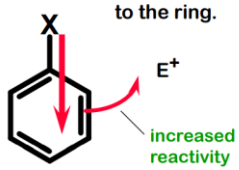
UNIVERSIDADE DE SÃO PAULO
Instituto de Química de São Carlos - IQSC
Grupo de Química Medicinal & Biológica do IQSC/USP
NEQUIMED/IQSC/USP. Email:
Carlos.Montanari@usp.br

Diretividade de substituintes simples do benzeno

ortho, para - Directing Groups

Groups that donate electron density to the ring.



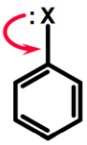
These groups also "activate" the ring, or make it more reactive.

PROFILE:

+I Substituent

CH_3-

R-



+R Substituent

CH_3-Ö-

CH_3-N̈-

-N̈H_2

-Ö-H

The +R groups activate the ring more strongly than +I groups.

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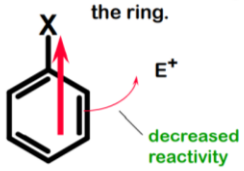
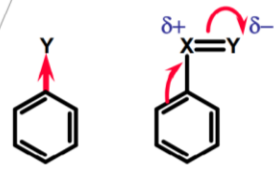
meta - Directing Groups

Groups that withdraw electron density from the ring.

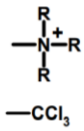


These groups also "deactivate" the ring, or make it less reactive.

PROFILE:

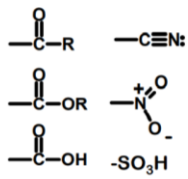


-I Substituent



$-CCl_3$

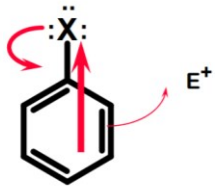
-R Substituent



NEQUIMED

THE EXCEPTION

Halides - *o,p* Directors / Deactivating



+R / -I / *o,p* / deactivating

-F
-Cl
-Br
-I

Halides represent a special case:

They are *o,p* directing groups that are deactivating

They are *o,p* directors (+R effect)

They are deactivating (-I effect)

Most other other substituents fall into one of these four categories:

1) +R / *o,p* / activating
2) +I / *o,p* / activating
3) -R / *m* / deactivating
4) -I / *m* / deactivating

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Diretividade de substituintes múltiplos do benzeno

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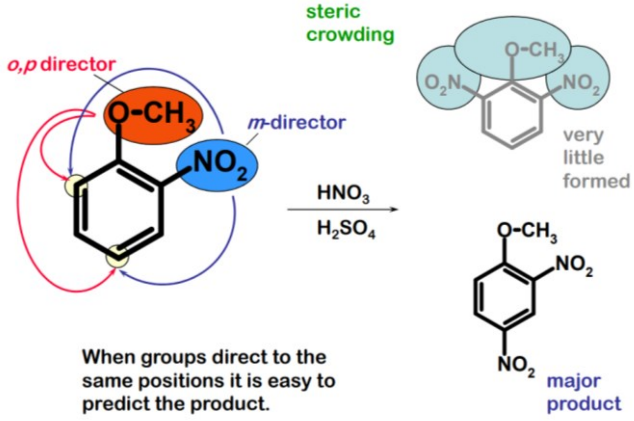
GROUPS ACTING IN CONCERT



When groups direct to the same positions it is easy to predict the product.

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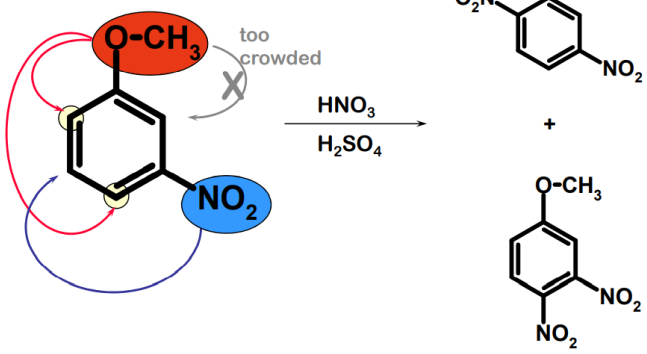
GROUPS COMPETING

o,p-directing groups win over *m*-directing groups



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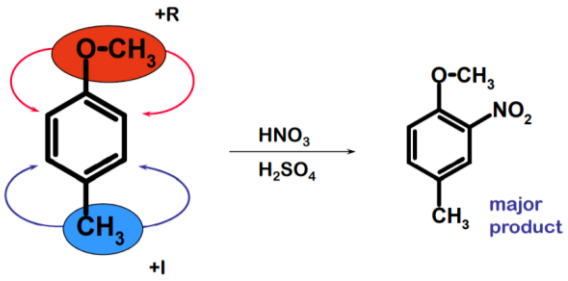
RESONANCE VERSUS INDUCTIVE EFFECT



resonance effects are more important than inductive effects

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Efeito de campo de vários grupos em relação ao hidrogênio

+I		−I	
O^-	NR_3^+	COOH	OR
COO^-	SR_2^+	F	COR
CR_3	NH_3^+	Cl	SH
CHR_2	NO_2	Br	SR
CH_2R	SO_2R	I	OH
CH_3	CN	OAr	C≡CR
D	SO_2Ar	COOR	Ar
			$C{\equiv}CR_2$

[a]The groups are listed approximately in order of decreasing strength for both –I and +I groups. [Reprinted with permission from Ceppi, E.; Eckhardt, W.; Grob, C.A. *Tetrahedron Lett.* **1973**, 3627.

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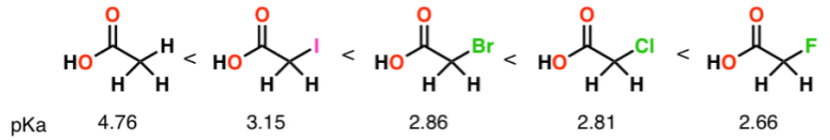
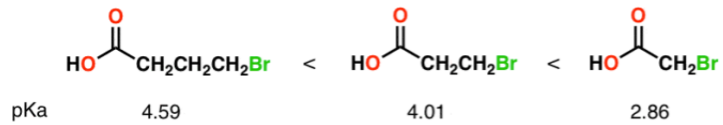
Efeitos Indutivo (campo) e Ressonância

Two principles - electron-withdrawing substituents can increase acidity of a nearby atom, which *increases with electronegativity* and *decreases with increasing distance to the atom*.

Electronegativity increases in the order F > Cl > Br > I :



More acidic



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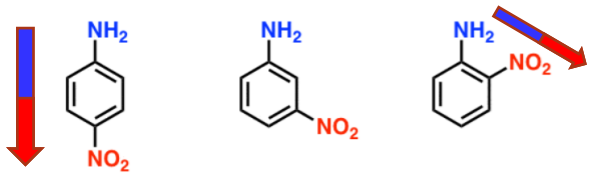
Por que a meta-nitroanilina é mais básica do que a para-nitroanilina, embora o grupo NO_2 esteja mais próximo da amina?



	p-nitroaniline	*m*-nitroaniline	*o*-nitroaniline
pK_aH	1.0	2.46	−0.26

most basic of the three amines pictured

Inductive effects alone can't explain this!

pK_aH, é o pK_a do ácido conjugado!

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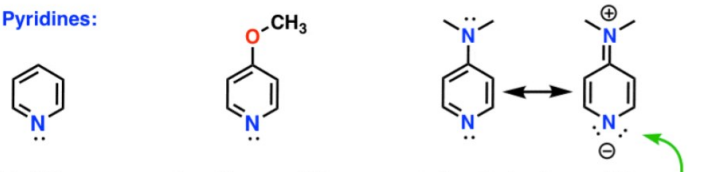
Em sistemas aromáticos, *EDG (ERG)* podem aumentar a basicidade

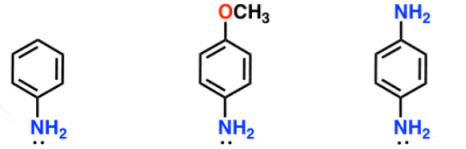
Pyridines:



Pyridine	**4-methoxypyridine**	**4-dimethylamino pyridine (DMAP)**
pKaH = 5.2	pKaH = 6.5	pKaH = 9.2

key resonance form

Anilines:



pKaH = 4.6	pKaH = 5.3	pKaH = 6.2

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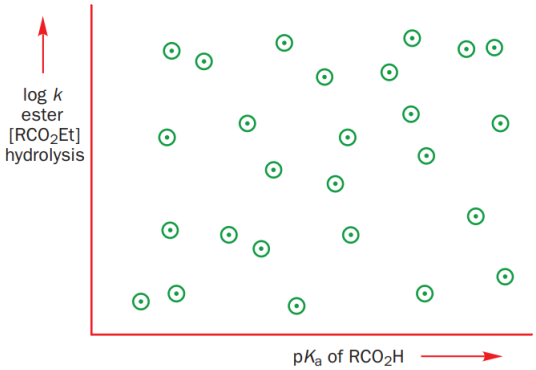
A correlação de Hammett



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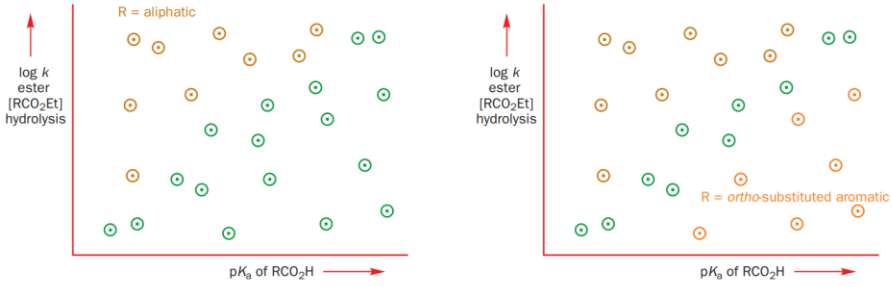
Alifáticos & o-Aromáticos



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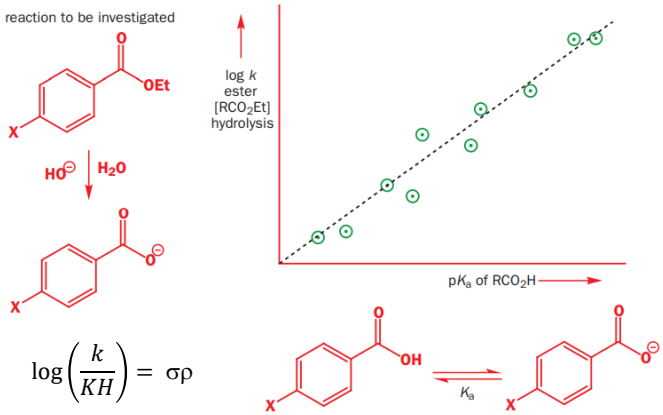
A correlação de Hammett



$$\log\left(\frac{k}{KH}\right) = \sigma\rho$$

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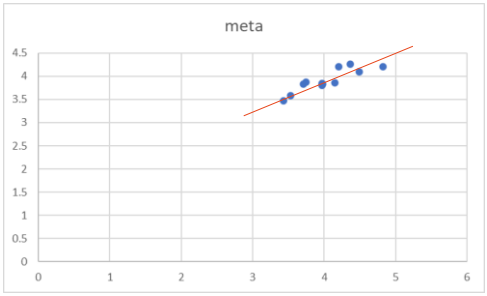
Efeitos Eletrônicos p- & m-

Substituent, X	pK_a of *p*-XC_6H_4COOH	pK_a of *m*-XC_6H_4COOH
NH_2	4.82	4.20
OCH_3	4.49	4.09
CH_3	4.37	4.26
H	4.20	4.20
F	4.15	3.86
I	3.97	3.85
Cl	3.98	3.83
Br	3.97	3.80
CO_2CH_3	3.75	3.87
$COCH_3$	3.71	3.83
CN	3.53	3.58
NO_2	3.43	3.47



$R^2 = 0.88$

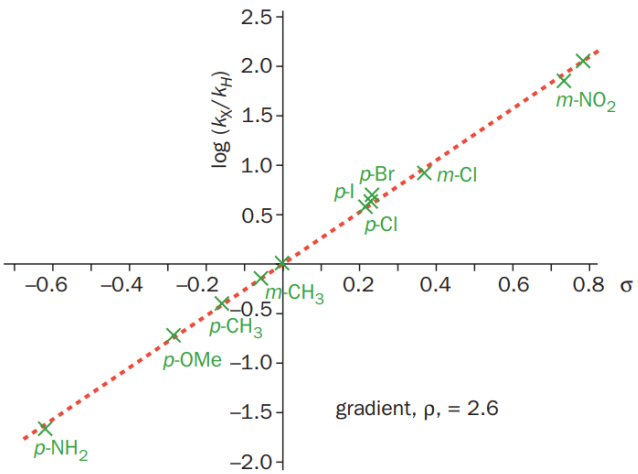
Substituent, X	σ_p	σ_m	Comments
NH_2	–0.62	0.00	groups that donate electrons have negative σ
OCH_3	–0.29	0.11	
CH_3	–0.17	–0.06	
H	0.00	0.00	there are no values for *ortho* substituents
F	0.05	0.34	
I	0.23	0.35	
Cl	0.22	0.37	$\sigma_p < \sigma_m$ for inductive withdrawal
Br	0.23	0.40	
CO_2CH_3	0.45	0.33	
$COCH_3$	0.49	0.37	$\sigma_p > \sigma_m$ for conjugating substituents
CN	0.67	0.62	
NO_2	0.77	0.73	groups that withdraw electrons have positive σ

Constante sigma de Hammett, σ

$$\sigma_X = \log\left(\frac{K_a(X\text{–}C_6H_4COOH)}{K_a(C_6H_5COOH)}\right) =$$

$$= pK_a(C_6H_5COOH) \; - pK_a(X\text{–}C_6H_4COOH)$$

$Log(K_X/K_H)$ vs σ



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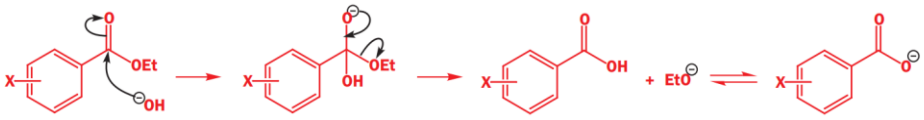
Mecanismo da reação



Carboxylic acids will protonate nucleophiles that are strong bases

Reaction you might ***think*** would happen:

Conversion of carboxylic acid to ester

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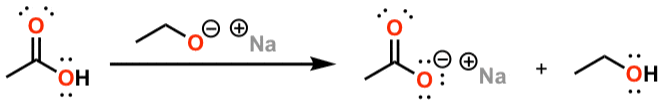
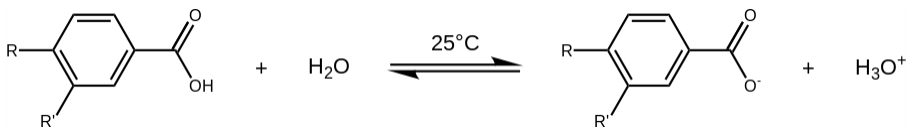
Mecanismo da reação

What actually happens:



Irreversible Acid base reaction between carboxylic acid and $CH_3CH_2O^{\ominus}$



https://www.masterorganicchemistry.com/

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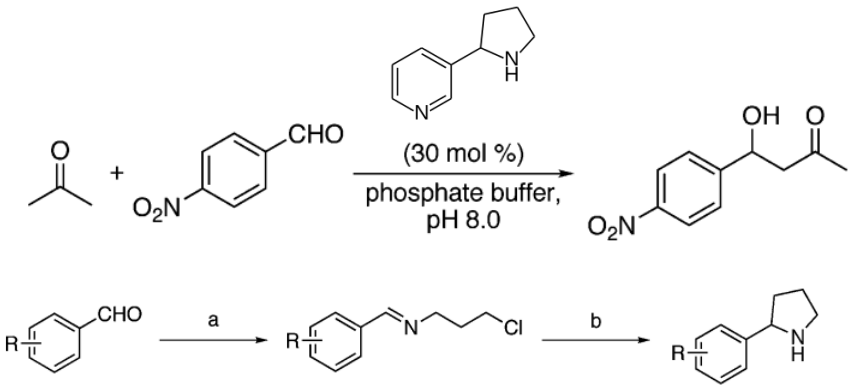
Nornicotine Catalyzed Aldol Reaction



a Reagents and conditions: (a) 3-chloropropylamine,HCl, Et_3N, $MgSO_4$, CH_2Cl_2. (b) Li wire, DTBB, THF, -78 °C.

J. Org. Chem., Vol. 70, No. 9, 2005

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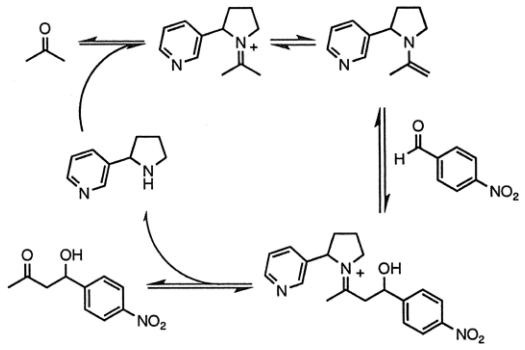
Catalysis appears to be due to a covalent enamine mechanism, an unprecedented reaction with small organic molecule catalysts in aqueous buffer.



https://doi.org/10.1073/pnas.222561699

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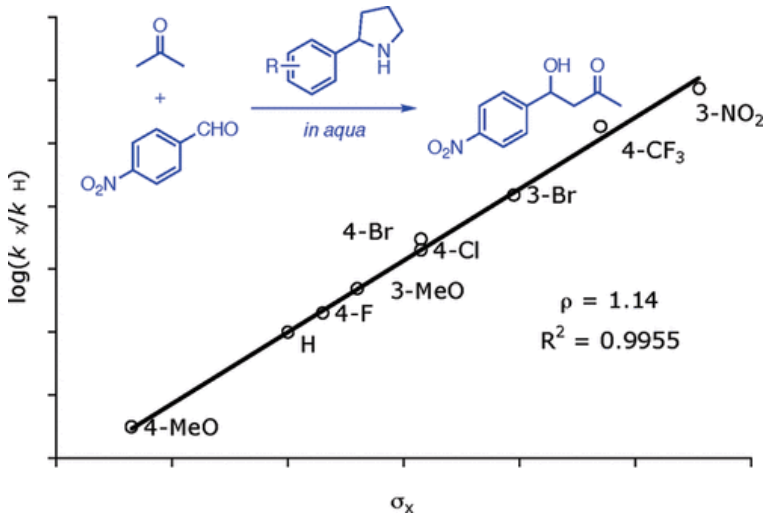
Hammett Correlation of Nornicotine Analogues in the Aqueous Aldol Reaction



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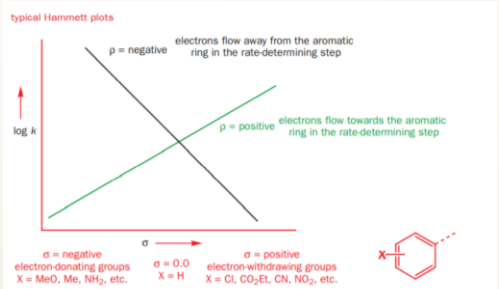
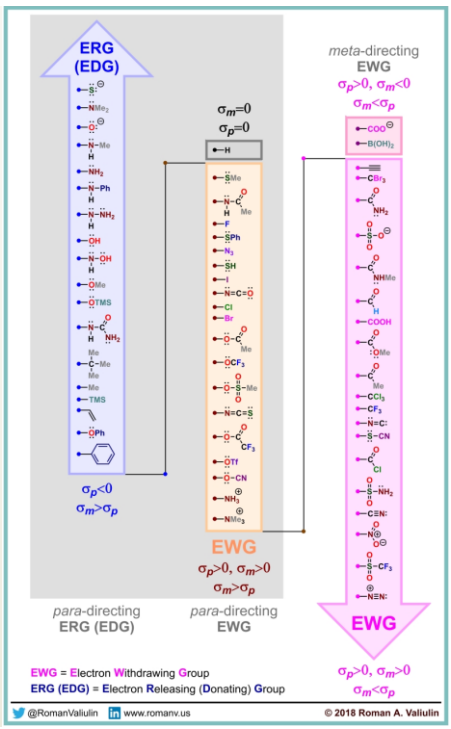
A correlação de Hammett





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Muito obrigado