SHORT PAPER

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The dinitration of dimethylacetanilides†

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The orientation of dinitration of the dimethylacetanilides has been examined by ^{1}H NMR methods and a possible enhancement of the hyperconjugative influence of a methyl group has been considered as an additional factor augmenting the effect of the steric inhibition of resonance on the orientation of substitution.

Keywords: dinitration, dimethylacetanilides

The unexpected nitration of 2,6-dimethylacetanilide to give 2,6-dimethyl-3-nitroacetanilide rather than the 4-nitro isomer, is a classic example of the consequences of the steric inhibition of resonance.[1-5] The effect is also shown to a lesser extent by 2,4-dimethylacetanilide which gives a mixture of 5- and 6-nitro compounds. The dinitration of some dimethylacetanilides has been reported[6-7] but the extent to which the steric inhibition of resonance might influence the orientation of the products was not considered. The nuclear Overhauser effect (nOe) in the ^{1}H NMR spectrum provides a simple method of confirming the orientation of substitution. In this paper we describe the use of nOe enhancements to fully establish the orientation of the dinitration products of the six dimethylacetanilides and 2,6-diethylacetanilide and we consider an additional factor which might contribute to the orientation of substitution.

In previous work the dinitration of 2,6-dimethylformanilide has been shown to give the 3,5-dinitro derivative.[4] The dinitration of 3,4-dimethylacetanilide by fuming nitric acid was reported[6] to give 3,4-dimethyl-2,6-dinitroacetanilide and in the presence of a large amount of sulfuric acid, 3,4-dimethyl-5,6-dinitroacetanilide. The orientation of the nitro groups was established by conversion into dinitroxylenes. The dinitration of 2,5-dimethylacetanilide has been reported[7] to give 2,5-dimethyl-4,6-dinitroacetanilide.

The dinitrations in the present work were carried out using a nitrating mixture of fuming nitric acid and concentrated sulfuric acid at 0°C over a period of 24 hours. The orientation of substitution was established by ^{1}H NMR methods based on irradiation of the N–H and aromatic methyl group resonances (see experimental). The spectra were determined in [$^2H_6$] dimethylsulfoxide to minimise exchange of the N–H. The results are given in Table 1.

The nitrations follow the pattern of the mononitrations[1] with in all cases except 2,4-dimethylacetanilide, the second nitro group entering the ring *meta* to the first. In the case of 3,4-dimethylacetanilide a small amount of 3,4-dimethyl-1,5-dinitrobenzene was isolated. This may arise from *ipso* attack and displacement of the acetylamino group.

Nitration of acetanilide in sulfuric acid has been shown[8] to occur by attack on the free amide. The classical view[2,3] of the effect of the 2,6-dimethyl groups on the orientation of substitution in 2,6-dimethylacetanilide, is that they prevent the amide group achieving co-planarity with the aromatic ring. This co-planarity is necessary for the resonance stabilisation of the Wheland intermediate for substitution at C-4. The hyperconjugative effect[9] of the methyl groups then determines the site of substitution. A possible additional feature might be the rotation of the carbonyl group of the amide so that it could enhance the hyperconjugative stabilisation of the Wheland intermediate for substitution at C-3 by the C-6 methyl group. The extreme canonical form associated with a hyperconjugative effect can be written as $C^{\delta-}..H^{\delta+}$. In the 2,6-dimethylacetanilide the amide carbonyl group may act as an internal base facilitating the weakening of the methyl C–H bond in sense $C^{\delta-}..H^{\delta+}$. A requirement for this is that the carbonyl group can approach the hydrogen atom of the methyl group that is orthogonal to the ring. The steric factors that lead to the twisting of the amide generate this conformation. Hence the methyl group could provide an enhanced stabilisation of the Wheland intermediate for substitution in the position para to the methyl group. This effect could also account for the formation of some 2,4-dimethyl-5-nitroacetanilide as well as the 6-nitro isomer in the mononitration of 2,4-dimethylacetanilide[1] and for the formation of the 5-nitro isomer in as much as 35% yield on mononitration of 2,3-dimethylacetanilide.[10] However, in the present work only the 4,6-dinitro compound was obtained.

Table 1 Dinitration of dimethylacetanilides

Substrate	Product	Yield/%
2,3-Dimethylacetanilide	2,3-dimethyl-4,6-dinitroacetanilide	94
2,4-Dimethylacetanilide	2,4-dimethyl-5,6-dinitroacetanilide	98
2,5-Dimethylacetanilide	2,5-dimethyl-4,6-dinitroacetanilide	80
2,6-Dimethylacetanilide	2,6-dimethyl-3,5-dinitroacetanilide	75
2,6-Diethylacetanilide	2,6-diethyl-3,5-dinitroacetanilide	98
3,4-Dimethylacetanilide	3,4-dimethyl-1,5-dinitrobenzene	Trace
	3,4-dimethyl-2,6-dinitroacetanilide	70
3,5-Dimethylacetanilide	3,5-dimethyl-2,4-dinitroacetanilide	80

Experimental

General experimental details: Light petroleum refers to the fraction b.p. 60–80°C. ^{1}H NMR spectra were recorded in [$^2H_6$]dimethylsulfoxide at 300MHz and nOe enhancements at 500 MHz. IR spectra were determined as nujol mulls. Fuming nitric acid was handled with care in a well-ventilated fume cupboard.

General nitration procedure: A nitrating mixture was prepared from conc. nitric acid (specific gravity 1.42)(8 cm^3) and conc. sulfuric acid (8 cm^3) at 0°C. Fuming nitric acid (specific gravity 1.5) (4 cm^3) was carefully added. The dimethylacetanilide (1.2 g, 7.5 mmmol) was then added in portions over a period of 15 minutes with cooling.

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The mixture was left stirring at 0°C for 24 h. The mixture was then poured onto crushed ice (*ca* 100 cm^3). The product was filtered, washed with water and recrystallised from ethanol. The course of the reaction was followed for the first six hours by TLC (ethyl acetate:light petroleum 1:1). The following products (for % yield see table 1, 100% = 1.86g) were obtained:

2,3-Dimethylacetanilide gave 2,3-dimethyl-4,6-dimethylacetanilide (1.78g,) as pale yellow needles, m.p. 150°C, (Found: M^+ 253.067 $C_{10}H_{11}N_3O_5$ requires M^+ 253.068), ν_{max}/cm^{-1} 3270,1653,1578,1539; δ_H 2.05 (3H, s, Ac), 2.26 (3H, s, 2-Me), 2.38 (3H, s, 3-Me), 8.27 (1H, s, 5-H), 10.28 (1H, s, NH). Irradiation at δ_H 10.28 enhanced the signals at δ_H 2.05(2.3%) and 2.26(2.2%). Irradiation at δ_H 2.26 enhanced the signal at δ_H 2.38(2.6%). Irradiation at δ_H 2.38 enhanced the signal at δ_H 2.26(1.9%). There was no enhancement of the signal at δ_H 8.27. EIMS 253(12), 211(89), 179(19). 2,4-Dimethylacetanilide gave 2,4-dimethyl-5,6-dinitroacetanilide (1.86 g) as pale yellow needles, m.p. 217°C (lit.,[11] 220°C), ν_{max}/cm^{-1} 3270, 1668, 1571, 1533; δ_H 2.00 (3H, s, Ac), 2.25 (3H,s, 2-Me), 2.32 (3H, s, 4-Me), 7.65 (1H, s, 3-H), 10.11 (1H, s, NH), Irradiation at δ_H 10.11 enhanced the signals at δ_H 2.00(2.5%) and 2.25(1.6%). Irradiation at δ_H 2.25 enhanced the signal at δ_H 7.65(8.3%). Irradiation at δ_H 2.32 enhanced the signal at δ_H 7.65(10.3%). EIMS 253(12), 235(31) 211(90) 194(37). 2,5-Dimethylacetanilide gave 2,5dimethyl-4,6-dinitroacetanilide (1.49 g) as pale yellow needles, m.p. 228°C (lit.,[7] 228°C), ν_{max}/cm^{-1} 3277, 1655, 1595, 1527; δ_H 1.99 (3H, s, Ac), 2.22 (3H,s, 2-Me), 2.26 (3H, s, 5Me), 8.10 (1H, s, 3-H), 10.10 (1H, s, NH). Irradiation at δ_H 10.10 enhanced the signals at 6H 1.99(4.5%) and 2.22(2.4%).

Irradiation at δ_H 2.22 enhanced the signals at δ_H 1.99(2.4%) and 8.10(9.4%). Irradiation at δ_H 2.26 did not enhance any signals. EIMS 253(20), 211(100) 194(49). 2,6-Dimethylacetanilide gave 2,6-dimethyl-3,5-dinitroacetanilide (1.40 g) as pale yellow needles, m.p. 225–226°C (lit.,[12] 225–226°C), ν_{max}/cm^{-1} 3280, 1650, 1599, 1531; δ_H 2.11 (3H, s, Ac), 2.30 (6H, s, 2-Me and 6-Me), 8.40 (1H, s, 4-H), 9.98 (lH, s, NH), EIMS 253(53),236(68), 211(62) 194(65). 2,6-Diethylacetanilide gave 2,6-diethyl-3,5-dinitroacetanilide (2 g) as white needles, m.p. 208–210°C (Found:M^+ 281.102 $C_{12}H_{15}N_3O_5$ requires M^+ 281.101), ν_{max}/cm^{-1} 3275, 1668, 1591, 1533; δ_H 1.50 (6H, t, J 7.5 Hz, 2- and 6-Et), 2.15 (3H, s, Ac), 2.85 (4H, q, J 7.5 Hz, 2- and 6-Et), 8.60 (1H, s, 4-H), 10.20(1H, s, NH); EIMS 281(5), 264(60), 222(84). 3,4-Dimethylacetanilide gave a mixture which was adsorbed onto silica and chromatographed. Elution with 2% ethyl acetate:light petroleum gave 3,4-dimethyl-1,5-dinitrobenzene (c.10 mg) as an oil which failed to crystallise,(lit.,[6] m.p. 75°C), ν_{max}/cm^{-1},1607, 1530; δ_H 2.36 (3H, s, 4-Me), 2.43 (3H, s, 3-Me), 8.31 (1H, d, *J* 2 Hz, 2-H), 8.46(1H, d, *J* 2 Hz, 6-H). Irradiation at δ_H 2.36 enhanced the signal at δ_H 2.43(3.1%). Irradiation at δ_H 2.43 enhanced the signals at δ_H 8.31(13.9%) and 2.36(3.2%). EIMS 196(25), 179(100). Further elution with 15% ethyl acetate:light petroleum gave 3,4-dimethyl-2, 6-dinitroacetanilide (1.30 g) as yellow needles, m.p. 221–222°C (lit.,[6] 223°C), ν_{max}/cm^{-1} 3268, 1660, 1590, 1545; δ_H 2.00 (3H, s, Ac), 2.20 (3H, s, 3-Me), 2.40 (3H, s, 4-Me), 8.00 (1H, s, 5-H), 10.03 (1H, s, NH). Irradiation at δ_H 10.03 enhanced the signal at δ_H 2.00(3.2%), Irradiation at δ_H 2.20 enhanced the signal at δ_H 2.40(2.8%). Irradiation at δ_H 2.40 enhanced the signals at δ_H 2.20(2.9%) and 8.00(13.7%). 3,5-Dimethylacetanilide gave 3,5-dimethyl-2,4-dinitroacetanilide (1.49 g) as pale yellow needles, m.p. 190–195°C, (Found: M^+ 253.067 $C_{10}H_{11}N_3O_5$ requires M^+ 253.068), ν_{max}/cm^{-1} 3270, 1665, 1595, 1530; δ_H 2.00 (3H, s, Ac), 2.12 (3H,s, 3-Me), 2.23 (3H, s, 5-Me), 7.45 (lHr s, 6H), 10.30 (1H, s, NH), Irradiation at δ_H 10.30 enhanced the signals at δ_H 2.45(2.8%) and 7.45(7.0%). Irradiation at δ_H 2.23 enhanced the signal at δ_H 7.45(8.2%). Irradiation at δ_H 2.12 did not enhance any signals. EIMS 253(20), 211(100) 194(49).

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