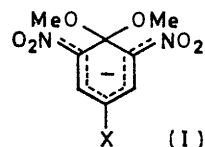


The Stabilities of Meisenheimer Complexes. Part VII.¹ Adducts from 4-Methoxy-3,5-dinitrobenzaldehyde

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In methanol 4-methoxy-3,5-dinitrobenzaldehyde is in equilibrium with its hemiacetal formed by solvent addition to the carbonyl group. ¹H N.m.r. measurements give the value of the equilibrium constant, K_s , for hemiacetal formation as 8. In the presence of methoxide ions a Meisenheimer complex is formed by base addition to the parent aldehyde. Visible spectral measurements allow the determination of the value of 210 l mol^{-1} for K_1 , the thermodynamic equilibrium constant for Meisenheimer complex formation.

THERE is considerable current interest in the Meisenheimer complexes² formed by methoxide ion addition to activated anisoles. At least two strongly electron-withdrawing groups, such as NO₂, are required for complex formation to be observed. The equilibrium constants for formation of complexes of structure (I)



from a number of 2,6-dinitro-4-X-anisoles have been determined either in methanol or referred to methanol as standard state. The values decrease in the order X = SO₂CF₃,³ $K_1 = 1.5 \times 10^6 \text{ l mol}^{-1}$; NO₂,⁴ 17,000; CN,⁴ 280; CO₂Me,⁵ 6; CF₃,^{5,6} 2; Cl,⁷ 4.3×10^{-3} ; H,⁷ 9×10^{-5} .

¹ Part VI, M. R. Crampton, *J.C.S. Perkin II*, 1973, 2157.

² For recent reviews see M. R. Crampton, *Adv. Phys. Org. Chem.*, 1969, **7**, 211; M. J. Strauss, *Chem. Rev.*, 1970, **70**, 667.

³ F. Millot, J. Morel, and F. Terrier, *Compt. rend.*, 1972, **274c**, 23.

⁴ J. H. Fendler, E. J. Fendler, and C. E. Griffin, *J. Org. Chem.*, 1969, **34**, 689.

⁵ M. R. Crampton and H. A. Khan, *J.C.S. Perkin II*, 1972, 1173.

⁶ F. Terrier, *Ann. Chim. (France)*, 1969, **4**, 153.

⁷ M. R. Crampton and H. A. Khan, *J.C.S. Perkin II*, 1972, 1178.

The aldehyde group has considerable electron-withdrawing ability as evidenced by σ or σ^- values⁸ and we thought it of interest to investigate Meisenheimer complex formation in an anisole containing this group. We were aware from previous studies with aldehydes⁹ of the possibility of a competitive reaction involving nucleophilic addition at the carbonyl group to give a hemiacetal or hemiacetal anion. The analogous reactions in water are well known;¹⁰⁻¹² e.g. substituted benzaldehydes have been shown recently to add hydroxide reversibly at the carbonyl group.¹³ In methanol the abnormal activation parameters for nucleophilic substitution of chlorine by methoxide in nitrochlorobenzenes containing CHO or CN substituents has been taken as evidence for hemiacetal or imido-ester formation.¹⁴

The results presented here show that there is indeed competition between Meisenheimer complex formation and hemiacetal formation. Thus in neutral methanol

⁸ H. van Bekkum, P. E. Verkade, and B. M. Wepster, *Rec. Trav. chim.*, 1959, **78**, 815.

⁹ Y. Ogata and A. Kawasaki, 'The Chemistry of the Carbonyl Group,' Interscience, New York, 1970, vol. 2, p. 1.

¹⁰ R. P. Bell, *Adv. Phys. Org. Chem.*, 1966, **4**, 1.

¹¹ J. F. Bunnett, J. H. Miles, and K. V. Nahabedian, *J. Amer. Chem. Soc.*, 1961, **83**, 2512.

¹² E. J. Forbes and M. J. Gregory, *J. Chem. Soc. (B)*, 1968, 205.

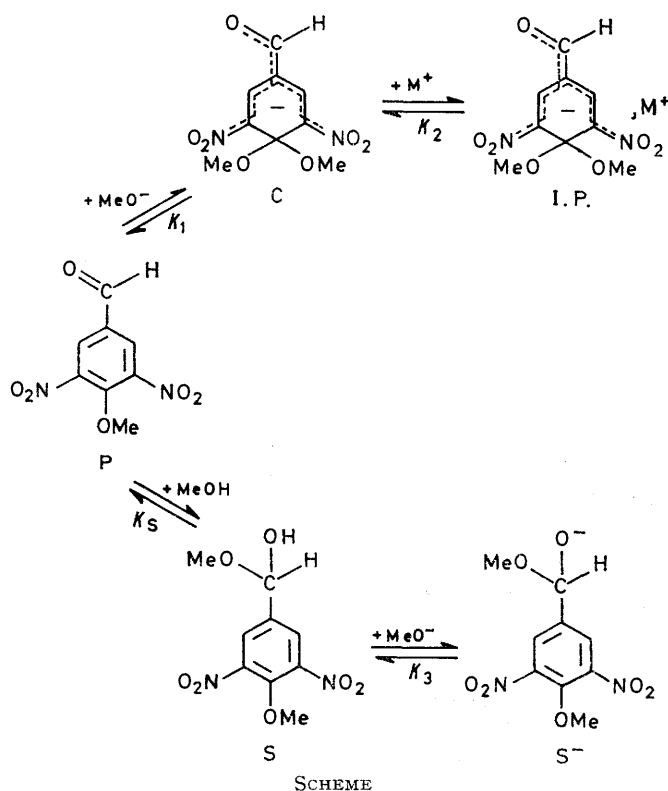
¹³ W. J. Bover and P. Zuman, *J.C.S. Perkin II*, 1973, 786.

¹⁴ J. Miller, *J. Amer. Chem. Soc.*, 1954, **76**, 448; R. L. Heppollette, J. Miller, and V. A. Williams, *ibid.*, 1956, **78**, 1975, 1978.

4-methoxy-3,5-dinitrobenzaldehyde exists largely in the form of the hemiacetal. In the presence of methoxide ions the hemiacetal anion and the Meisenheimer complex (I; X = CHO) are produced. As with other Meisenheimer complexes¹⁵ there is evidence for stabilisation of complex (I; X = CHO) by association with cations.

RESULTS AND DISCUSSION

¹H N.m.r. Spectra.—The spectrum of 4-methoxy-3,5-dinitrobenzaldehyde in deuteriochloroform shows three sharp singlets with shifts (δ) 10.1, 8.6, and 4.2 and relative intensities 1 : 2 : 3 attributed respectively to the aldehydic, aromatic, and methoxy-protons. The spectrum in dimethyl sulphoxide is similar with bands at δ 10.1, 8.8, and 4.1. Addition of a little concentrated methanolic sodium methoxide to a solution of the parent substrate in dimethyl sulphoxide results in the appearance of new bands at δ 9.13, 8.28, and 3.02 with relative intensities 1 : 2 : 6. As the mole ratio of base to parent is increased to unity these bands grow at the expense of those due to parent. The new bands are attributed to the Meisenheimer complex (I; X = CHO). The shifts to high field observed on complex formation are similar to those found in analogous systems.²



Spectra in methanol are more complicated. A solution of the parent in neutral methanol shows three small bands at δ 10.03, 8.67, and 4.1 attributed to the unchanged aldehyde. In addition more intense bands are observed due to the hemiacetal (designated S, for

¹⁵ M. R. Crampton and H. A. Khan, *J.C.S. Perkin II*, 1972, 2286; 1973, 1103.

solvate, in the Scheme); the ring protons give a singlet at δ 8.22, while the CH and OH protons absorb at

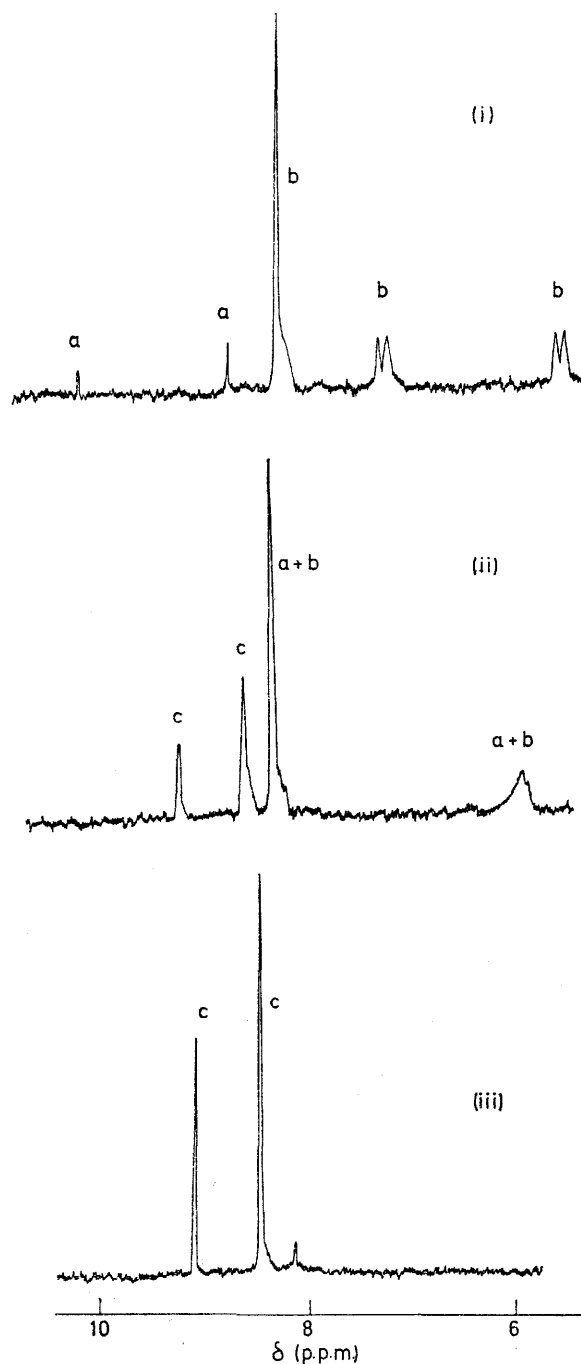


FIGURE 1 ¹H N.m.r. spectra (90 MHz) of 4-methoxy-3,5-dinitrobenzaldehyde (0.2M) in methanol with [NaOMe]_{stoleh} (i) 0; (ii) 0.08M; (iii) 0.8M. Bands labelled a are due to parent aldehyde, b to hemiacetal, and c to Meisenheimer complex

5.60 and 7.25 respectively and exhibit spin-coupling. Bands are also observed due to the two types of methoxy-protons in the hemiacetal. The low-field part of the spectrum is shown in Figure 1. Our spectral assignments are confirmed by a spectrum of the parent in

tetraduteriomethanol which is similar to that in methanol except that the bands due to the methanol added at the carbonyl group are missing. It is interesting that at 25° methanol addition is fairly slow so that the equilibrium proportions of parent aldehyde and hemiacetal are not achieved for some minutes. Measurement of the relative intensities of the ring proton

TABLE 1
Chemical shift data [δ (p.p.m.)]

Parent aldehyde (P)					
Solvent	CHO	Ring protons	OMe		
Deuteriochloroform	10.1	8.6	4.2		
Dimethyl sulphoxide	10.1	8.8	4.1		
Methanol	10.03	8.67	4.1		
Tetraduteriomethanol	10.03	8.67	4.10		
Meisenheimer complex (C)					
Solvent	CHO	Ring protons	OMe		
Dimethyl sulphoxide	9.13	8.28	3.02		
Methanol	9.11	8.53	3.0		
Hemiacetal (S)					
Solvent	CH	Ring protons	OMe (ring)	OMe	OH
Methanol	5.60 ^a	8.22	4.02	3.5	7.25 ^a
Tetraduteriomethanol	5.60	8.23	4.02		

^a These bands exhibit spin coupling with J ca. 7 Hz.

resonances when equilibrium had been reached gave a value for the equilibrium constant $K_S (= [S]/[P])$ of 8 ± 1 . This method of quantitatively studying hemiacetal formation is widely applicable and measurements are in progress with other substituted benzaldehydes.

The addition of a little sodium methoxide to the solution of the parent in methanol is sufficient to remove the hydroxy-resonance of the hemiacetal through proton exchange with the solvent. Also combined resonances are now observed both from the ring protons of parent aldehyde and hemiacetal, and from the aldehydic proton of the parent and the C-H proton of the hemiacetal. This indicates fairly fast exchange, on the n.m.r. timescale, of the species. As the methoxide concentration is increased bands due to Meisenheimer complex increase in intensity at the expense of the combined peaks of the parent and hemiacetal (Figure 1). When the base added is sodium methoxide there is eventual complete conversion to Meisenheimer complex at a base concentration of ca. 1M. A different situation pertains when lithium methoxide is used as the added base. In this case it is only possible to achieve ca. 50% conversion to Meisenheimer complex even at high base concentrations. Chemical shift data are collected in Table 1.

Visible Spectra.—Solutions in methanol of 4-methoxy-3,5-dinitrobenzaldehyde are colourless. In the presence of sodium methoxide a red colour is produced with maxima at 370 and 500 nm. The hemiacetal anion, S^- , where the negative charge is isolated from the ring would not be expected to be coloured so that this absorption is attributed to the Meisenheimer complex, C.

The shape of the visible spectrum is independent of base concentration but the optical density increased with increasing base concentration up to a concentration of ca. 1M when further increase caused no spectral change. Spectra of similar shape were obtained using lithium or tetra-n-butylammonium methoxide, however the limiting optical density at high base concentration using lithium methoxide was only about half that obtained using the other two methoxides. This result is in agreement with the n.m.r. data which indicate that with sodium methoxide it is possible to achieve complete conversion into Meisenheimer complex though with lithium methoxide this is not so.

Spectra in methanol-dimethyl sulphoxide mixtures are similar to those in methanol but with maxima shifted slightly to longer wavelengths. In media rich (>90%) in dimethyl sulphoxide it is possible to observe the formation of a transient species, λ_{max} 398 (ϵ 1.7×10^4 l mol⁻¹ cm⁻¹) and 465 nm (1.7×10^4), formed prior to the time-stable species. By analogy with previous work^{2,16} this transient species is the isomeric Meisenheimer complex formed by methoxide addition at C-2. In methanol-rich media the stability of this complex is too low for its observation.

Equilibrium Constants.—Measurements of optical density were made at 500 nm in methanol solutions containing lithium, tetra-n-butylammonium, or sodium

TABLE 2
Optical densities and equilibrium constants for reaction of 4-methoxy-3,5-dinitrobenzaldehyde (3.9×10^{-5} M) with lithium methoxide in methanol at 25°

[LiOMe]/M	O.D. (500 nm)	K_C /l mol ⁻¹
0.0096	0.083	17.3
0.0192	0.13	15
0.038	0.17	11
0.058	0.195	8.7
0.096	0.22	6.4
0.193	0.24	3.7
0.92	0.29	(1.1)

TABLE 3
Optical densities and equilibrium constants for reaction of 4-methoxy-3,5-dinitrobenzaldehyde (3.9×10^{-5} M) with tetra-n-butylammonium methoxide in methanol at 25°

[Bu ₄ NOMe]/M	O.D. (500 nm)	K_C /l mol ⁻¹	K_C (calc.) ^a
0.0105	0.10	20	20
0.021	0.16	18	18
0.042	0.23	15.5	16
0.063	0.27	14	14
0.084	0.30	13	13
0.10	0.32	12	13
0.80	0.56		

^a Calculated from equation (4) with the values, $K_1 = 210$ l mol⁻¹, $K_2 = 10$ l mol⁻¹, $K_3 = 30$ l mol⁻¹, $K_S = 8$.

methoxides. Data are in Tables 2–4. Colour formation was fairly slow and the values quoted are those after attainment of equilibrium. We interpret these measurements as shown in the Scheme.

In neutral methanol the parent aldehyde is in equilibrium with solvate S with an equilibrium constant K_S

¹⁶ F. Terrier, J. C. Halle, and M. P. Simmonin, *Org. Magnetic Resonance*, 1971, **3**, 361.

whose value was directly determined from n.m.r. measurements. By analogy with similar systems⁹⁻¹⁴ there will, in basic solutions, be an equilibrium between the hemiacetal S and its anion S⁻, $K_3 = [S^-]/[S][MeO^-]$.

TABLE 4

Optical densities and equilibrium constants for reaction of 4-methoxy-3,5-dinitrobenzaldehyde ($3.9 \times 10^{-5}M$) with sodium methoxide in methanol at 25°

[NaOMe]/M	O.D. (500 nm)	$K_C/l \text{ mol}^{-1}$	$K_C(\text{calc.})^a$
0.0096	0.115	26	24
0.0192	0.19	25	24
0.029	0.26	28	25
0.048	0.33	27	25
0.067	0.37	26	25
0.115	0.43	25	25
0.67	0.56		
1.0	0.58		
1.4	0.58		
0.01 ^b	0.25	76	74
0.02 ^b	0.32	62	61
0.04 ^b	0.38	47	45

^a Calculated from equation (4) with the values, $K_1 = 210 \text{ l mol}^{-1}$, $K_2 = 30 \text{ l mol}^{-1}$, $K_3 = 30 \text{ l mol}^{-1}$, $K_8 = 8$. ^b Made up to constant ionic strength, 0.1M, with sodium chloride.

We recognise that in basic media there is a direct path between P and S⁻ involving methoxide attack at the carbonyl group and it is possible to define an equilibrium constant K_4 relating these species; $K_4 = K_3K_8 = [S^-]/[P][MeO^-]$.

The equilibrium constant for Meisenheimer complex formation is $K_1 (= [C]/[P][MeO^-])$. There is considerable evidence¹⁵ for ion pairing of Meisenheimer complexes with cations in methanol, $K_2 = [I.P.]/[C][M^+]$. Such association constants generally decrease with cation in the order barium > sodium > tetra-n-butylammonium. However there is little association of lithium ions with Meisenheimer complexes.

The n.m.r. results show that in the presence of sodium methoxide there is, at sufficiently high base concentration, virtually complete conversion into Meisenheimer complex. Hence we take the value of optical density of 0.58 to correspond to complete conversion into complex (plus ion pair). The visible spectral shape does not change over the whole range of base concentrations and we assume that the extinction coefficients of complex C, and its ion pair, I.P., will be identical. Then we define a stoichiometric equilibrium constant K_C given by equations (1) and (2). It is easily shown that equation

$$K_C = \frac{\text{O.D. (500 nm)}}{\{(0.58 - \text{O.D. (500 nm)})\} [MeO^-]_{\text{free}}} \quad (1)$$

$$= \frac{[C] + [I.P.]}{([P]_{\text{stoich}} - [C] - [I.P.])[MeO^-]_{\text{free}}} \quad (2)$$

(3) holds and in the present case where $K_8 = 8$ this

$$K_C = \frac{K_1(1 + K_2[M^+])}{1 + K_8 + K_8K_3[MeO^-]} \quad (3)$$

reduces to (4).

$$K_C = \frac{K_1(1 + K_2[M^+])}{9 + 8K_3[MeO^-]} \quad (4)$$

When the base used is lithium methoxide it is reasonable to assume, in view of previous measurements,¹⁵ that the ion-pair association constant K_2 is equal to zero. Rearrangement of equation (4) then gives (5).

$$\frac{1}{K_C} = \frac{9}{K_1} + \frac{8K_3}{K_1} [MeO^-] \quad (5)$$

In agreement with the prediction of this equation a plot (Figure 2) of $1/K_C$ versus $[LiOMe]$ is linear. From the intercept and slope are obtained the values $K_1 = 210 \pm 40 \text{ l mol}^{-1}$ and $K_3 = 30 \pm 6 \text{ l mol}^{-1}$.

Tetra-n-butylammonium ions are known¹⁵ to stabilise Meisenheimer complexes, probably by dispersion interaction, the effect being largely independent of the nature of ring substituents in the complexes. In similar

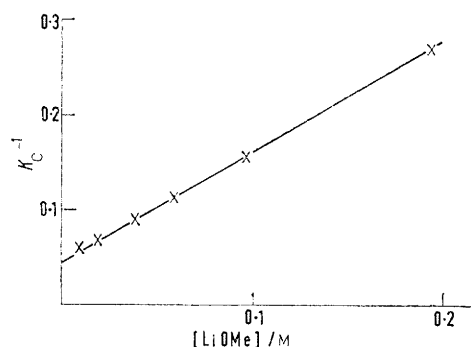


FIGURE 2 Plot of equation (5) for reaction of 4-methoxy-3,5-dinitrobenzaldehyde with lithium methoxide

systems¹⁵ association constants, K_2 , have values of ca. 10 l mol^{-1} . Using this value for K_2 and the values of K_1 and K_3 calculated using lithium methoxide excellent agreement is obtained between experimental and calculated values of K_C (Table 3). In the case of sodium or barium ions it has been suggested¹⁵ that in the ion associate the cation is held by a cage effect by the two methoxy-groups at the position of addition and by the electronegative *ortho*-substituent. For sodium ions¹⁵ association constants are in the range 20–100 l mol^{-1} depending upon the ring substituents in the Meisenheimer complex. Taking a value of $K_2 = 30 \text{ l mol}^{-1}$ experimental and calculated values of K_C are found to agree well for the sodium methoxide data (Table 4).

The n.m.r. results show that while in dimethyl sulphoxide there is straightforward formation of Meisenheimer complex, in methanol there is a competitive process forming the hemiacetal and its anion. Similarly a recent study¹⁷ of methoxide ion addition to a cyanothiophen derivative shows that while in dimethyl sulphoxide base attack occurs at a ring carbon atom in methanol attack is at the cyano-group. It would therefore seem preferable for structural studies to be made using methanol as solvent when possible

¹⁷ G. Doddi, G. Illuminati, and F. Stegel, *Tetrahedron Letters*, 1973, 3221.

EXPERIMENTAL

4-Methoxy-3,5-dinitrobenzaldehyde was prepared in three stages starting from 4-bromobenzaldehyde. Mononitration of the starting material gave 4-bromo-3-nitrobenzaldehyde. Further nitration by the method of Hodgson and Smith¹⁸ gave 4-bromo-3,5-dinitrobenzaldehyde contaminated with a considerable amount of the mono- and di-nitro-carboxylic acids. These impurities were removed by washing with aqueous sodium hydrogen carbonate solution. Reaction of 4-bromo-3,5-dinitrobenzaldehyde with 1 equiv. of sodium methoxide in methanol gave 4-methoxy-3,5-dinitrobenzaldehyde, m.p. 87° (lit.,¹⁸ 86°).

Solvents and solutions of base were prepared and/or purified as before.¹⁵ Visible spectral measurements were made at 25° using Unicam SP 500, SP 800, and SP 8000

instruments. ¹H N.m.r. measurements were made using tetramethylsilane as internal reference at 60 MHz with a Varian HA 56/60 instrument or at 90 MHz with a Bruker HX 90 instrument. The latter measurements were at 25°.

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¹⁸ H. H. Hodgson and E. W. Smith, *J. Soc. Chem. Ind.*, 1930, **49**, 408.
