Kinetics and Mechanism of Side-chain Reactions in Some Substituted Phenethyl Chlorides and Benzyl Chlorides.

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Hydrolysis rate constants have been determined in water–alcohol or water–acetone in the presence or absence of potassium hydroxide, for the following chlorides: Phenethyl, *o*-, *m*-, and *p*-methoxyphenethyl, benzyl, *o*-, *m*-, and *p*-methoxybenzyl. The mechanisms by which such molecules react in the various conditions have been identified as S_N1, S_N2, $E2$, and the values of the rate constants are correlated with the electronic concentration at the carbon atom to which the side chain is linked.

WHEN the theory of the mechanism of nucleophilic substitution reactions at a saturated carbon atom, as developed by Ingold and Hughes (see Ingold, " Structure and Mechanism in Organic Chemistry," Chapter VII, Bell & Sons, Ltd., London, 1953), is applied to side-chain reactions in benzene derivatives, the influence of the various substituents in the benzene ring can be interpreted according to Hammett's σ-values (" Physical Organic Chemistry," Chapter VII, McGraw-Hill Book Co. Inc., New York, 1940). His theory has recently been discussed on a quantum-mechanical basis by Jaffé (*J. Chem. Phys.*, 1952, **20**, 279, 778, 1554; 1953, **21**, 415), who adopts the hypothesis that substituents in the *meta*- or *para*-position to a side chain in a compound affect the reaction of the side chain by virtue of their influence on the electron density of the reactive centre. The substituent changes the distribution of the π electrons in the benzene ring; the change in the charge on the carbon atom to which the side chain is bound is transmitted to the reactive centre in a manner dependent on the nature of the side chain, but the change itself is essentially independent of the nature of the side chain. It is possible in this way to correlate the rates of side-chain reactions with the electronic concentrations at the carbon atom to which the chain is linked.

As a first application to nucleophilic substitutions we consider the reaction between *o*-, *m*-, and *p*-methoxybenzyl chloride and water. (Hammett's theory refers to *meta*- and *para*-substituents only: here *ortho*-substituents are included, but steric effects or, more generally, *ortho*-effects must be taken into account.)

Since it is assumed that the variation in electronic concentration at the various points of the ring is independent of the nature of the side chain, we have calculated electron densities in the positions *ortho*, *meta*, and *para* to the methoxyl group in the anisole molecule. The calculation was performed according to Jaffé (*loc. cit.*, where values obtained for the hydroxyl group are indicated, which involve parameters with slightly different values), by the M.O. method in its standard L.C.A.O. approximation. The parameter values adopted were: 0·52 [in resonance integral for the carbon–carbon bond in benzene (β) units] for the Coulomb integral of the oxygen atom (α); 0·55 for the oxygen–carbon resonance integral (γ); $(1/3)^n\alpha$ for the Coulomb integrals of the carbon atoms separated from the oxygen atom by n bonds. We obtained the following values for the electronic densities (in electronic charge units):

ortho: 1·036	*meta*: 0·992	*para*: 1·017

Hammett's σ values for the methoxyl group are: $\sigma_m = +0{\cdot}115$; $\sigma_p = -0{\cdot}268$.

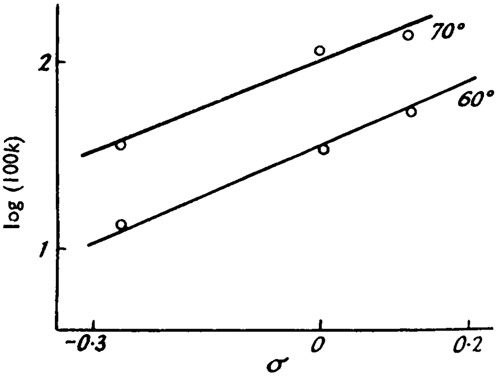
We measured the rate of the reaction of the corresponding benzyl chlorides with water; since the reactivity varies considerably from one compound to the other, we had to employ acetone–water mixtures of varying composition as solvents. The results are given in Table 1 (k_1 in hr.$^{-1}$). The velocity constants are not directly comparable owing to the different composition of the solvents: however, the reactivity of the compounds in solvolytic reactions is definitely in the order *para* > *ortho* > (unsubstituted) > *meta*, *i.e.*, the same order as the electronic concentration at the carbon atom to which the chain is linked, except for the *para–ortho* inversion due to steric effect.

The kinetics were strictly of the first order in all the experiments.

Benzyl chloride and its *meta*-substituted derivative were tested also in the presence of potassium hydroxide, but now the S_N1 mechanism was altered to $S_N2 + S_N1$. This is confirmed not only by the change in the order of the reaction but by a marked alteration in the velocity itself (*e.g.*, for benzyl chloride at 60° in aqueous alcohol the degree of hydrolysis rises from 10·55% in 2 hr. in the absence of alkali to 43·3% in 1 hr. in the presence of 1 mol. of potassium hydroxide). Further, in the alkaline solution the difference between the rates of reaction of the two compounds is greatly diminished, and it is probable that if only the S_N2 mechanism operated the order of reactivity would be inverted. (Naturally, in aqueous alcoholic solutions the alcohol also has a solvolytic function.)

TABLE 1.

Compound	Solvent	k_1 at 60°	k_1 at 40°
p-Methoxybenzyl chloride	Acetone–water (5 : 1)	—	0·404
o- ,, ...	,, (5 : 1)	0·0378	—
	,, (2 : 1)	0·738	0·0924
Benzyl chloride	,, (2 : 1)	0·00684	—
m-Methoxybenzyl chloride	,, (2 : 1)	0·00459	—



The log k against σ curve for the reaction between methoxyphenethyl chlorides and potassium hydroxide in aqueous alcohol.

$\rho_{70°} = 0{\cdot}0156$
$\rho_{60°} = 0{\cdot}0164$

We next examined the reactions of methoxy-substituted phenethyl chlorides with potassium hydroxide in aqueous solution. The process is complicated, since substitution takes place simultaneously with elimination: furthermore, the styrenes so formed may polymerise, thus complicating the process.

It must be borne in mind that the methoxy-group may also be hydrolysed, but conductometric analyses of the solutions and of specimen solutions of phenol–anisole mixtures indicated that this process was inappreciable. By determining the ionisable chlorine by titration with silver nitrate we were able to calculate constants for the combined $S_N2 + E2$ reactions; in an attempt to obtain the separate constants, we determined the olefins present in the solution at the various times, but this failed, probably because the polymerisation processes affected the quantity of determinable double bonds. It is therefore desirable that these velocities of polymerisation be determined and we are endeavouring to do this. Furthermore, unlike the process with benzyl derivatives, there is no agreement between the values of chloride ion as determined by Volhard's method and acidimetrically; the latter values also do not permit calculation of the total constants, probably because the base is involved in secondary reactions. On the other hand, the total constants obtained by the other method are very good; on the whole, the reactions are of second order and agree with the $S_N2 + E2$ mechanism.

The values of the constants (k_2 in hr.$^{-1}$ mole^{-1} l.) are indicated in Table 2 [chloro-derivative 0·1N; KOH, 0·1N in ethyl alcohol–water (2 : 1)]. They agree excellently with the theory (apart from the usual *ortho–para* inversion). The data for the non-substituted compound can be used in conjunction with the graph above to work out the values of Hammett's ρ constant for the whole reaction in our experimental conditions.

We have also measured the velocity at which chloride ion is formed at 95° in the absence of potassium hydroxide (again in ethyl alcohol–water, 2 : 1); the following are the values of the constants k_1 (in hr.$^{-1}$) : Phenethyl chloride, 0·0034; *p*-methoxyphenethyl chloride, 0·0105. It is apparent that in passing from the S_N2 to the S_N1 mechanism the order of reactivity between the two compounds is inverted, while at the same time the velocity of reaction is greatly diminished. Therefore both benzyl and the phenethyl derivatives can give rise to chloride ions by both mechanisms, the single-stage and the two-stage.

TABLE 2.

	At 60°	At 70°		At 60°	At 70°
Phenethyl chloride	0·340	1·080	*m*-Methoxyphenethyl chloride	0·510	1·410
o-Methoxyphenethyl chloride...	0·0725	0·224	*p*- ,,	0·125	0·370

Baddeley and Bennett's results (*J.*, 1935, 1819) on bimolecular reaction with potassium iodide in acetone seem partly to conflict with the data and the interpretation given above. At 75° these authors found the following values for k_2 (in hr.$^{-1}$ mole^{-1} l.) : Phenethyl chloride, 0·735; *p*-methoxyphenethyl chloride, 1·040. This might be a case of bimolecular reaction where the predominating factor is the fission of the existing bond instead of the formation of the new bond. Before advancing this or any other explanation, however, we intend to repeat Baddeley and Bennett's experiments and to extend them to the *meta*- and *ortho*-substituted compounds.

EXPERIMENTAL

Materials.—Phenethyl chloride, prepared by chlorination of 1-phenylpropan-1-ol with thionyl chloride (Ward, *J.*, 1927, 453) and dried (K_2CO_3), was fractionally distilled; it had b. p. 83—84°/14 mm.

o-Methoxyphenethyl chloride was obtained from the corresponding alcohol by chlorination as for the *meta*-isomer (Bergmann and Weizmann, *J. Org. Chem.*, 1939, **4**, 266). The alcohol, prepared by interaction of the Grignard reagent from *o*-bromoanisole with an ice-cold solution of ethylene oxide in ether, had b. p. 135°/13 mm., and the chloride had b. p. 117°/20 mm. *m*-Methoxyphenethyl chloride, b. p. 122—123°/18 mm., and the *para*-isomer, b. p. 130°/20 mm., were prepared by the same method.

Benzyl chloride, obtained from a commercial sample by distillation, had b. p. 77°/20 mm., n_D^{15} 1·54148. *o*-Methoxybenzyl chloride was prepared as follows: Salicylaldehyde was methylated with methyl sulphate in presence of alkali (Hell and Hofmann, *Ber.*, 1905, **38**, 1676), the *o*-methoxybenzaldehyde was treated with alkali, methanol, and formaldehyde (Davidson and Bogert, *J. Amer. Chem. Soc.*, 1935, **57**, 905), the resulting alcohol was chlorinated with thionyl chloride in presence of pyridine, and the chloro-compound was purified by distillation : it had b. p. 108°/15 mm.

The same procedure was followed in the preparation of the *para*-isomer from anisaldehyde : from the alcohol (a white solid, m. p. 23°) by chlorination we got *p*-methoxybenzyl chloride, b. p. 120°/20 mm. (Found : Cl, 22·3. Calc. for $C_8H_7O_2Cl$: Cl, 22·4%). The *meta*-isomer was prepared from *m*-hydroxybenzaldehyde by methylation, reduction, and chlorination as for the *ortho*-isomer. The aldehyde was obtained from *m*-nitrobenzaldehyde by reduction, diazotisation, and hydrolysis (Woodward, *Org. Synth.*, **25**, 55). *m*-Methoxybenzyl chloride had b. p. 124°/13 mm. (Found : Cl, 22·2%).

Acetone was purified by Conant and Kirner's method (*J. Amer. Chem. Soc.*, 1924, **46**, 245) and fractionated. Commercial absolute alcohol was dried by Smith's method (*J.*, 1927, 1288) as modified by Manske (*J. Amer. Chem. Soc.*, 1931, **53**, 1106) and fractionated.

Kinetic Measurements.—For the reactions with water or potassium hydroxide a known amount of the organic compound was dissolved in alcohol or acetone, and the solution was made up to volume. In each experiment appropriate volumes of the organic solution and of standard potassium hydroxide at the required reaction temperature were mixed so that the final mixture was 0·1N with respect to the organic compound; the time of mixing was taken as the zero time for reaction. The thermostats were steady to within 0·05°. After known times samples of 25 ml. were withdrawn.

(i) When the solute was a phenethyl chloride the sample was added to 20 ml. of 0·3N-nitric acid. After titration of the acidity with 0·1N-potassium hydroxide in presence of phenolphthalein and acidification with dilute nitric acid the solution was shaken with 50 ml. of carbon tetrachloride, and the organic layer was washed with water and used for the determination of olefin by Hughes and Shapiro's method (*J.*, 1937, 1192); the aqueous layer and the water used in washing the organic layer were used for determination of chloride ion (Volhard).

TABLE 3.

0·1N-Phenethyl chloride with 0·1N-KOH in ethyl alcohol–water (2 : 1) at 70°.

t (hr.)	1	2	3	4	5	6	7	8
Cl^-	2·52	4·13	6·30	7·55	8·73	9·72	10·37	11·02
Olefin	10·95	14·02	15·55	17·13	28·95	32·53	35·20	40·25
k_2	1·120	0·990	1·120	1·080	1·070	1·060	1·010	0·985

0·1N-*o*-Methoxybenzyl chloride in acetone–water (2 : 1) at 50°.

t (min.)	0	30	60	120	180
KOH	0·739	4·164	6·649	10·760	13·480
k_1	—	0·3036	0·2790	0·2670	0·2700
$AgNO_3$	0·850	4·077	6·612	10·997	14·354
k_1	—	0·2850	0·2718	0·2712	0·2730

0·1N-Benzyl chloride in ethyl alcohol–water (2 : 1) at 70°.

t (min.)	0	150	180	240	300
KOH	0·335	7·645	8·887	11·130	12·900
k_1	—	0·140	0·142	0·144	0·142
$AgNO_3$	0·350	7·675	8·839	11·120	12·867
k_1	—	0·141	0·141	0·144	0·144

TABLE 4. *Benzyl chloride derivatives* (0·1N).

Substituent	Solvent	Temp.	k_1	E_a
o-OMe	$COMe_2$–H_2O (2 : 1)	40°	0·0924	20·600
		50	0·275	
		60	0·738	
p-OMe	$COMe_2$–H_2O (5 : 1)	20	0·0535	18·300
		30	0·156	
		40	0·404	
m-OMe	$COMe_2$–H_2O (1 : 1)	40	0·00295	19·550
		50	0·00840	
		60	0·0205	

Substituent	Solvent	Temp.	k_1	E_a
(H)	EtOH–H_2O (2 : 1)	60°	0·0560	21·100
		70	0·142	
(H)	$COMe_2$–H_2O (2 : 1)	60	0·00684	—
m-OMe	$COMe_2$–H_2O (2 : 1)	60	0·00459	—
o-OMe	$COMe_2$–H_2O (5 : 1)	60	0·0378	—
(H)	EtOH–H_2O * (2 : 1)	60	7·20 †	—
m-OMe	EtOH–H_2O * (2 : 1)	60	5·70 †	—

* With addition of 0·1N-KOH. † Values are those of k_2.

TABLE 5. *Phenethyl chloride derivatives* (0·1N) *with* 0·1N-KOH *in alcohol–water* (2 : 1).

Substituent	Temp.	k_2	E_a	Substituent	Temp.	k_2	E_a	Substituent	Temp.	k_2	E_a
(H)	50°	0·118	24·800	*p*-OMe	60°	0·124	24·600	*m*-OMe	60°	0·510	23·020
	55	0·205			70	0·370			70	1·410	
	60	0·340		*o*-OMe	60	0·0725	25·350	(H)	95	0·0033 *	—
	65	0·588			70	0·224		*p*-OMe	95	0·0105 *	—
	70	1·080									

* KOH was omitted in these experiments and values are those of k_1.

(ii) When the solutes were benzyl chlorides the sample was added to 25 ml. of carbon tetrachloride; after shaking and removal of the organic layer, the aqueous layer was washed with a further 10 ml. of carbon tetrachloride, diluted with water, and titrated first with 0·1N-potassium hydroxide, and then, after acidification with dilute nitric acid, with silver nitrate. (Reaction mixtures containing potassium hydroxide were not titrated for acidity.)

In the annexed record of our experiments, the amount of chloride ion present in the sample is expressed in ml. of 0·1N-silver nitrate or potassium hydroxide, and the olefin in ml. of 0·02N-sodium thiosulphate; k_1 (in hr.$^{-1}$) and k_2 (in hr.$^{-1}$ mole^{-1} l.) are first- and second-order rate coefficients. A few typical runs are given in Table 3, and Tables 4 and 5 summarise the results.

Inverse Reactions.—50 ml. of a 0·12N-solution of *p*-methoxybenzyl alcohol in acetone were treated with 10 ml of 0·6N-hydrochloric acid for 4 hr. at 40°; 25 ml. of the mixture needed 24·37 ml. of 0·1N-silver nitrate at the beginning and 24·27 ml. at the end of the reaction.

40 ml. of a 0·15N-solution of *o*-methoxybenzyl alcohol in acetone were treated with 20 ml. of

0·3N-hydrochloric acid for 15·5 hr. at 60°; titration at the beginning, 24·03 ml. of 0·1N-silver nitrate, and at the end 24·01 ml.

30 ml. of a 0·2N-solution of *m*-methoxybenzoyl alcohol in acetone were treated with 30 ml. of 0·2N-hydrochloric acid for 8 hr. at 60°; the titration as above were 25·3 and 25·2 ml., respectively.

Reaction Products.—5·95 g. of *o*-methoxybenzyl chloride in 100 ml. of acetone and 50 ml. of water were heated at 60° for 5 hr. After neutralisation, the acetone and the water were removed under vacuum, the residue was dissolved in ether, the solution filtered from the potassium chloride, and the ether removed. By distillation of the residue 3·5 g. of o-methoxybenzyl alcohol were obtained (b. p. 128°/20 mm.; n_D^{17} 1·54973). Similarly, 2·375 g. of *p*-methoxybenzyl chloride in 50 ml. of acetone and 25 ml. of water at 40° for 5 hr. gave 1·5 g. of the corresponding alcohol (b. p. 135—140°/20 mm.; n_D^{15} 1·5479), and 2·28 g. of the *meta*-isomer in 50 ml. of acetone and 50 ml. of water at 60° for 40 hr. gave 1 g. of the benzyl alcohol (b. p. 141°/25 mm.; n_D^{28} 1·55418).

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