Tetrahedron Vol. 34, pp. 3611-3615
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0040-4020/78/1215-3611/$02.00/0

STERIC ENHANCEMENT OF RESONANCE

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(*Received in UK* 13 *June* 1978; *Accepted for publication* 11 *July* 1978)

Abstract—The rate constants and the activation energies for the alkaline hydrolysis of some substituted ethyl benzoates furnish evidence for the phenomenon of steric enhancement of resonance. For 3-substituted-4-alkoxybenzoic esters the rate constants calculated on the basis of the principle of additivity of substituent effects are appreciably higher than the observed values, indicating that the 3-substituent does not sterically inhibit the resonance interaction of the alkoxy and ester groups but actually enhances it. The cause of this steric enhancement of resonance is explained. The rates of quaternization of some N,N-dimethylanilines with methyl iodide have also been determined. The observed rate constants of 4-alkoxy-3-methyl-N,N-dimethylanilines are significantly higher than the values predicted on the basis of additivity of group effects. Thus there is enhanced resonance interaction of the alkoxy group with the dimethylamino group increasing the nucleophilicity of the dimethylamino group. A similar steric enhancement of resonance is observed in the case of 3-methyl-4-methylthio-N,N-dimethylaniline also.

Though steric inhibition of resonance is well-known, steric enhancement of resonance was almost unknown until this phenomenon was discovered by Baliah and Uma[1] while studying the electric dipole moments of some substituted anisoles. Convincing evidence for steric enhancement of resonance may also be seen in the rate data given by Balasubramanian[2a] and Baddeley *et al.*[2b] for the solvolysis of substituted benzyl chlorides (Table 1). 4-Methoxy-3-methylbenzyl chloride undergoes solvolysis at a much higher rate than *p*-methoxybenzyl chloride indicating steric enhancement of resonance, while 4-methoxy-3,5-dimethylbenzyl chloride undergoes solvolysis at a much slower rate than *p*-methoxybenzyl chloride indicating steric inhibition of resonance. With a view to studying this phenomenon further, the present investigation was undertaken. The work reported in this paper is a continuation of what we published earlier as a brief communication.[3]

Table 1. Solvolysis of substituted benzyl chlorides in 90% aqueous ethanol: Rate constants

Substituents	$10^4 k_{25^\circ}$ (min.$^{-1}$)	Relative rate
H	8.3^a	1.0
m-Me	10.8^a	1.3
p-OMe	130^b	15.7
3-Me, 4-OMe	510^b	61.4
3-Me, 4-OMe, 5-Me	3.70^b	0.4

[a] Ref. 2a. [b] Ref. 2b.

RESULTS AND DISCUSSION

In the rate data of Jones and Robinson[4] for the alkaline hydrolysis of substituted ethyl benzoates (Table 2) it is found that if the entropy factor is assumed to be constant, the change in the energy of activation produced by a substituent or substituents may be calculated by means of the relation:

$$\Delta E' = -2.303\, RT \log \frac{k_s}{k_u}$$

where k_s and k_u are the velocity constants of substituted and unsubstituted esters respectively. If the substituent effects are additive, the observed increment in activation energy due to two substituents will be the sum of increments due to each substituent alone, i.e.

$$\Delta E'_{XY} = \Delta E'_X + \Delta E'_Y.$$

The difference of 100 or less than 100 calories between $\Delta E'_{(\text{observed})}$ and $\Delta E'_{(\text{predicted})}$ is considered to be well within the probable deviation which could occur without infringement of additive relationship. The additive relationship exists in the case of esters where the possibility of group interaction is at a minimum. On the other hand, in the case of 3-substituted-4-alkoxybenzoic esters, the difference is in the order of 200 calories indicating that the additivity relationship is not applicable here, presumably due to the fact that the 3-substituent enhances the resonance interaction of the alkoxy groups with –COOEt.

For the disubstituted esters of the above type $XYC_6H_3 \cdot COOEt$ for which the contributions to activation energy of the groups X and Y are additive, the following relationship holds good:

$$k_{XY} = \frac{A_{XY}\dfrac{k_X}{A_X}\dfrac{k_Y}{A_Y}}{\dfrac{k_U}{A_U}}$$

where k_{XY}, k_X, k_Y and k_U are the velocity coefficients of the alkaline hydrolysis of the esters $XYC_6H_3 \cdot COOEt$, $XC_6H_4 \cdot COOEt$, $YC_6H_4 \cdot COOEt$ and $C_6H_5 \cdot COOEt$,

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Table 2. Observed and calculated rate constants and activation energies for the alkaline hydrolysis of substituted ethyl benzoates

Substituents	$10^3 k_{25}$, (l.mole^{-1}sec.$^{-1}$) obs.[a]	calc.	$\Delta E'_{(observed)} - \Delta E'_{(predicted)}$[a]	$k_{calc.}/k_{obs.}$
3-Cl, 4-OMe	0.709	1.02	+210	1.43[b]
3-Br, 4-OMe	0.728	1.08	+230	1.48[b]
3-NO$_2$, 4-OMe	6.36	9.09	+210	1.43[b]
3-Cl, 4-OEt	0.649	0.923	+200	1.42
3-Br, 4-OEt	0.663	0.981	+230	1.48
3-Cl, 4-OPr^i	0.701	0.900	+150	1.28
3-Br, 4-OPr^i	0.699	0.957	+190	1.37
3-NO$_2$, 4-OPr^i	5.05	8.07	+280	1.60
3-Me, 4-Me	0.194	0.197	+ 20	1.02
3-Me, 5-Me	0.302	0.305	+ 10	1.01
3-Cl, 4-Me	1.97	2.12	+ 40	1.08
3-Br, 5-Br	39.6	39.9	+ 10	1.01
3-Br, 5-Me	3.45	3.49	+ 10	1.01
3-OMe, 5-OMe	1.04	1.07	+ 20	1.03

[a] Ref. 4. [b] Ref. 5.

respectively, and A_{XY}, A_X, A_Y and A_U are their respective Arrhenius factors.

On the assumption[3] that (i) $A_{XY} = A_X$ and (ii) $A_U = A_Y$ the above equation reduces to $k_{XY} = [(k_X k_Y)/k_U]$. The rates may then be calculated using this reduced equation and compared with the observed values.

The data given in Table 2 indicate that 3-substituted-4-alkoxybenzoic esters violate seriously the additivity rule of group effects. The rule is, however, obeyed by the other esters within the limits of experimental error. The appreciable deviation from the additivity rule in the case of 3-substituted-4-alkoxybenzoic esters is presumably due to enhanced conjugative interaction of the *p*-alkoxy groups with the ester group. For these compounds the calculated rate constants are 30-60% higher than the observed values. If the enhanced resonance interaction of the alkoxy and ester groups is caused by the 3-substituent, it is clearly a case of steric enhancement of resonance. The 3-substituent makes the O-alkyl group adopt a preferred orientation *trans* to it (I). Thus the probability of the alkoxy group becoming coplanar with the benzene ring increases as the alkyl group can no longer rotate freely. Such a situation results in enhanced resonance interaction of the alkoxy and ester groups.

I

The data obtained in the present investigation for the kinetics of quaternization of N,N-dimethylanilines with methyl iodide also indicate steric enhancement of resonance in 3 - substituted - 4 - alkoxy - N,N - dimethylanilines. The results are shown in Table 3. A sample kinetic run is given in Table 4.

p-Alkoxy-N,N-dimethylanilines react about 4 times faster than N,N-dimethylaniline (Table 3). The reaction rates are still higher (nearly 6 times) for 4 - alkoxy - 3 - methyl - N,N - dimethylanilines and this increase in rate does not seem to be solely due to the 3-methyl group because the observed rate constants of 4 - alkoxy - 3 - methyl - N,N - dimethylanilines are 14% higher than the values predicted on the basis of the additivity of group effects (see Table 3). The 3-Me group, therefore, does not sterically inhibit the resonance interaction of the alkoxy group with the aromatic ring but actually enhances it. The expected steric inhibition of resonance, however, does exist in 4 - methoxy - 3,5 - dimethyl - N,N - dimethylaniline as may be seen from its rate of quaternization—the rate is only half of what it is for 4 - methoxy - 3 - methyl - N,N - dimethylaniline.

It is of interest to note that there exists steric enhancement of resonance in 3 - methyl - 4 - methylthio - N,N - dimethylaniline also. *p* - Methylthio - N,N - dimethylaniline has a lower rate constant than N,N-dimethylaniline. This becomes understandable if we assume that the electron-accepting 3d-orbital resonance effect of the *p*-SMe group is greater than its electron-releasing mesomeric effect in *p*-methylthio-N,N-

Table 3. Rate constants for the reaction of substituted N,N-dimethylanilines with methyl iodide

Substituent	$10^4k_{obs.}$ (l.mole^{-1}sec.$^{-1}$)		$10^4k_{calc.}$ (l.mole^{-1}sec.$^{-1}$)	$\frac{k_{obs.}}{k_{calc.}}$
	35°	45°	45°	45°
H	1.20	2.71 2.71^{a}		
p-OMe	5.29 5.72^{b}	10.6 11.4^{b}		
p-SMe	0.87	1.87		
p-OEt	5.50	11.2		
m-Me	1.64 1.75^{b}	3.45 3.74^{b}		
3-Me, 4-OMe	7.70	15.4	13.5	1.14
3-Me, 4-OEt	7.78	16.2	14.3	1.14
3-Me, 4-SMe	1.62	3.45	2.38	1.45
2-Me, 4-OMe	-	0.103		
3-Me, 4-OMe, 5-Me	3.96	8.13		

[a] Ref.5. [b] Ref.6.

Table 4. Kinetic run on *p*-ethoxy-N,N-dimethylaniline

$[CH_3I] = [\text{Amine}] = 0.09895N$: $[AgNO_3] = 0.01015N$: temp. = 35°

Time sec.	x	a-x	k x 10^4 l.mole^{-1}sec.$^{-1}$
2387	0.01147	0.08748	5.55
3645	0.01639	0.08256	5.50
5639	0.02324	0.07571	5.50
7012	0.02730	0.07165	5.49
8452	0.03115	0.06780	5.49
9925	0.03473	0.06422	5.51
11660	0.03830	0.06065	5.47
14530	0.04378	0.05517	5.52
			Mean = 5.50 ± 0.02

dimethylaniline.[7] However, it is interesting that 3 - methyl - 4 - methylthio - N,N - dimethylaniline reacts 45% faster than what is predicted on the basis of substituent effects. This indicates that the –SMe group, which functions as an electron-acceptor in *p* - methylthio - N,N - dimethylaniline, becomes an electron-donor in 3 - methyl - 4 - methylthio - N,N - dimethylaniline owing to enhancement of the electron-releasing resonance of the –SMe caused by the ortho methyl group.

A similar evidence for steric enhancement of resonance is found[3] in the rate data of Crocker and Jones[5] given in Table 5 for the reaction of N,N-dimethylaniline with allyl bromide. The observed reaction rates of 3,5 - disubstituted - N,N - dimethylanilines are very close to the predicted values indicating a strict additivity of substituent effects. For the 3,4-disubstituted compounds the observed rates are, however, 55–120% higher than the predicted values. Indeed the velocity ratios increase for the 3 - halogeno - 4 - methoxy - N,N - dimethylanilines in the order 3-F < 3-Cl < 3-Br < 3-I, indicating that there is greater steric enhancement of resonance with increasing bulk of the 3-substituent.

EXPERIMENTAL

p-Methoxy-,[8] *p*-methylthio-[9] and *m* - methyl - N,N - dimethylaniline[8] were prepared and purified[5] as described in the literature.

p-*Ethoxy-N,N-dimethylaniline.* This was obtained from *p*-phenetidine adopting a procedure similar to the one used for the preparation of *m* - methylthio - N,N - dimethylaniline.[10] The tertiary amine, after purification, distilled at 104–106°/2.9 mm.

4-*Methoxy*-3-*methyl*-1-*nitrobenzene.* To a soln of 4 - hydroxy - 3 - methyl - 1 - nitrobenzene[11] (20 g) in acetone (150 ml) was added anhyd K_2CO_3 (20 g) and the mixture was heated under reflux on a water bath, adding MeI (40 g) in portions slowly. After 6 hr the mixture was diluted with water. The separated solid was filtered off, yield: 80%, m.p. 63–64° (EtOH) (lit.[11] 64°).

4-*Methoxy*-3-*methylaniline.* A soln of the above nitro compound (0.1 mole) and hydrazine hydrate (98%; 0.5 mole) in EtOH (450 ml) was warmed to 50° and a pinch of Raney Ni was added. When the initial frothing had subsided some more Raney Ni was added and heated under reflux on a water bath for nearly 2 hr. The catalyst was then filtered off and the solvent removed almost completely. The residue was mixed with ice-cold water. The separated oily amine solidified soon, yield: 95%, m.p. 58–59° (petroleum spirit 40–60°) (lit.[12] 59–59.5°).

4 - *Methoxy* - 3 - *methylphenyltrimethylammonium iodide.* Quaternization of 4 - methoxy - 3 - methylaniline by dimethyl sulphate and alkali and subsequent treatment of the resulting quaternary sulphate with a saturated soln of KI afforded this methiodide. The procedure adopted was similar to the one employed for the quaternization of 4-amino-4′-fluorodiphenyl ether,[13] yield: 80%. The crude product melted at 202–204° (lit.[14] 206°).

4-*Methoxy*-3-*methyl*-N,N-*dimethylaniline.* The above methiodide, when perfectly dry, was decomposed in vacuum. The tertiary amine distilled at 135–140°/23 mm. It was further purified through the amine hydrochloride. During another distillation, the fraction boiling at 138–140°/23 mm was collected, yield: 39%. (Found: C, 72.30; H, 9.00. $C_{10}H_{15}NO$ requires: C, 72.64; H, 9.16%).

4 - *Hydroxy* - 3,5 - *dimethyl* - 1 - *nitrobenzene.* 2,6-Dimethylphenol (40 g) in AcOH (400 ml) was added dropwise to a soln of HNO_3 (sp. gr. 1.42; 16 ml) in AcOH (50 ml) under ice-cooling and with stirring. The mixture was agitated for 2 hr while keeping in an ice bath. The resulting mass was poured into excess of water (500 ml), filtered off and washed with water. The crude material was treated with 10% NaOH aq when a part of it dissolved. The non-phenolic part was extracted with ether, the aqueous layer was separated and acidified with conc HCl. The yellow ppt was filtered off, washed with water, yield: 48%, m.p. 168–70° (MeOH) (lit.[15] 169–70°).

4 - *Methoxy* - 3,5 - *dimethyl* - 1 - *nitrobenzene.* Methylation of the foregoing phenol as described earlier afforded this compound, yield: 80%, m.p. 91–92° (EtOH) (lit.[16] 91°).

4-*Methoxy*-3,5-*dimethylaniline.* This was obtained by the reduction of the foregoing nitro compound with hydrazine hydrate and Raney Ni, yield: 95%, m.p. 60–61° (H_2O) (lit.[16] 61°).

4 - *Methoxy* - 3,5 - *dimethylphenyltrimethylammonium iodide.* Quaternization of the above amine afforded this salt (80%); m.p. of the crude methiodide 208–210°.

4 - *Methoxy* - 3,5 - *dimethyl* - N,N - *dimethylaniline.* The foregoing methiodide, when perfectly dry, was decomposed under reduced pressure. The tertiary amine was purified through its hydrochloride, yield: 60%, b.p. 140°/20 mm (lit.[17] 125–6°/15 mm).

4 - *Ethoxy* - 3 - *methyl* - 1 - *nitrobenzene.* 4 - Hydroxy - 3 - methyl - 1 - nitrobenzene[11] (20 g) was dissolved in acetone (150 ml) and anhyd K_2CO_3 (20 g) was added. The mixture was heated under reflux on a water bath and EtI (21 g) was added slowly. After 10 hr, the mixture was diluted with water, yield: 95%, m.p. 72–3° (dil EtOH) (lit.[18] 71°).

Table 5. Observed and calculated rate constants for the reaction of disubstituted N,N-dimethylanilines with allyl bromide[a]

Substituents	$10^4 k_{20°}$ (l. mole^{-1} sec.$^{-1}$) obs.	calc.	$\frac{k_{obs.}}{k_{calc.}}$
3-Cl, 5-OMe	0.438	0.441	0.99
3-Br, 5-OMe	0.418	0.424	0.99
3-Me, 5-OMe	4.92	4.88	1.01
3-F, 4-OMe	5.99	3.81	1.57
3-Cl, 4-OMe	5.95	3.17	1.88
3-Br, 4-OMe	5.90	3.04	1.94
3-I, 4-OMe	7.04	3.42	2.06
3-NO_2, 4-OMe	1.53	0.703	2.18

[a] Ref.5.

4-Ethoxy-3-methylaniline. This was obtained in 95% yield by the reduction of the foregoing compound with hydrazine hydrate (98%) in the presence of Raney Ni. The crude product was purified through its hydrochloride.

4 - Ethoxy - 3 - methylphenyltrimethylammonium iodide. Quaternization of the above amine afforded this methiodide, yield: 95%, m.p. 181–4°.

4 - Ethoxy - 3 - methyl - N,N - dimethylaniline. When the above quaternary iodide was decomposed in vacuum, the amine was obtained, yield: 84%, b.p. 109–111°/2.5 mm (Found: C, 73.50; H, 10.00. $C_{11}H_{17}NO$ requires: C, 73.35; H, 10.00%).

4-Amino-3-methyl-1-nitrobenzene. This was prepared according to Sanielevici and Floru,[19] m.p. 129–31° (lit.[19] 130–31°).

3-Methyl-4-methylthio-1-nitrobenzene. The procedure adopted by Bolsens *et al.*[20] was followed to prepare this compound from the above amine, m.p. 77–9° (Petroleum spirit 40–60°) (lit.[20] 78–9°).

3-Methyl-4-methylthioaniline. Raney Ni-hydrazine hydrate (98%) reduction of the foregoing nitro compound gave this amine, yield: 97%, m.p. 66–7° (EtOH) (lit.[21] 67°).

3 - Methyl - 4 - methylthio - N,N - dimethylaniline. To a suspension of the foregoing amine (7.5 g) in water (100 ml) were added $NaHCO_3$ (13 g) and Me_2SO_4 (16 g) with constant stirring. The mixture was kept at 30° until the evolution of CO_2 ceased and then at 50–60° for 60 min. On cooling, an oil separated. This was extracted with ether, the ether extract was dried over Na_2SO_4, and the solvent was removed. The amine was purified by treatment with Ac_2O, yield: 34%, b.p. 130–133°/3 mm. The aqueous layer was treated with sat KI aq when 3 - methyl - 4 - methylthiophenyltrimethylammonium iodide separated. This was filtered off, dried and decomposed under reduced pressure. The amine distilled at 129–132°/3 mm, yield: 44%. The total yield of 3 - methyl - 4 - methylthio - N,N - dimethylaniline was 78% (Found: C, 66.45; H, 8.42. $C_{10}H_{15}NS$ requires: C, 66.24; H, 8.36%).

4-Hydroxy-2-methyl-1-nitrobenzene. A well-cooled soln of *m*-cresol (70 g) in glacial AcOH (70 g) was added dropwise to a mechanically-stirred mixture of HNO_3 (sp. gr. 1.5; 100 g) and AcOH (200 g). The temp. was maintained at 0–5°. The stirring was continued for further 2 hr and the product was poured onto crushed ice (about 1 kg). Next day the solid was collected and subjected to steam-distillation until no more 6 - hydroxy - 2 - methyl - 1 - nitrobenzene came over. On cooling, the oily residue in the distillation flask solidified, yield: 23%, m.p. 122–6° (H_2O) (lit.[22] 128°).

4-Methoxy-2-methyl-1-nitrobenzene. Methylation of the foregoing phenol as described earlier afforded this compound, yield: 71%, m.p. 51–2° (Petroleum spirit 40–60°) (lit.[23] 53°).

4-Methoxy-2-methylaniline. This was obtained by the reduction of the above nitro compound using hydrazine hydrate (98%) and Raney Ni, yield: 97%, b.p. 170–72°/20 mm (lit.[24] 188–89°/25 mm).

4 - Methoxy - 2 - methyl - N,N - dimethylaniline. Dimethylation of the foregoing amine with Me_2SO_4 and $NaHCO_3$ yielded this compound, yield: 50%, b.p. 89–91°/3 mm. (Found: C, 73.00; H, 9.31. $C_{10}H_{15}NO$ requires: C, 72.64; H, 9.16%).

Purification of the commercial samples of N,N-dimethylaniline,[5] MeI,[6] MeOH, AcOH was done by methods described in the literature. The commercial variety of petroleum spirit 60–80° was distilled through an efficient fractionating column.

Kinetics. These were measured as described in the literature[6] and the velocity coefficients were calculated as described.[25]

Acknowledgement—One of the authors (V.M.K.) thanks the Annamalai University for giving financial assistance during the course of this work.

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