\underset{O}{}}$$

对硝基酚   **对硝基苯甲酸**
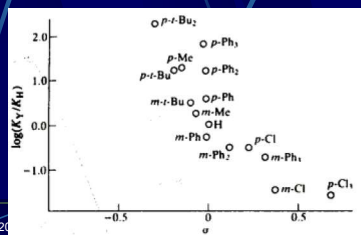
Fig. 4.7 Ar$_3$C-Cl在液态SO$_2$中电离的Hammett关系图

Slide 22
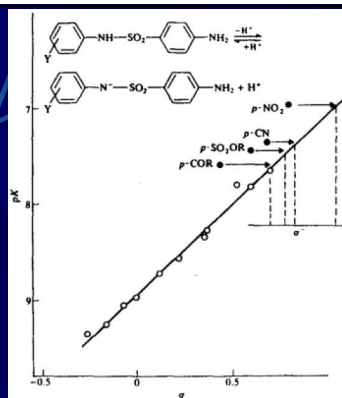
Fig. 4.8 Hammett plot of acid dissociation constants of sulphonamides p-X—C$_6$H$_4$—NHSO$_2$Ph + B ⇌ p-X—C$_6$H$_4$N̄—SO$_2$Ph + BH$^+$ showing deviant points of Z-type substituents and their fitting to the σ^--scale.

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Brown-Okamoto方程：

$$\lg k_Y/k_H = \rho^+\sigma^+ \ (or \ \rho^-\sigma^-)$$

这里引入两个新的σ（σ$^+$和σ$^-$）来表示增强共轭性质。

当富电子的反应中心与强吸电子取代基直接共轭时，采用σ$^-$(or ρ$^-$)

当缺电子的反应中心与强供电子取代基直接共轭时，采用σ$^+$(or ρ$^+$)

P$_{166}$, Fig. 4.7

Slide 24
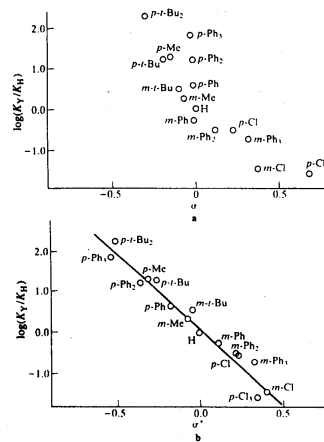
Fig. 4.7 a. Hammett plot of the ionization of Ar$_3$C—Cl in liquid SO$_2$. b. Brown–Okamoto plot of the same reaction.

4

Table 4.4
Some reactions that obey the Brown-Okamoto equation, Eq. (4.2). (See also Table 10.7.)

	ρ^+	Ref.
Ionizations		
ArCMe$_2$—Cl (90% aq. acetone, 25 °C)	−4·45	56
ArCMe$_2$—Cl (EtOH, 25 °C)	−4·67	57
ArCPh$_2$—Cl (EtOH/Et$_2$O)	−2·57	58
ArCPh$_2$—Cl (liquid SO$_2$, 0 °C)	−3·73	59
ArCPh$_2$—OH (H$_2$SO$_4$, 25 °C)	−3·64	60, 61
ArCMe$_2$—ODnb (solvent-assisted, aq. acetone)	−2·47	62
ArCMe$_2$—ODnb (neighbouring-group-assisted, aq. acetone)	−7·07	
ArCOOH + H$^+$ → ArĊ(OH)$_2$	−1·1	58
Electrophilic attack at a π-system		
ArH + ketene/AlCl$_3$	−6·6	63
ArH + Br$_2$ (liquid SO$_2$)	−9·05	64
ArCH(OH)—CH=CHMe + H$^+$ (rearrangement)	−2·97	65
ArC≡CH + Cl$_2$	−4·19	66
ArCHROH oxidation	−2·14	67
Ar$_2$C(OH)N$_3$ rearrangement	−2·69	68
ArCH=CH$_2$ hydroboration	−0·49	69
Rotation of protonated bithiophenes	+4·8	57
Ar—N̈ + N$_2^-$	+3·7	71
ArCHO + CH$_2$(CN)$_2$	+1·45	70

	ρ^-	Ref.
Reactions correlating with σ^-		
Acid dissociation of ArOH	+2·23	71
Acid dissociation of ArNH$_3$	+2·89	72
ArCl + OMe$^-$ → ArOMe + Cl$^-$ (MeOH, 50 °C)	+8·5	73
ArS$^-$ + PhC≡C·COOEt	−0·83	73

---

3. 变化的共轭相互作用

Yukawa & Tsuno利用Hammett的σ与反映直接共轭的σ⁺或σ⁻综合考虑，提出方程：

$$\lg k_Y/k_H = \rho[\sigma + r(\sigma^+ - \sigma)]$$

适用于供电子对位取代基。对于吸电子的对位取代基，用σ⁻代替σ⁺，r参数反映了在一个特定反应中直接共轭作用的大小。规定对枯基氯(2-芳基-2-氯代丙烷)的溶剂解的r值为1，苯甲酸的解离r值为0。

P170, Table 4.5

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Hammett关系

Brown-Okamoto关系

Table 4.5
Reaction parameters fitting the Yukawa–Tsuno equation (Eq. (4.4)).[28]

Substrate	Reaction	ρ	r
ArCOOH	Ionization (water, 25 °C)	1·000	0
ArCMe$_2$Cl	Hydrolysis (90% aq. acetone)	−4·52	1·00
Ar$_2$CHCl	Methanolysis (25 °C)	−4·02	1·23
ArN=NPh	Protonation (20% aq. ethanol)	−2·29	0·85
ArH	Nitration (HNO$_3$, in MeNO$_2$N)	−6·38	0·90
ArH	Bromination (Br$_2$, AcOH)	−10·6	1·2
ArSiMe$_3$	Protodesilylation (H$^+$)	−5·7	0·70
ArSiMe$_3$	Bromodesilylation (Br$_2$)	−6·8	0·79
ArGeMe$_3$	Protodegermylation (H$^+$)	−4·4	0·62
ArPbMe$_3$	Protodeplumbylation (H$^+$)	−2·42	0·63
ArMeCN=NOH	Beckmann rearrangement (H$^+$)	−1·98	0·43
Ar$_2$N$_2$	Esterification by PhCOOH	−1·57	0·19
ArCOCHN$_2$	Acid-catalysed decomposition	−0·82	0·56
ArC≡CH	Acid-catalysed hydration	−4·3	0·81

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4.4 双参数相关：Taft模型

σ反映取代基的电子效应。人们尝试把σ分成只反映诱导、共轭或空间效应的取代基常数。Taft方程就是一个只与诱导效应有关的线性方程。

$$\text{Y—CH}_2\text{COOEt} \underset{OH^-,\ k^B}{\overset{H^+,\ k^A}{\rightleftharpoons}} \text{Y—CH}_2\text{COOH} + \text{EtOH}$$

$$\left[\text{Y—CH}_2\overset{\overset{\delta^-O}{\parallel}}{\underset{\delta^-OH}{C}}\text{—OR'} \right]^{\ddagger} \qquad \left[\text{Y—CH}_2\overset{\overset{\delta^+OH}{\mid}}{\underset{\delta^+OH_2}{C}}\text{—OR'} \right]^{\ddagger}$$

碱性   酸性

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$$\lg k_Y/k_H = \rho_I\sigma_I + E_S$$

即， $\lg k_Y^A/k_H^A = \rho_I\sigma_I + E_S$ （a）

$\lg k_Y^B/k_H^B = \rho_I'\sigma_I + E_S$ （b）

Ingold认为酸催化条件下，$\rho_I\sigma_I$可忽略：

$$\lg k_Y^A/k_H^A = E_S$$

(b)-(a)得，

$$\lg k_Y^B/k_H^B - \lg k_Y^A/k_H^A = \rho_I'\sigma_I = \rho^*\sigma^* \qquad \textbf{P173, Table 4.6}$$

即Taft方程。σ*是饱和碳上的取代基常数，只反映诱导效应。

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Table 4.6
Taft inductive substituent constants, σ*.[71]

Y	$\sigma^*(Y)$	$\sigma^*(CH_2Y)$	Y	$\sigma^*(Y)$	$\sigma^*(CH_2Y)$
Me	0·00	−0·10	OH		0·555
Et	−0·10	−0·10	OMe	−0·22	+0·52
n-Pr	−0·10	−0·13	OPh		+0·85
n-Bu	−0·13		OEt		
isoPr	−0·19		F		+1·1
isoBu	−0·125		Cl		+1·05
t-Bu	−0·300	−0·165	Br		+1·00
neoPe	−0·165		I		+0·85
Ph	+0·60		NO$_2$		+1·40
PhCH$_2$	+0·215	+0·08	CN		+1·30
PhCH$_2$CH$_2$	+0·08		CF$_3$		+0·92
			CH$_3$CO		+0·60

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脂肪族类RCOOEt的酸催化水解反应，对取代基的电子效应不敏感，但分子中R空间效应不能忽略。$Y-CH_2-$相对于$-CH_3$的空间效应，E_S

$$\lg k_{Y-CH_2-COOEt}/k_{HCH_2COOEt} = E_S \qquad \text{（Y不包括-CH}_2\text{）}$$

♠ 除Cl外，所有取代基的E_S值都为负值。

♠ 除甲酸酯外，任何酯的水解速率都比CH_3COOEt慢。

对于许多脂肪族的反应：

$$\lg k_Y/k_{Me} = \rho^*\sigma^* (+\rho_S E_S) \qquad \text{（Y包括-CH}_2\text{）}$$

P173, Table 4.7

Taft-Ingold方程。

Table 4.7
Some reactions correlating with the Taft–Ingold equation, Eq. [4.13].

Reaction*	ρ^*	$\log(k_{Me}/s^{-1})$
1 Alkaline hydrolysis of esters, Y—COOEt	+2·48	−4·536
2 Alkaline hydrolysis of esters, Y—CH₂COOEt	+0·97	−4·536
3 Ionization of acids, Y—CH₂COOH	+1·72	−4·65
4 Hydrolysis of acetals, Y—CH(OEt)₂	−3·65	−0·73
5 Esterification, Y—CH₂COOH + Ph₂CN₂	+1·17	−1·94
6 H⁺ exchange, Y—CH₂OH + isoPrO⁻	+1·36	−0·07
7 Decomposition of NH₃NO₂ by SCH₂COO⁻	−1·42	−0·37
8 Bromination of PhCOCHYY′ (Br₂, H₂O)	+1·59	−4·63
9 Acidic hydrolysis of Y—CH—CH₂	−1·83	−2·52
10 Acetolysis of YY′CHOBros	−3·49	
11 Ethanolysis of YY′Y′C—Cl	−3·29	
12 Ethanolysis of YCH₂OTos	−0·74	

* For identities of Y, see Table 4.6.

问题：

1 The following table sets out values of the pK_A of halogen-substituted benzoic acids and phenols.

	Benzoic acid, 4·76			Phenol, 10·00		
	o-	m-	p-	o-	m-	p-
F	3·83	4·42	4·70	8·70	9·21	9·91
Cl	3·48	4·39	4·53	8·53	9·13	9·42
Br	3·41	4·37	4·49	8·54	9·03	9·36
I	3·42	4·41	4·46	8·51	9·06	9·30

Construct a Hammett plot from these values and examine the fit for *ortho*, *meta* and *para* series. Calculate the reaction constant, ρ, and comment upon its magnitude.

2 Using the values above for monochlorophenols and the following pK_a values for polychlorophenols, examine the postulate that substituent effects are additive, i.e. $pK_a \propto \sum \sigma$.

2,3-Dichloro	7·70	2,3,4-Trichloro	7·59
2,4-Dichloro	7·85	2,3,5-Trichloro	7·23
2,5-Dichloro	7·51	2,3,6-Trichloro	6·12
		2,4,6-Trichloro	6·46
		3,4,5-Trichloro	7·74
2,3,4,5-Tetrachloro	5·22		
2,3,4,6-Tetrachloro	5·22		
2,3,5,6-Tetrachloro	5·44		

3 For the elimination reaction,

$$Y—PhCH{=}N—Cl + OH^- \rightarrow Y—Ph—C{\equiv}N + H_2O + Cl^-,$$
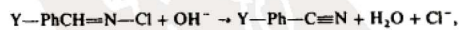
rate constants for different Y were found to be:

Y:	p-MeO	p-Me	H	p-Cl	m-Br	p-COOEt
$10^3 k/M^{-1} s^{-1}$:	4·31	8·43	17·3	100	117	168

Do these rates conform with the Hammett equation and, if so, what mechanistic interpretation may be placed upon them? Estimate the rate of reaction when Y = p-CF₃.

4 The rate constants for bromination of *p*-bromophenol and its conjugate base are found to be as follows:

$$Br{-}\langle\rangle{-}OH \qquad Br{-}\langle\rangle{-}O^-$$

$$k = 3.2 \times 10^{-3}\ M^{-1}s^{-1} \qquad 7.8 \times 10^9\ M^{-1}s^{-1}$$
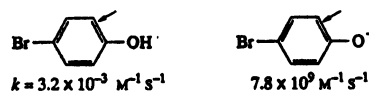
Estimate σ^+ for the —O⁻ substituent if the reaction is assumed to have $\rho^+ = -10$. [*J. Chem. Soc.*, 63 (1961); cf. *J. Chem. Soc., Perkin II*, 1797 (1984).]

5 Iodine does not react appreciably with substituted benzenes unless very highly activating substituents are present. It will react much more readily under electrolytic conditions:
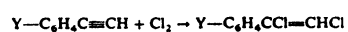
$$ArH + I_2/MeCN \xrightarrow{\text{electrolysis}} ArI,$$
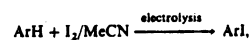
for which $\rho^+ = -6.27$. Suggest a mechanism for this reaction.

6

6 The rates of chlorination of arylacetylenes,

$$Y—C_6H_4C≡CH + Cl_2 → Y—C_6H_4CCl=CHCl$$

are sensitive to substituents:

Y:	p-OMe	p-Me	p-F	H	p-Cl	p-Br	m-NO$_2$	p-NO$_2$
k:	19 500	190	14·9	10·6	4·15	2·81	0·0165	0·003 25
log k	4.290	2.279	1.173	1.025	0.618	0.449	-1.782	-2.488

Determine whether log k is better correlated with σ or with σ^+ and hence infer the nature of the transition state. [*J. Org. Chem.*, 45, 2377 (1980).]

@阅读：

　　参考书：第4章；

@课后练习：

　　Page 188-189，　　1, 2, 3, 6

A, Miller, *Writing Reaction Mechanisms in Organic Chemistry*, Academic Press: San Diego, 1992.