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Chemical Education

A New Insight on Substituent Additive Effects to Physical-Organic Chemistry Class-Room

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ABSTRACT

Since the discovery of Hammett equation in mid 1930s, the interest in its use is ever increasing among physical-organic chemists in elucidating the reaction mechanisms and the site of attack in several aromatic systems. In this article we have tried to explore the cumulative effects of substituents on the reaction rates by Hammett equation and on the activation energies in the reactions of polysubstituted benzene derivatives. In the correlation of Hammett equation while explaining the cumulative effects of substituents, we have used σ^- *values for conjugative electron withdrawing substituents and* σ^+ *values for mesomerical electron donating substituents if the normal substituent constants failed to give good correlation. To exemplify the title concept, we have considered several reactions of polysubstituted benzene derivatives.*

Keywords: Hammett equation, cumulative effects of substituents, additive effects.

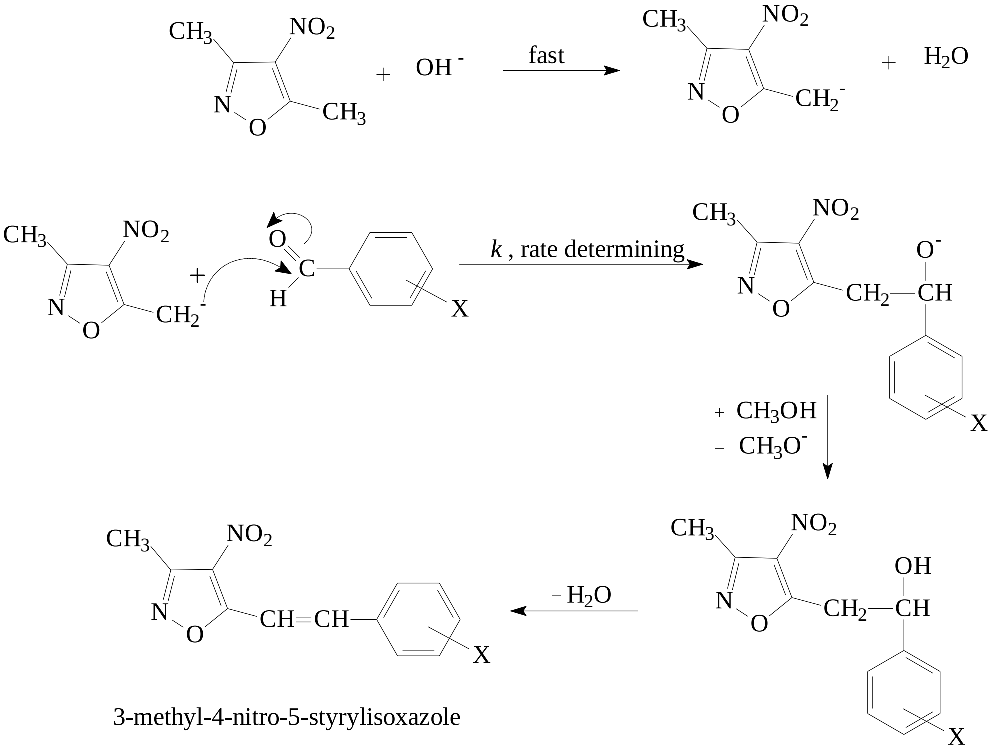
INTRODUCTION

In continuation of our crusade on chemical education [1-4], we are presenting this treatise on additive properties of substituents in polysubstituted benzene derivatives. Ever since the Hammett equation was developed [5, 6], there were several hundreds of redox, condensation, disproportionation, nucleophilic and electrophilic substitution, and addition reactions with *meta*- and *para*- substituted benzene derivatives in the literature, for which the Hammett reaction (ρ) constants were reported. It is one of the most celebrated equations in physical organic chemistry and was formulated as $\log (K/K_o) = \rho\sigma$ or $\log (k/k_o) = \rho\sigma$ where K and K_o refer to the dissociation equilibrium constants of substituted and parent benzoic acids, respectively, and, k and k_o refer to the rates of reactions of *meta*- or *para*- substituted benzene and un-substituted benzene derivatives, respectively. Here σ refers to the substituent constant of a particular substituent and ρ refers to the reaction constant. Hammett equation using σ^-, σ^+ and Hammett normal substituent constants values to methoxide ion catalyzed condensation of mono and di-substituted benzaldehydes with 3,5-dimethyl-4-nitroisoxazole in methanol medium, with several other ketones in methanol-water mixtures, several solvolysis reactions, and correlation of cation-π binding energies in the nicotinic receptors to witness the cumulative effects of substituents and the activation energies on rates are the new features of the present article.

Discussion: The observation of cumulative effects of substituents in polysubstituted benzene derivatives on rates or equilibriums started with Hammett himself [7]. Later, assuming the entropies of activation are essentially constant, in several reactions the effect of substituents on activation energies in polysubstituted compounds could be expressed as the sum of the individual effects of the substituents in the corresponding monosubstituted compounds [8-10]. Since in those reaction series, the effects of multiple substituents on rate (or equilibrium) constants must be the sum of the effects of the individual substituents, Hammett has given a substituent constant for the 3,4-dimethyl substituent (-0.229) which appears to agree well with the sum of the values for m- and p- methyl groups [7]. Therefore it appeared worth for us for a physical-organic chemistry graduate class-room as a curriculum, to see substituent constants and the activation energies are in general additive in polysubstituted benzene derivatives.

For this purpose we started with the work that was published form our laboratory [11]. 3,5-dimethyl-4-nitroisoxazole was known to condense with benzaldehydes in the presence of mild bases to give 3-methyl-4-nitro-5-styrylisoxazole [12]. The mechanism of the reaction is depicted in scheme 1.

Scheme 1



On the basis of the mechanism, the condensation reaction of aldehyde and isoxazole depends upon the ease of C-C bond formation between the carbanion of isoxazole and the carbonyl carbon atom of the aldehyde. This is more easily formed when the carbonyl carbon atom of aldehyde is more electrophilic. That is, the presence of electron withdrawing substituents increase the rate and electron donating substituents decrease the rate. This could be seen from the effect of substituents on the rates of condensation of aldehydes with isoxazole (Table 1, Figure 1). Hammett plot is first constructed for *meta* substituents using σ^m values and looked further for *para* substituents to be on the line of correlation (plot not shown). But the *para* substituents did not fall on the line. This is due to the presence of multi component substituent effects of *para* substituents. Hence Hammett plot (Figure 1) is constructed taking log *k* values as a function of substituent constants σ^- and σ^+ which gave a $\rho^{(-/+)}$ value of + 0.45 and with correlation coefficient of 0.95. Though the Hammett plot is a bit away from a good correlation but the overall trend is unmistakable. Here we have used the σ^- values for conjugative electron withdrawing substituents and σ^+ values for mesomerical electron donating substituents. The substituent constant values σ^- and σ^+ are from literature [13]. Three di-substituted benzaldehydes, i.e. compounds with serial numbers 2, 3, and 13 in the table 1 and the graph also correlated very well using the $\sum\sigma^+$ and $\sum\sigma^-$ values. This shows a good cumulative effect of di-substituted benzaldehydes on rates. Here the $\sum\sigma^+$ value of 2,4-dimethoxy benzaldehyde is taken as the sum of the σ^+ values of the 2- and 4- methoxy two mono substituted benzaldehydes {$\sum\sigma^+ = [-0.78 + (-0.28) = -1.00$}. Similarly $\sum\sigma^+$ for the 3,4-diemthoxy benzaldehyde and $\sum\sigma^-$ for 2,6-dichloro benzaldehyde were computed. Also the cumulative effect was seen in the activation energies. As an example the experimentally observed value of activation energy of 2,4-dimethoxy benzaldehyde is 95.8 kJ mol^{-1}. If the activation energies of benzaldehyde, 2-methoxy and 4-methoxy benzaldehydes are represented as E_1, E_2 and E_3 respectively, then the calculated activation energy for 2,4-dimethoxy benzaldehyde is given by $\Delta E^{\neq}_{(calculated)} = E_1 + (E_2 - E_1) + E_3 - E_1) = 116 + (108 - 116) + (104 - 116)$ and which was found to be 96.0 kJ mol^{-1}. Hence there is a good correlation of cumulative effects of disubstituted benzaldehydes toward the activation energies. Similarly the other two benzaldehydes (3 and 13 from the table) also gave a good correlation.

Table 1: Effect of substituents in the benzaldehydes on rate of methoxide ion catalyzed condensation with 3,5-dimethyl-4-nitroisoxazole in methanol medium at 301 K. The data given in this table is from reference 11.

S.No.	Substituent (X)	Hammett substituent constant	*k* X 10^2 mol^{-1} sec^{-1}	$\Delta E^{\neq}$ (kJ mol^{-1})	
				Experimental	*Calculated
1	4-MeO	-0.78	1.18	104	
2	2,4-diMeO	-1.00	4.12	95.8	96.0
3	3,4-diMeO	-0.67	6.71	87.8	88.6
4	2-MeO	-0.22	6.84	108	
5	3-O^- (3-OH)	-0.20	6.00	94.1	
6	H	0.00	7.08	116	
7	3-MeO	0.11	6.51	100	
8	4-Cl	0.11	9.80	98.0	
9	3-Cl	0.37	9.90	105	
10	3-Br	0.39	9.62	98.3	
11	2-Cl	0.37	15.6	106	
12	3-NO_2	0.71	23.0	71.8	
13	2,6-diCl	0.74	25.8	96.2	95.8
14	4-NO_2	1.27	30.0	72.7	

*$\Delta E^{\neq}$ (disusbtituted benzaldehyde) = $E_1 + (E_2 - E_1) + (E_3 - E_1)$ where E_1 is the activation energy of unsubstituted benzaldehyde, and E_2 and E_3 are of the two mono-substituted *ortho* and *para* benzaldehydes respectively.

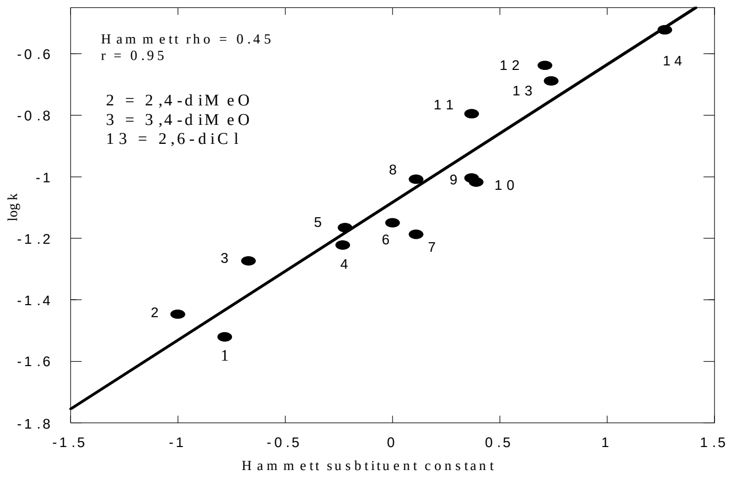
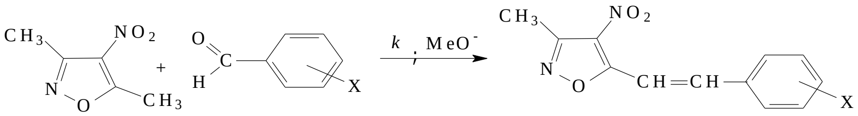


Figure 1: Hammett plot of log k versus Hammett substituent constants



The following are some of the putative examples which explain the title concept very well in several reactions [14-19] (Table 2- 10 and figures 2-10) to mention here but a few instances were explained in this article. This kind of observation was recently witnessed in the solvolysis of 2-chloro-2-(3,4-disubstituted) phenylpropanes [20].

Table 2: Hydroxide ion catalyzed condensation of benzaldehydes with acetone in 50% aqueous ethanol at temp 303 K (Reference 14)

S.No.	Substituent (X)	Hammett substituent constant	*k* X 10^3 mol^{-1} sec^{-1}	$\Delta E^{\neq}$ (kJ mol^{-1})	
				Experimental	*Calculated
1	4-NO_2	1.27	124	38.0	
2	3-NO_2	0.71	45.7	43.9	
3	2,4-dichloro	0.48	28.0	41.8	44.3
4	3-Cl	0.37	17.0	41.8	
5	2-Cl	0.37	12.6	53.9	
6	4-Cl	0.11	10.8	47.7	
7	3-OMe	0.11	9.80	43.9	
8	H	0.00	5.50	57.3	
9	3-OH	-0.2	9.00	46.0	
10	2-OMe	-0.22	14.7	40.1	
11	3-MeO, 4-OH	-0.49	4.20	40.1	38.9
12	4-OH	-0.6	2.60	52.3	
13	3,4-diMeO	-0.67	5.00	34.3	38.3
14	4-MeO	-0.78	3.30	51.4	
15	2-MeO, 4-OH	-0.88	15.7	30.5	31.4
16	2,4-MeO	-1.00	20.0	35.1	34.6

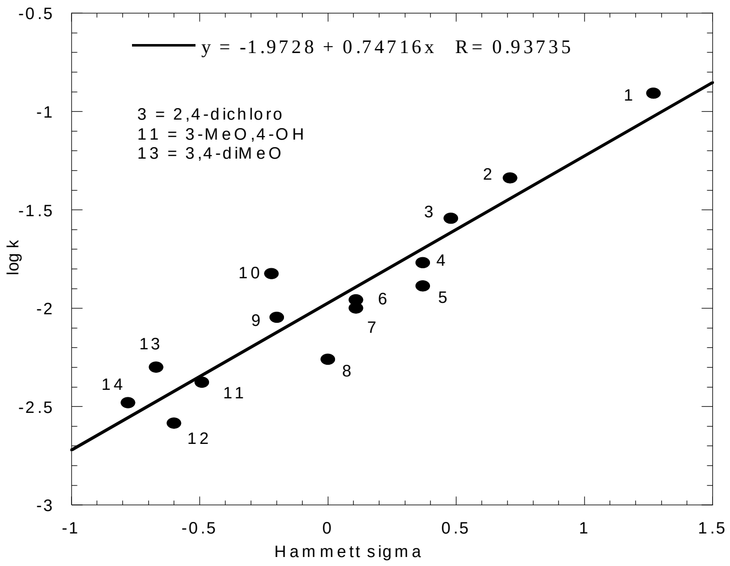


Figure 2: Hammett plot in the condensation reactions of benzaldehydes and acetone

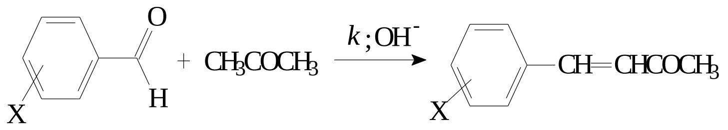


Table 3: Hydroxide ion catalyzed condensation of benzaldehydes with ethyl methyl ketone in 50% aqueous ethanol at temp 303 K (Reference 14)

S.No.	Substituent (X)	Hammett substituent constant	k X 10^3 mol^{-1} sec^{-1}	$\Delta E^{\neq}$ (kJ mol^{-1})	
				Experimental	*Calculated
1	4-NO_2	1.27	92	40.1	
2	3-NO_2	0.71	49.4	42.2	
3	2,4-dichloro	0.48	12.3	38.3	38.5
4	3-Cl	0.37	14.1	42.2	
5	2-Cl	0.37	16.0	50.7	
6	4-Cl	0.11	5.20	44.0	
7	3-OMe	0.11	5.80	46.0	
8	H	0.00	7.40	57.4	
9	3-OH	-0.2	5.60	47.8	
10	2-OMe	-0.22	9.70	36.8	
11	3-MeO, 4-OH	-0.49	2.10	47.8	49.7
12	4-OH	-0.6	1.30	61.2	
13	3,4-diMeO	-0.67	2.00	41.1	42.6
14	4-MeO	-0.78	1.60	51.7	
15	2-MeO, 4-OH	-0.88	1.90	40.6	41.4
16	2,4-MeO	-1.00	1.74	30.6	31.8

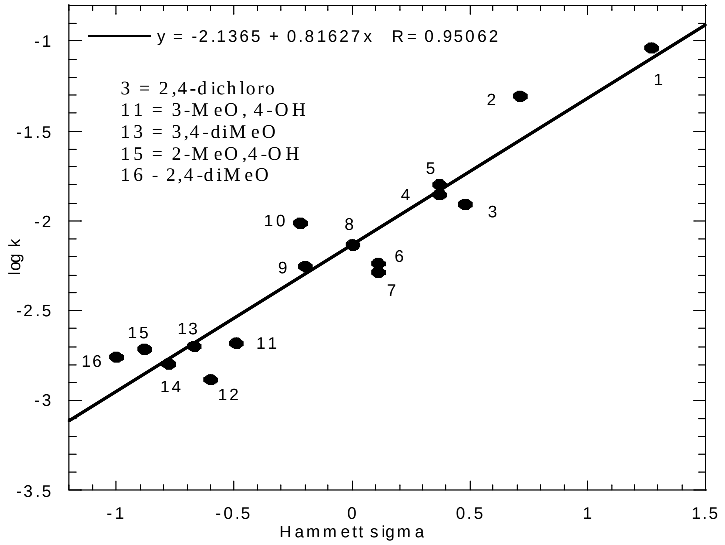


Figure 3: Hammett plot in the reactions of benzaldehydes with ethyl methyl ketone

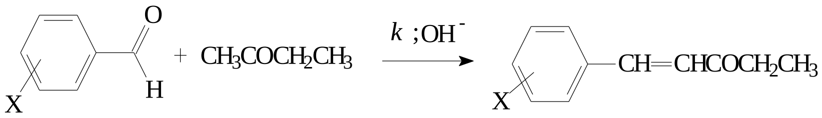


Table 4: Hydroxide ion catalyzed condensation of benzaldehydes with cyclohexanone in 50% aqueous ethanol at temp 303 K (Reference 15)

S.No.	Substituent (X)	Hammett substituent constant	k X 10^3 mol^{-1} sec^{-1}	$\Delta E^{\neq}$ (kJ mol^{-1})	
				Experimental	*Calculated
1	4-NO_2	1.27	220	38.0	
2	3-NO_2	0.71	121	41.4	
3	2,4-dichloro	0.48	54.7	43.1	42.1
4	3-Cl	0.37	23.0	59.4	
5	2-Cl	0.37	26.6	51.8	
6	4-Cl	0.11	11.3	47.7	
7	3-OMe	0.11	11.0	51.0	
8	H	0.00	6.65	57.3	
9	3-OH	-0.2	10.3	53.5	
10	2-OMe	-0.22	8.00	42.3	
11	3-MeO, 4-OH	-0.49	3.24	55.6	56.4
12	4-OH	-0.6	2.72	62.7	
13	3,4-diMeO	-0.67	4.56	53.5	54.5
14	4-MeO	-0.78	3.56	60.6	
15	2-MeO, 4-OH	-0.88	3.22	48.5	47.7
16	2,4-MeO	-1.00	2.14	45.1	45.6

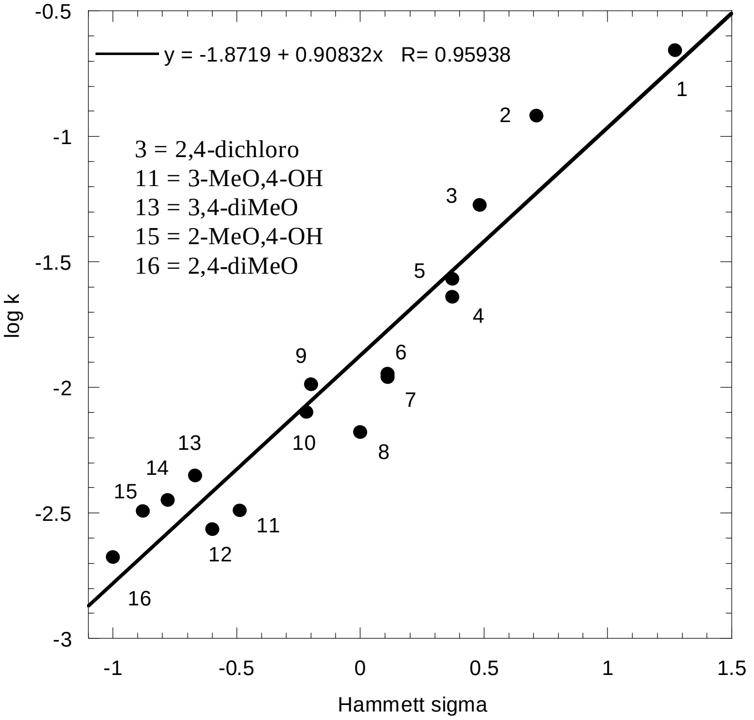


Figure 4: Hammett plot in the reactions of benzaldehydes with cyclohexanone

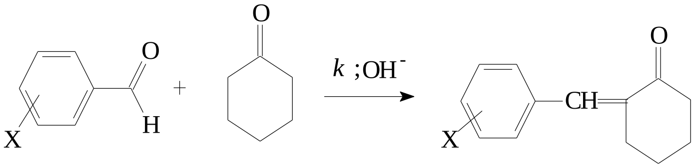


Table 5: Hydroxide ion catalyzed condensation of benzaldehydes with acetophenone in 50% aqueous ethanol at temp 303 K (Reference 14)

S.No.	Substituent (X)	Hammett substituent constant	k X 10^3 mol^{-1} sec^{-1}	$\Delta E^{\neq}$ (kJ mol^{-1})	
				Experimental	*Calculated
1	4-NO_2	1.27	43.9	36.4	
2	3-NO_2	0.71	24.9	38.0	
3	2,4-dichloro	0.48	13.3	34.7	35.1
4	3-Cl	0.37	20.0	41.0	
5	2-Cl	0.37	10.6	40.1	
6	4-Cl	0.11	6.70	41.8	
7	3-OMe	0.11	7.90	41.4	
8	H	0.00	7.76	46.8	
9	3-OH	-0.2	7.10	42.2	
10	2-OMe	-0.22	11.3	42.2	
11	3-MeO, 4-OH	-0.49	3.80	48.1	49.3
12	4-OH	-0.6	2.60	53.9	
13	3,4-diMeO	-0.67	3.20	48.9	47.7
14	4-MeO	-0.78	3.40	52.3	
15	2-MeO, 4-OH	-0.88	3.74	48.5	48.5
16	2,4-MeO	-1.00	3.21	45.6	46.8

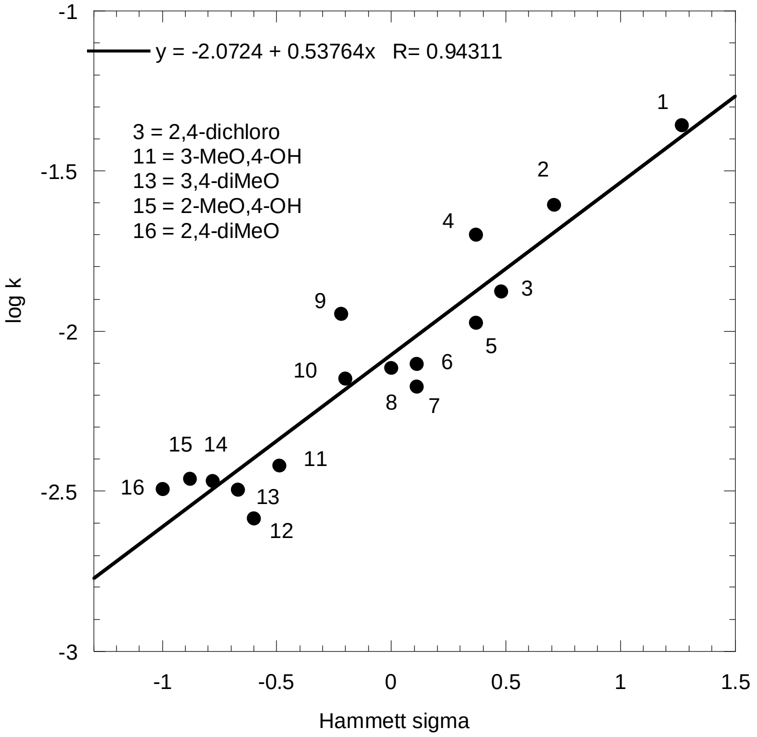


Figure 5: Hammett plot in the reaction of benzaldehydes with acetophenone

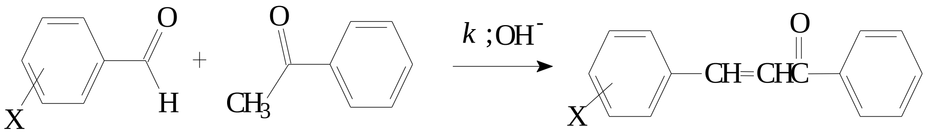


Table 6: Hydroxide ion catalyzed condensation of benzaldehydes with 2-OH-4-OMe-propiophenone in 50% aqueous ethanol at temp 303 K (Reference 14)

S.No.	Substituent (X)	Hammett substituent constant	k X 10^3 mol^{-1} sec^{-1}	$\Delta E^{\neq}$ (kJ mol^{-1})	
				Experimental	*Calculated
1	4-NO_2	1.27	39.0	42.2	
2	3-NO_2	0.71	16.9	47.7	
3	2,4-dichloro	0.48	9.01	48.9	49.7
4	3-Cl	0.37	10.5	53.5	
5	2-Cl	0.37	7.50	57.3	
6	4-Cl	0.11	5.52	51.8	
7	3-OMe	0.11	6.52	55.2	
8	H	0.00	5.32	59.4	
9	3-OH	-0.2	6.13	56.4	
10	2-OMe	-0.22	4.42	48.1	
11	3-MeO, 4-OH	-0.49	3.20	51.8	53.5
12	4-OH	-0.6	1.75	64.8	
13	3,4-diMeO	-0.67	1.40	53.9	52.7
14	4-MeO	-0.78	1.92	64.0	
15	2-MeO, 4-OH	-0.88	3.01	59.4	60.6
16	2,4-MeO	-1.00	1.64	61.4	59.8

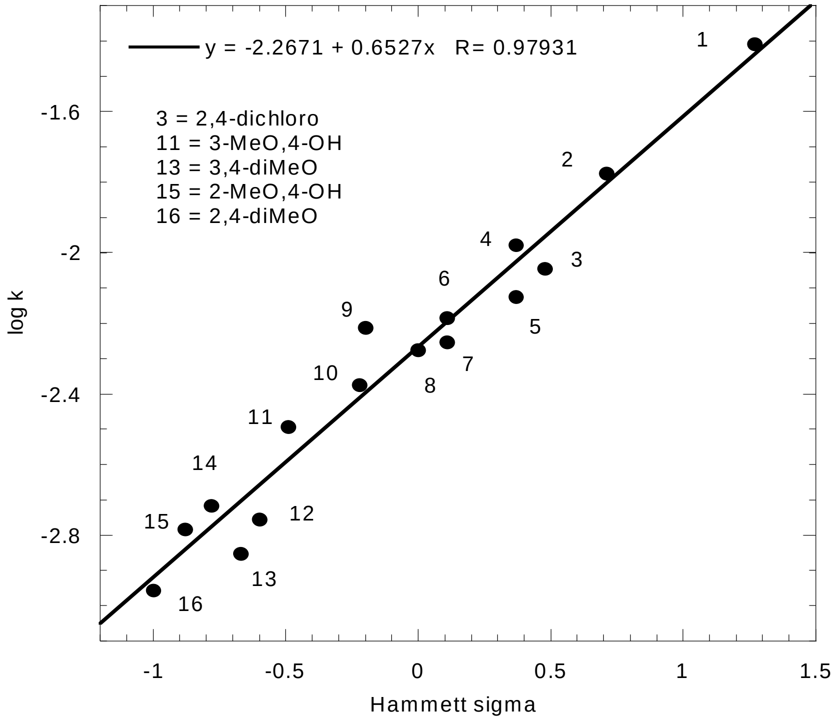


Figure 6: Hammett plot in the reaction of benzaldehydes with 2-OH-4-MeO-propiophenone

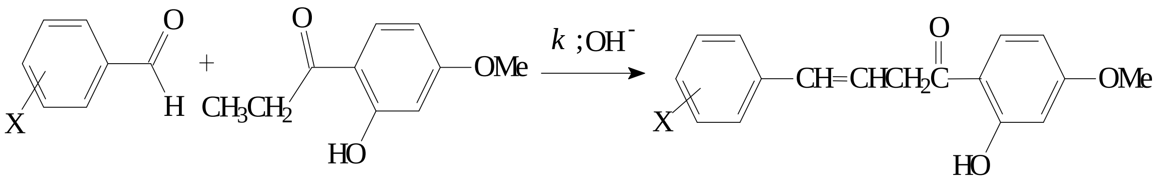


Table 7: Dissociation of benzoic acids in 57.6 % ethanol in water at 25°C (Reference 9)

S.No.	Substituent (X)	Hammett σ	K X 10^5
1	p-NO_2	0.78	31.6
2	H	0.00	1.2
3	3,5-$(CH_3)_2$	-0.12*	0.741
4	3,5-$(C_2H_5)_2$	-0.14*	0.588
5	3,4,5-$(CH_3)_3$	-0.29*	0.49
6	3,4,5-$(C_2H_5)_3$	-0.29*	0.38

*these are ∑σ values

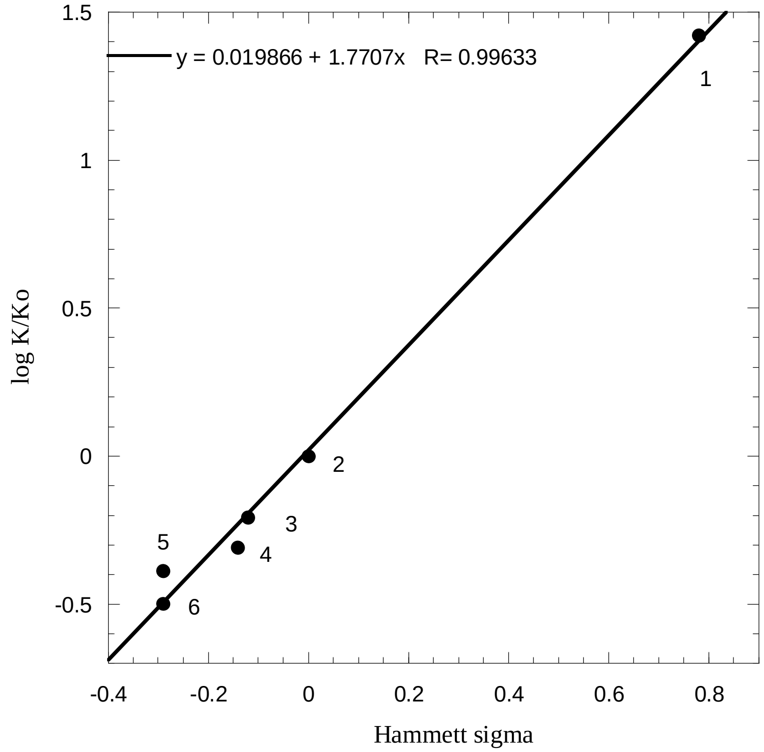


Figure 7: Hammett plot for dissociation of benzoic acids in 57.6% ethanol in water at 298 K

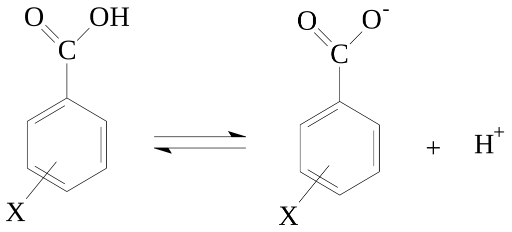


Table 8: Solvolysis of t-cumyl chlorides in 90% aqueous dioxane at 25^{o}C (Reference 17)

S.No.	Substituent (X)	Hammett substituent constant	10^5 X k_{solv}/sec^{-1}	$\Delta H^{\neq}$ kcals. mol^{-1}	
				Experimental	Calculated
1	H	0.00	12.4	18.8	
2	4-i-PrOH	-0.15	221	17.4	
3	3-Me	-0.06	24.8	18.6	
4	4-CycloPrOH	-0.462[a]	1947	16.1	
5	3-Methyl-4-cycloPrOH	-0.522	2133	16.0	15.9
6	3,5-diMe	-0.12	47.3	-	
7	3,5-diMe-4-cycloPrOH	-0.582	460	16.9	15.7

[a] The sigma value is from Hahn, R. C. Corbin, T. F. and Shechter, H. *J. Am. Chem. Soc*. 1968, **90**, 3403

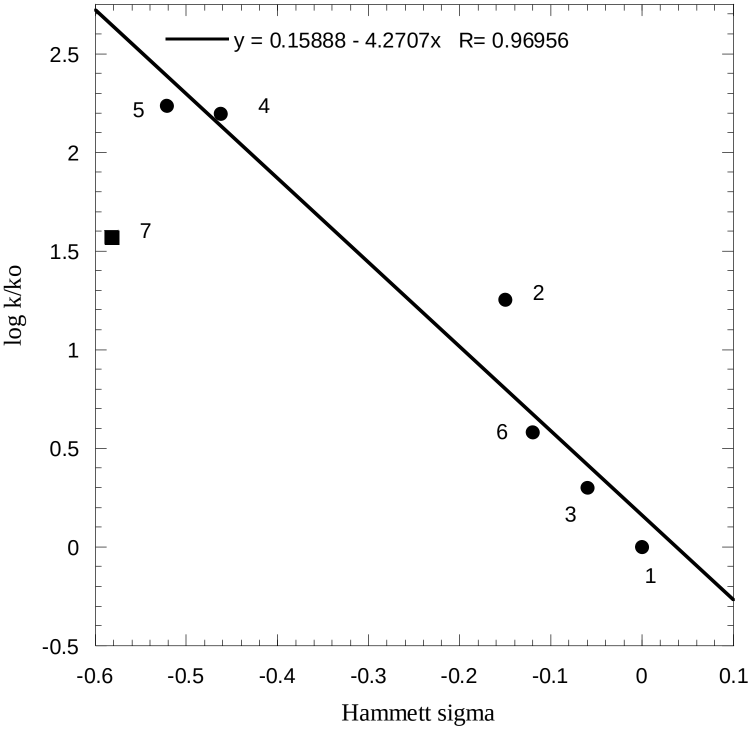


Figure 8: Hammett plot for solvolysis of t-cumyl chlorides in 90% aq. dioxane

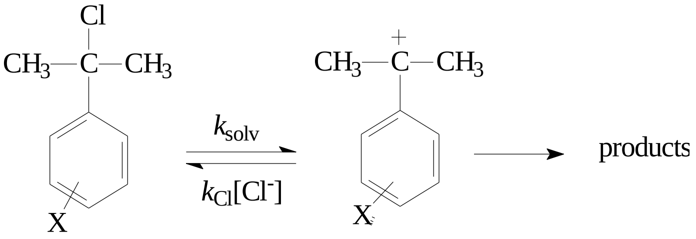


Table 9: Rate constants, relative rates, and activation parameters for the solvolysis of substituted phenyl(methy1)ethyl chlorides in 90% aqueous acetone 25^{o}C (Reference 18)

S.No.	Substituent (X)	Hammett sigma	10^5 X k_{solv}/sec	Relative rate	$\Delta E^{\neq}$ kcals/mol	
					Experimental	Calculated
1	H	0.00	12.4	1	19.5	
2	3-Me	-0.06	24.8	2	19.4	
3	4-Me	-0.17	322	26	17.8	
4	4-t-Bu	-0.2	178	14.4	17.9	
5	3-Cl	0.37	0.194	0.0156	21.3	
6	3,5-Me_2	-0.12	47.3	3.82	-	
7	3-Cl-4-Me	0.2	3.83	0.313	19.8	19.6
8	3-Cl-4-t-Bu	0.17	1.22	0.0996	20.8	19.7

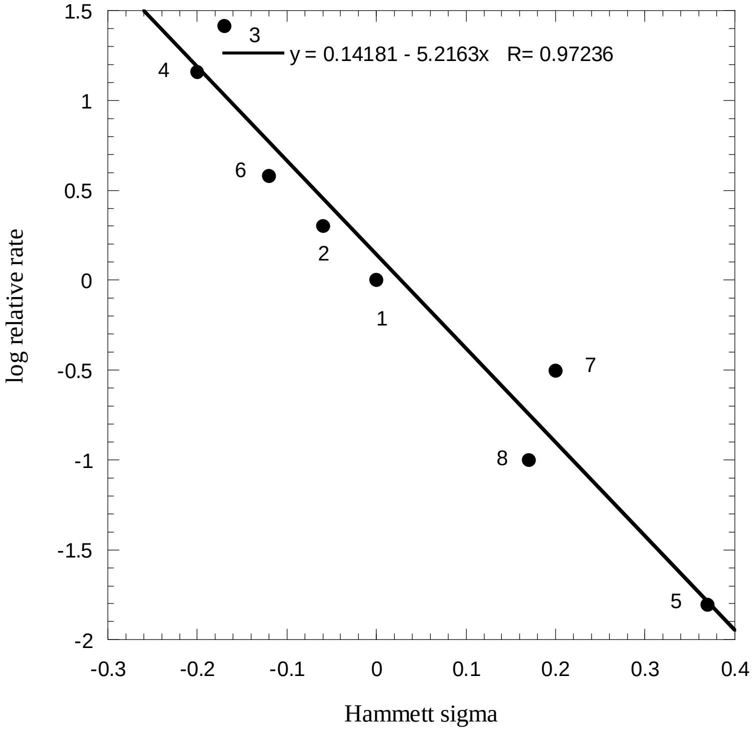


Figure 9: Hammett plot for the solvolysis of substituted phenyl(methyl)ethyl chlorides in 90% aqueous acetone

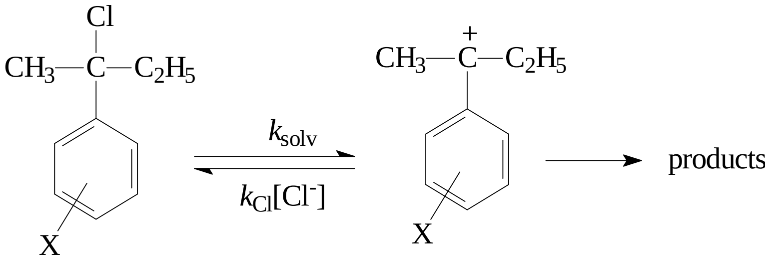


Table 10: Plot of log [EC_{50}/EC_{50}(wt)] vs. cation-π binding ability for various Trp mutants at position α149 (Reference 19)

S.No.	Side chain	Cation-π binding ability kcals/mol	EC_{50} μM	EC_{50}(wt) Corrected μM
1	H-Trp	32.6	1.2	50
2	5-F-Trp	27.5	4.7	200
3	5,7-F2-Trp	23.3	13	550
4	5,6,7-F3-Trp	18.9	34	1400
5	4,5,6,7-F4-Trp	14.4	65	2700

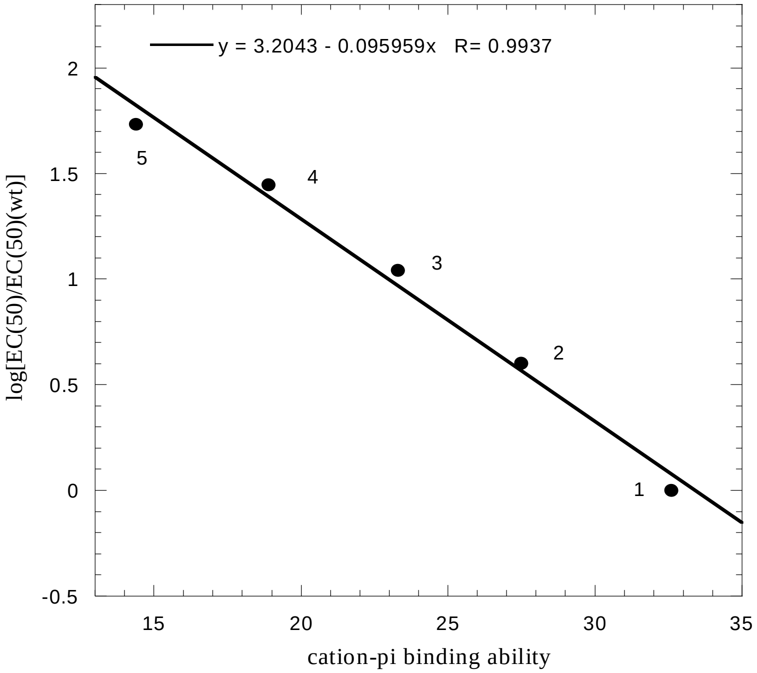
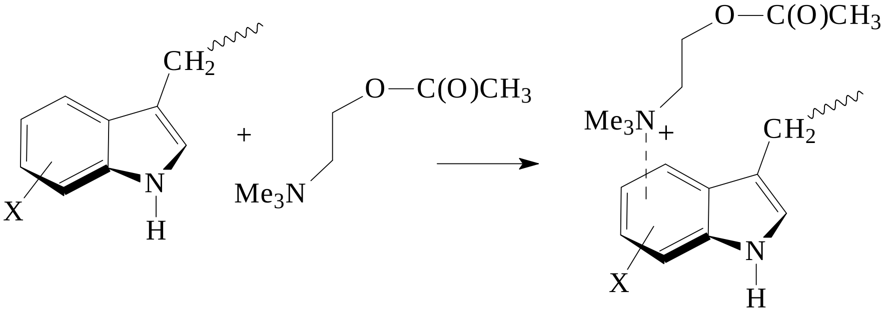


Figure 10: Plot of log [EC(50)/EC(50)(wt)] versus cation-pi binding ability for various Trp mutants at position alpha-149.



X = H, 5-F, 5,7-F_2, 5,6,7-F_3, 4,5,6,7-F_4

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