Reactions in Strongly Basic Media. Part 9.[1] Correlation of the Rates of Methoxide-catalysed Methanolysis of 1-Substituted 2,4-Dinitrobenzenes and 2-Substituted 5-Nitropyridines in Methanolic Dimethyl Sulphoxide with an Acidity Function. Details of the Mechanistic Pathway

Keith Bowden * and Nighat S. Nadvi
Department of Chemistry, University of Essex, Wivenhoe Park, Colchester, Essex CO4 3SQ

The rate coefficients for the methoxide-catalysed methanolysis of a series of 1-substituted 2,4-dinitrobenzenes and 2-substituted 5-nitropyridines have been measured in methanolic DMSO at 20.0 or 21.0 °C. For the 2-substituted 5-nitropyridines and for the 1-substituted 2,4-dinitrobenzenes below *ca.* 55 mol% DMSO, the rates have been correlated with an acidity function of the medium. The slopes of these linear relations are discussed. The 1-substituted 2,4-dinitrobenzenes above *ca.* 55 mol% DMSO give rise to Meisenheimer complexes as intermediates and/or as the product of the reaction. The product of the reaction then becomes the 1,1-Meisenheimer complex of methoxide and 2,4-dinitroanisole. For the 1-fluoro substrate the formation of the latter becomes rate determining. For other 1-substituted substrates the decomposition of a 1,3-Meisenheimer complex becomes rate determining.

Many studies have been made of bimolecular nucleophilic aromatic substitution reactions.[2] In particular the methoxide-catalysed methanolysis of a wide range of substrates, with varied activating substituents and leaving groups, has been investigated.

An acidity function, H_-, has been constructed for methanolic dimethyl sulphoxide (DMSO) containing methoxide.[3] No studies of nucleophilic aromatic substitutions have apparently been made under these conditions. However, Schaal *et al.*[4] made a study of methanolysis of 1,2- and 1,4-dinitrobenzenes in methanol containing alkali-metal methoxides. They found linear correlations between log k_{obs} and the acidity function H_M + log [MeOH] with unit slope and concluded that reactions proceed *via* a rate-determining methoxide anion addition. Bowden and his co-workers[5-7] have studied the alkaline hydrolysis of a wide range of activated aromatic and heteroaromatic substrates in aqueous DMSO containing hydroxide. They have obtained linear correlations between log k_{obs} and H_- + log a_w with various slopes which they have related to the structure of the substrates. Meisenheimer intermediates have been detected, coincident with discontinuities in the correlations, and details mechanisms have been put forward.

Numerous studies[8] have been made on the occurrence and structures of Meisenheimer complexes. Many instances have been recorded of complexes formed from activated aromatic and heteroaromatic compounds with alkoxides.

The present study describes an investigation of the methoxide-catalysed methanolysis of a series of activated substrates in methanolic DMSO. Correlations between the rates of reaction and an acidity function have been made and the occurrence of Meisenheimer intermediates delineated to give rise to a detailed mechanism for the reactions.

Experimental

Materials.—DMSO, methanol, and sodium methoxide were prepared and used as described previously.[5,6,9] The substrates and isolated products had been obtained or synthesised previously.[5-7] They were recrystallised till their m.p.s were in satisfactory agreement with literature values.

Kinetic Measurements.—These were either, for 'slow' reactions, carried out by a method described previously[5,6] using a Unicam SP 800 spectrophotometer or, for 'fast' reactions, made using a Durrum–Gibson model D-110 stopped-flow spectrophotometer. For the reaction of 1-fluoro-2,4-dinitroanisole at DMSO contents greater than *ca.* 40 mol% the rates were followed using the 'stopped-flow' method as they were too fast for the conventional technique.

Formation of Meisenheimer Complexes.—In the study of the reaction of 1-substituted 2,4-dinitrobenzenes it was found that, in solvent mixtures containing base and > 55 mol% DMSO, an instant purple colouration appeared on adding the substrate. This changed to reddish brown on shaking and the reacting mixture developed a large peak at 500 nm with a consequent decrease in the product, 2,4-dinitroanisole, peak. It was found that the latter product gave rise to a similar peak under the same conditions and it was attributed to the formation of a Meisenheimer intermediate.[8] The formation of this complex was 'fast' and the 'stopped-flow' technique was employed to follow its formation. It appeared that there were two types of absorption at 500 nm, the first corresponding to a very rapid reaction ($t_{\frac{1}{2}}$ *ca.* 5 ms), the 'unstable' complex, followed by a decay and subsequent formation of a second and 'stable' complex. By varying the time scale, the rate of formation and decay of the 'unstable' complex and of formation of the 'stable' complex could be measured. The 'stable' complex itself decayed extremely slowly ($t_{\frac{1}{2}}$ > 5 h). The complete spectrum of the 'stable' complex could be recorded, but that of the 'unstable' complex was too transient.

Reaction Products.—The expected product of the nucleophilic substitution of 1-substituted 2,4-dinitrobenzenes is 2,4-dinitroanisole which can be isolated quantitatively in preparative-scale reactions. A spectrum of 2,4-dinitroanisole in methanolic DMSO was identical with that of the spectra of the kinetic mixture at the end of the reaction, allowing for other absorbing products that may be present. The $\lambda_{max.}$ of 2,4-dinitroanisole was in the range 290—300 nm depending on the composition of the solvent and the reaction was normally followed at 295 nm.

The expected product of the nucleophilic substitution of 2-substituted 5-nitropyridines is 2-methoxy-5-nitropyridine which can be isolated quantitatively in preparative-scale reactions. The spectral identity of the product from preparative

Table 1. Rate coefficients k_{obs} for the methanolysis of 1-substituted 2,4-dinitrobenzenes in methanolic DMSO containing 0.1M-sodium methoxide at 20.0 °C, together with the values of the acidity function*

		$10^3k_{obs}/s^{-1}$							
		1-Substituent				1-Phenoxy substituent			
Mol% DMSO	H_- + log a_{MeOH}	F	Cl	Br	I	H	*m*-Br	*m*-Cl	*m*-NO_2
0	12.83	1 370	1.89	1.25	0.376	0.371	1.18	1.20	3.14
2.91	13.06		2.82	1.94	0.457_5	0.677	2.04	1.72	4.52
5.95	13.29	2 970	4.20	2.69	0.834_5	0.836	2.66	2.51	6.03_5
12.5	13.72	5 950	9.09	5.63	1.51	2.21	6.26	5.20	13.0
19.6	14.11	12 200	21.0	12.6	3.44	4.04_5	13.3	11.1	29.5
27.5	14.52	26 950	46.0	27.5	6.88	11.2	31.6	30.0_5	70.2
36.3	14.97	62 500	116	64.0	16.4	26.9_5	72.8	69.0	168
46.1	15.43	166 000	326	171	34.5	73.1_5		239	
57.1	15.92		927†	582	112				

* Rate coefficients are reproducible to ±5%. † Rate coefficients are reproducible to ±8%.

Table 2. Rate coefficients k_{obs} for the methanolysis of 2-substituted 5-nitropyridines in methanolic DMSO containing 0.1M-sodium methoxide at 20.0 °C, together with the values of the acidity function*

		$10^3k_{obs}/s^{-1}$						
		2-Substituent			2-Phenoxy substituent			
Mol% DMSO	H_- + log a_{MeOH}	Cl	Br	I	H	*m*-Me	*m*-Cl	*m*-NO_2
0	12.83	1.09	1.01					
2.91	13.06	1.39	1.26					
5.95	13.29	1.81	1.56					0.463
12.5	13.72	3.07	2.61	1.32		0.0980	0.361	0.812
19.6	14.11	5.63	4.80	2.79_5	0.222	0.237_5	0.863	0.184
27.5	14.52	10.5	10.1	5.20	0.477	0.402	1.91	4.62_5
36.3	14.97	24.5	20.2	10.3_5	1.35	1.17_5	5.02	13.9
46.1	15.43	57.9	52.8_5	23.8	3.42_5	3.67	14.5	43.5
57.1	15.92				12.4	12.3		
69.5	16.56				61.6	44.4		

* See Table 1.

Table 3. Rate coefficients k_{obs} for the formation of the 'stable' Meisenheimer complex from 1-substituted 2,4-dinitrobenzenes in methanolic DMSO containing 0.1M-sodium methoxide at 21.0 °C, together with the values of the acidity function*

Mol% DMSO	57.1	63.1	69.5	76.3	83.7
H_- + log a_{MeOH}	15.92	16.21	16.56	16.88	17.30
1-Substituent			k_{obs}/s^{-1}		
OMe	1.12	1.07	2.03	2.80	8.12
F	1.13	1.01	1.71	2.98	7.05
Cl	0.603	0.758_5	0.987	0.613	
Br	0.398	0.455	0.618_5	0.378	
I	0.127	0.249	0.365	0.276	
OPh	0.240_5	0427	0.971	1.81	2.24
OC_6H_4m-Cl	0.555	0.807	1.15_5	2.09	1.57_5
OC_6H_4m-Br	0.547	0.804	1.15	2.17	1.66
OC_6H_4m-NO_2	0.674	0.829	1.26	1.77	1.06

* Rate coefficients are reproducible to ±10%.

and kinetic runs was again found. The latter compound had $\lambda_{max.}$ *ca.* 305 nm and the product formation was followed at 300 nm, except for 2-(*m*-nitrophenoxy)-5-nitropyridine where, because of an isosbestic point, 275 nm was used.

Results

The reactions of 1-substituted 2,4-dinitrobenzenes and 2-substituted 5-nitropyridines with methoxide anion were overall

Table 4. Rate coefficients k_{obs} for the formation of the 'unstable' Meisenheimer complex 1-substituted 2,4-dinitrobenzenes in methanolic DMSO containing 0.1M-sodium methoxide at 21.0 °C, together with the values of the acidity function*

Mol% DMSO	57.1	63.1	69.5	76.3	83.7
H_- + log a_{MeOH}	15.92	16.21	16.56	16.88	17.30
1-Substituent			k_{obs}/s^{-1}		
Cl	160	95	98	110	55
Br	120	70	76	86	47
I	160	70	53	56	49
OPh				110	63
OC_6H_4m-Cl		120	110	110	64
OC_6H_4m-Br		130	110	85	66
OC_6H_4m-NO_2	150	99	86	93	44

* Rate coefficients are reproducible to ±15 to 25%.

Table 5. Rate coefficients k_{obs} for the decay of the 'unstable' Meisenheimer complex from 1-substituted 2,4-dinitrobenzenes in methanolic DMSO containing 0.1M-sodium methoxide at 21.0 °C, together with the values of the acidity function*

Mol% DMSO	63.1	69.5	76.3	83.7
H_- + log a_{MeOH}	16.21	16.56	16.88	17.30
1-Substituent		k_{obs}/s^{-1}		
Cl	5.6	5.0	4.2	0.36
Br	5.9	5.2	5.9	0.69

* See Table 4.

second order, being first order in both substrate and methoxide anion. This was confirmed by following the reaction as a function of product formation in excess of base the latter being varied in concentration. The substrate concentration was *ca.* 1×10^{-4}M and the base 0.1M, except, for the latter, when the order was being investigated. Rate coefficients were normally reproducible to ±3% except where stated or for the formation and decay of the Meisenheimer complexes. The reproducibility of the latter for the formation of the 'stable' complex was *ca.* ±10%; those for the 'unstable' were 15—25%. The solvent compositions are considered to be accurate to 0.2%.

Rate coefficients for the methanolysis of 1-substituted 2,4-dinitrobenzenes are shown in Table 1, and those for 2-substituted 5-nitropyridines in Table 2. Table 3 shows the rate coefficients for the formation of the 'stable' Meisenheimer complexes of 1-substituted 2,4-dinitrobenzenes and Tables 4 and 5 show the

Table 6. Regression analysis for equation (i) correlating the methanolysis of 1-substituted 2,4-dinitrobenzenes and 2-substituted 5-nitropyridines in methanolic DMSO containing 0.1 M-sodium methoxide at 20.0 °C

Substrate	l	c	Correlation coefficient
1-Fluoro-2,4-dinitrobenzene	0.80	−10.15	0.999
1-Chloro-2,4-dinitrobenzene	0.87	−13.96	0.999
1-Bromo-2,4-dinitrobenzene	0.85	−13.84	0.998
1-Iodo-2,4-dinitrobenzene	0.80	−13.70	0.999
1-Phenoxy-2,4-dinitrobenzene	0.87_5	−14.64	0.999
1-(*m*-Chlorophenoxy)-2,4-dinitrobenzene	0.87	−14.22	0.997
1-(*m*-Bromophenoxy)-2,4-dinitrobenzene	0.83	−13.62	0.999
1-(*m*-Nitrophenoxy)-2,4-dinitrobenzene	0.82	−13.05	0.998
2-Chloro-5-nitropyridine	0.66	−11.52	0.996
2-Bromo-5-nitropyridine	0.66	−11.54	0.994
2-Iodo-5-nitropyridine	0.72	−12.73	0.999
2-Phenoxy-5-nitropyridine	1.10	−19.34	0.986
2-(*m*-Methylphenoxy)-5-nitropyridine	1.03	−18.20	0.992
2-(*m*-Chlorophenoxy)-5-nitropyridine	0.93	−16.15	1.000
2-(*m*-Nitrophenoxy)-5-nitropyridine	0.94	−15.95	0.995

rate coefficients for the formation and decay of the 'unstable' Meisenheimer complexes.

The values of the acidity function, $H_- + \log a_{MeOH}$, are also shown in Tables 1—5 and have been obtained from the H_- values of Stewart *et al.*[3] and the activity coefficients for methanol in methanolic DMSO[10] by interpolation and correction for the base concentration change (0.025—0.1 M).[11] Correlations between the logarithm of the observed rate coefficient and the acidity function, $H_- + \log a_{MeOH}$, have been made for rates of methanolysis in Tables 1 and 2 using equation (i) and a least-mean-squares treatment. The results are shown in Table 6.

$$\log k_{obs} = l(H_- + \log a_{MeOH}) + c \qquad \text{(i)}$$

Discussion

A wide range of reactivities of both the 1-substituted 2,4-dinitrobenzenes and 2-substituted 5-nitropyridines towards methoxide in methanolic DMSO is shown in Tables 1 and 2. For the 1-substituted 2,4-dinitrobenzene series reactivities are in the order: fluoro ⩾ *m*-nitrophenoxy > chloro > *m*-bromophenoxy > *m*-chlorophenoxy ~ bromo > phenoxy > iodo. The order remains the same throughout the range of the linear correlations. This order agrees well with those quoted in the literature[2,11] and that found by Bowden and Cook[6] for the alkaline hydrolysis of the same substrates in aqueous DMSO. The substrates are more reactive in methanolic DMSO than in aqueous DMSO due to the greater nucleophilicity of methoxide than hydroxide, *cf.* ref. 2. For the 2-substituted 5-nitropyridine series the reactivities are in the order: chloro > bromo > *m*-nitrophenoxy ~ iodo > *m*-chlorophenoxy > phenoxy > *m*-methylphenoxy. Again this is consistent with the orders previously found[2,12] and that found by Bowden and his co-workers[7] for the alkaline hydrolysis in aqueous DMSO when substrates are reacting by the same pathway. The change in reactivity is also the same as above in passing from methoxide to hydroxide.

It is clear that the substrates are reacting with methoxide by the S_NAr) pathway.[12] The mechanisms are shown in (ii) and (iii).

In both cases the rate-determining step is the addition of the nucleophile to the ring, k_1. For the *m*-substituted phenoxy substrates, the effect of substitution shows that the reaction is increased by electron-withdrawing substituents. The Hammett

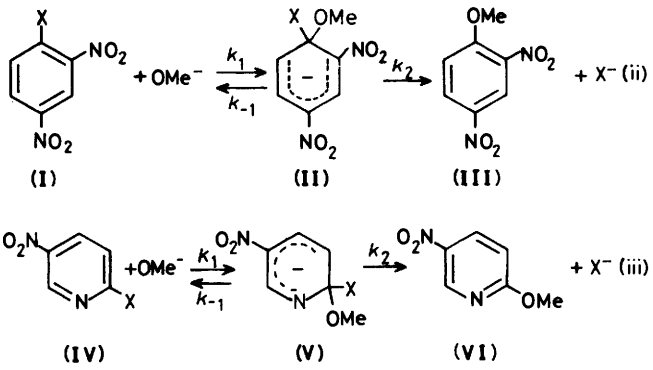


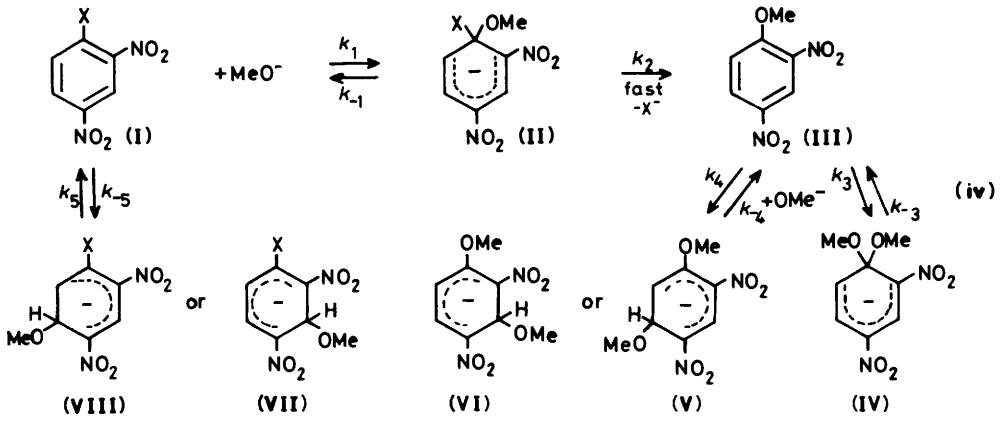
Table 7. Reaction constants ρ for the effects of *m*-substitution in the phenoxy groups*

Substrate	Solvent mol% DMSO	ρ	log k_0	s	r	n
1-Phenoxy-2,4-dinitrobenzene	5.95	1.212	-3.066_5	0.035	0.999	4
	19.6	1.219	-2.389_5	0.051	1.000	4
	36.3	1.117	−1.574	0.016	1.000	4
2-Phenoxy-5-nitropyridine	19.6	1.229	-3.580_5	0.119	0.991	4
	36.3	1.407	−2.846	0.041	0.999	4
	46.1	1.455	−2.394	0.106	0.999	4

* s = standard deviation, r = correlation coefficient, and n = number of substituents.

reaction constant, ρ, has been found for both systems at various solvent compositions are shown in Table 7. The values are *ca.* 1.2 for the 1-phenoxy-2,4-dinitrobenzenes and 1.4 for the 2-phenoxy-5-nitropyridines. This corresponds to values for the alkaline hydrolysis in aqueous DMSO of *ca.* 0.7 and 1.3, respectively.[6,7] The significant difference for the 1-phenoxy-2,4-dinitrobenzene system presumably indicates a more 'advanced' transition state in methanolic than in aqueous DMSO.

Good linear relationships between log k_{obs} and the acidity function $H_- + \log a_{MeOH}$ are observed for the methanolysis of both the 2-substituted 5-nitropyridines and the 1-substituted 2,4-dinitrobenzenes. In the case of the latter this does not include the region of higher DMSO contents where Meisenheimer complexes intervene (see later). The justification of these linear relationships has been examined previously.[5] The slopes of such linear relationships have been interpreted to indicate to what extent the transition state resembles the indicator anions constructing the scale and/or to the extent the transition state has 'advanced'.[5,6] Furthermore, it was suggested that there is a relation between the reactivity of the substrate and its response to medium effects, as in a reactivity–selectivity principle. Johnson[13] has reviewed the evidence and found a lack of support for such principles. The present results do not indicate any evidence for such a relation. Thus, for the 1-substituted 2,4-dinitrobenzenes the substrate reactivity varies by $> 10^3$ and the value of l ranges from 0.80 to 0.87_5. On the other hand, for the 2-substituted 5-nitropyridines the substrate reactivity varies by only a factor of 10, while the value of l ranges from 0.66 to 1.10. The evidence in the present study indicates that there appears to be little dependence on substrate reactivity. The definition of the slope originates from the indicators and their anions, with their solvation requirements implicitly involved. The most satisfactory interpretation of the slopes, l, of the correlations at this time appears to lie, mainly, in the requirements for protic solvation in going from the initial to the transition state. In general, an 'advanced' transition state will give rise to an



increase in *l* as less protic solvation will be required. However, the demand for protic solvation will be very much a function of the substituents stabilising the transition state. Furthermore, steric interactions at and around the reaction site appear to result in less 'advanced' transition states and, consequently, a lower value of *l*.

Meisenheimer Intermediates.—In solvent composition of 55 mol% DMSO, 2,4-dinitroanisole reacts with sodium methoxide to give a transient reddish purple colouration on initial mixing. This colouration becomes increasingly persistent with increasing DMSO concentration and is accompanied by a decrease in the u.v. absorption due to 2,4-dinitroanisole. The spectral characteristics of the new product are $\lambda_{max.}$ 500 nm and a shoulder at 345 nm. This is consistent with the product being a Meisenheimer complex[8] and, in particular, the stable 1,1-complex (**IV**). A complete scheme, showing all possible intermediates and reactions, is shown in equation (iv). Both the 1,1- and the 1,3-complexes (**IV**) and (**V**) or (**VI**), respectively, have been reported in DMSO containing methoxide.[14,15] An initially formed unstable complex rapidly collapses and a stable 1,1-complex (**IV**) forms.

In the present study 2,4-dinitroanisole was observed to give only the 'stable' 1,1-complex (**IV**), as did all 1-substituted 2,4-dinitrobenzenes as their final product at high DMSO contents (> *ca.* 55 mol%). The results in Table 3 show that the observed rates of formation of this 'stable' complex are the same, within experimental reproducibility, for *both* 2,4-dinitroanisole and 1-fluoro-2,4-dinitrobenzene. Thus for the latter substrate, the rate-determining step switches from k_1 to k_3 in process (iv). As neither of the above substrates shows evidence of the formation of (**V**) or (**VI**), the latter complexes may be dismissed from further consideration. However, the other 1-substituted 2,4-dinitrobenzenes all give rise to a kinetically favoured, 'unstable' complex which rapidly decays to form the 'stable' complex (**IV**). The 'unstable' complex must therefore be (**VII**) or (**VIII**). The structure (**VIII**) appears more likely as it only has one nitro group '*ortho*' to the reaction site; but there is no evidence as to which actually occurs. The formation of (**VII**) or (**VIII**) is confirmed by the observed rates of formation of the 'stable' complex (Table 3) in which the effect of *m*-substituents in the phenoxy group switches at high DMSO content from a positive to a negative dependence on electron-withdrawing substituents. Thus at high DMSO contents the rate-determining step switches from k_1 to k_5 in process (iv). This behaviour is analogous to that found for the same substrates in aqueous DMSO,[7] except that *here* the final product can be itself a complex (**IV**). The observed rates of formation and decomposition of the complexes shown in Tables 3—5 are, in general, too complex to interpret in terms of discrete steps in process (iv) as they are composed of both formation and decay.

Our conclusions are that below *ca.* 55 mol% DMSO the predominant reaction pathway is S_NAr reaction of methoxide with substrate (**I**) to give product (**III**), with k_1 being the rate-determining step. Above *ca.* 55 mol% DMSO the product becomes the Meisenheimer complex (**IV**). For the 1-fluoro substrate k_3 becomes rate determining. For all other substrates k_5 becomes rate determining.

References

1 Part 8, preceding paper.
2 J. Miller, 'Aromatic Nucleophilic Substitution,' Elsevier, Amsterdam, 1968,
3 R. Stewart, J. P. O'Donnell, D. J. Cram, and B. Rickborn, *Tetrahedron*, 1962, **18**, 917.
4 R. Schaal and F. Peure, *Compt. rend.*, 1963, **256**, 4020; *Bull. Soc. Chim. Fr.*, 1963, 2638; R. Schaal and J.-C. Latour, *ibid.*, 1964, 2177.
5 K. Bowden and R. S. Cook, *J. Chem. Soc. B*, 1971, 1765.
6 K. Bowden and R. S. Cook, *J. Chem. Soc. B*, 1971, 1771.
7 Part 7, K. Bowden, S. Prasannan, and R. J. Ranson, *J. Chem. Soc., Perkin Trans. 2*, 1987, 181.
8 E. Buncel, M. R. Crampton, M. J. Strauss, and F. Terrier, 'Electron Deficient Aromatic and Heteroaromatic Base Interaction,' Elsevier, Amsterdam, 1984.
9 K. Bowden and G. R. Taylor, *J. Chem. Soc. B*, 1971, 1395.
10 K. Quitzsch, H. Ulbrecht, and G. Geisler, *Z. Phys. Chem. (Leipzig)*, 1967, **234**, 33.
11 K. Bowden, *Chem. Rev.*, 1966, **66**, 119.
12 J. F. Bunnett and R. E. Zahler, *Chem. Rev.*, 1951, **49**, 273.
13 C. D. Johnson, *Chem. Rev.*, 1975, **75**, 755.
14 Y. Hasegawa, *Bull. Chem. Soc. Jpn.*, 1974, **47**, 2186.
15 C. F. Bernasconi, *J. Am. Chem. Soc.*, 1968, **90**, 4982.

Received 27*th March* 1986; *Paper* 6/605