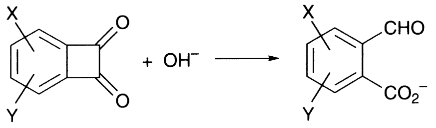
Reactions of carbonyl compounds in basic solutions. Part 24.[1] The mechanism of the base-catalysed ring fission of substituted benzocyclobutene-1,2-diones

Keith Bowden* and M. Vahid Horri

Department of Biological and Chemical Sciences, Central Campus, University of Essex,
Wivenhoe Park, Colchester, Essex, UK CO4 3SQ

The rate coefficients for the base-catalysed ring fission of a series of substituted benzocyclobutenediones to give the corresponding 2-formylbenzoic acids have been determined in water at 25.0 and 60.0 °C. The effects of 4-substituents and 4,5-di-substituents on the rates have been correlated using a modified Hammett equation to give a reaction constant, ρ, equal to *ca.* 3.6 at 25.0 °C. The activation parameters have been calculated. The effect of solvent composition on the rates has been studied. The kinetic solvent isotope effect, product composition and enrichment in ^{18}O-enriched water have also been studied. All the evidence indicates a mechanistic pathway which proceeds by rapid reversible addition of hydroxide anion to the dione, followed by intramolecular nucleophilic attack on the second carbonyl group and formation of a carbanionic intermediate.

The chemistry of benzocyclobutenediones (bicyclo[4.2.0]octa-1,3,5-triene-7,8-diones) has been reviewed.[2] The base-catalysed ring fission of benzocyclobutenediones **1** has been shown to give the anions of 2-formylbenzoic acids **2**.[2,3] This reaction is in stark contrast to that same reaction of simple substituted cyclobutenediones which results in the formation of the anions of substituted 2-oxobut-3-enoic acids.[2,4] The former reaction involves fission between the carbonyl carbons, while the latter reaction involves fission between the carbonyl carbon and the olefinic carbon. Both these reactions are also in contrast to the benzilic acid rearrangement, the base-catalysed rearrangement of benzils and other α-diketones, in which there is a 1,2-aryl shift.[5,6] However, benzils can also react with base to give either aryl–carbonyl or carbonyl–carbonyl fission. These appear to be limiting reactions resulting from extremes of substituent effects.[6] Furthermore, a study of the base-catalysed ring fission benzocyclobutenones indicates that cleavage of both the aryl carbon–carbonyl carbon bond and benzyl carbon–carbonyl carbon bond can occur.[7]



1 **2**

a X, Y = H
b X = 4-CH_3, Y = H
c X = 4-OCH_3, Y = H
d X = 4-Cl, Y = H
e X = 4-CH_3, Y = 5-CH_3
f X = 3-CH_3, Y = 6-CH_3
g X = 4-Cl, Y = 5-Cl

The present report describes a study of the kinetics and products of the base-catalysed ring fission of 4-substituted and symmetrically 3,6- and 4,5-di-substituted benzocyclobutenediones. The effects of substitution, solvent composition and solvent kinetic isotope, as well as product enrichment in ^{18}O-enriched water and activation parameters, are discussed and a mechanism is suggested.

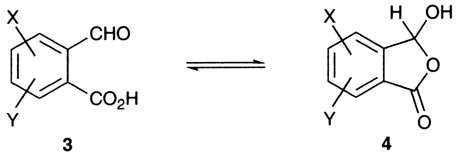
Results

Table 1 Rate coefficients (k_2) for the base-catalysed ring fission of substituted benzocyclobutenediones in water (μ = 0.1 mol dm^{-3})[a,b]

	k_2/dm^3 mol^{-1} s^{-1}		
Substituent(s)	at 25.0 °C	at 60.0 °C	λ/nm[c]
H	283 (490)[d]	1030	302.5
4-CH_3	93.4	400	303
4-OCH_3	37.1	265	325
4-Cl	3750	11 800	305
4,5-$(CH_3)_2$	25.2	89.9	306, 316
3,6-$(CH_3)_2$	0.0733	0.975	331.5
4,5-$(Cl)_2$	38 500	62 500	315

[a] Water containing 0.33% (v/v) DMSO. [b] Rate coefficients were reproducible to ±5%. [c] Wavelengths used to monitor the reactions. [d] In deuterium oxide.

The base-catalysed ring fission of the substituted benzocyclobutene-1,2-diones gives the corresponding 2-formylbenzoic acid anions in quantitative yield. The reaction is of first order in both the diones and hydroxide anion. Rate coefficients for the base-catalysed ring fission of the substituted benzocyclobutene-1,2-diones in water at 25.0 and 60.0 °C are shown in Table 1, as well as that for the parent dione in D_2O. The rates of reaction are relatively very fast and k_2 for the unsubstituted dione at 25 °C in water is 283 dm^3 mol^{-1} s^{-1}. The activation parameters for the reactions of these compounds are shown in Table 2. The effects of increasing concentrations of dimethyl sulfoxide (DMSO) and dioxane on the rate of ring fission are shown in Table 3. The products of ring fission are the anions of the substituted 2-formylbenzoic acids **2**. For the unsubstituted and symmetrically di-substituted diones only one product, **3**/**4**, was isolated, as expected. However, for the 4-substituted diones, the product can be the 4- or 5-substituted 2-formylbenzoic acids,



3 **4**

a X, Y = H
b X = 4-CH_3, Y = 5-CH_3
c X = 3-CH_3, Y = 6-CH_3
d X = 4-Cl, Y = 5-Cl

Table 2 Activation parameters for the base-catalysed ring fission of substituted benzocyclobutenediones in water ($\mu = 0.1$ mol dm^{-3}) at 30 °C^{a,b}

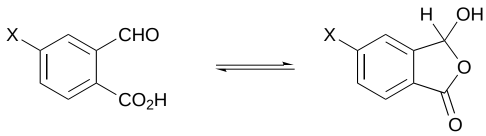
Substituent(s)	$\Delta H^‡$/kcal mol^{-1}	$\Delta S^‡$/cal mol^{-1} K^{-1}
H	6.7	−25
4-CH$_3$	7.6	−24
4-OCH$_3$	10.5	−16
4-Cl	5.9	−23
4,5-(CH$_3$)$_2$	6.6	−30
3,6-(CH$_3$)$_2$	14.0	−17
4,5-(Cl)$_2$	2.1	−30

[a] See Table 1. [b] Values of $\Delta H^‡$ and $\Delta S^‡$ are considered accurate to within ±300 cal mol^{-1} and ±2 cal mol^{-1} K^{-1}, respectively (1 cal = 4.184 J).

Table 3 Rate coefficients (k_2) for the base-catalysed ring fission of benzocyclobutendione in aqueous DMSO and dioxane ($\mu = 0.1$ mol dm^{-3}) at 25.0 °C^{a,b}

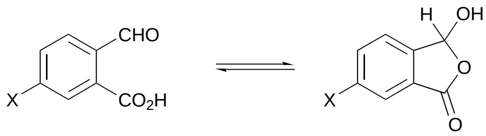
Volume (%) non-aqueous solvent	k_2/dm^3 mol^{-1} s^{-1} DMSO	Dioxane
0	283	283
30	376	165
50	1070	140
60	1610	146
70	3760	138

[a,b] See Table 1.



5 **6**

a X = CH$_3$
b X = OCH$_3$
c X = Cl



7 **8**

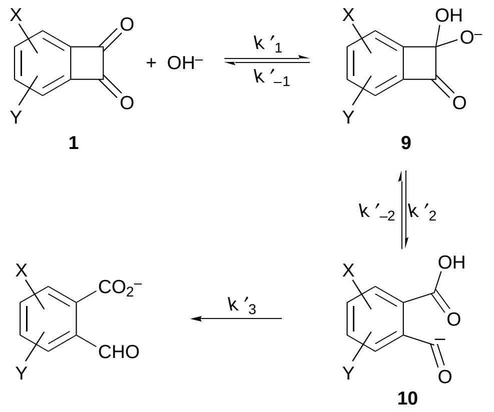
a X = CH$_3$
b X = OCH$_3$
c X = Cl

5/**6** and **7**/**8**, respectively. The 4-methoxy and 4-chloro diones gave only the 5-substituted 2-formylbenzoic acids, **7**/**8**; but the 4-methyl dione gave the 4- and 5-substituted 2-formylbenzoic acids in the ratio 1:3.3.

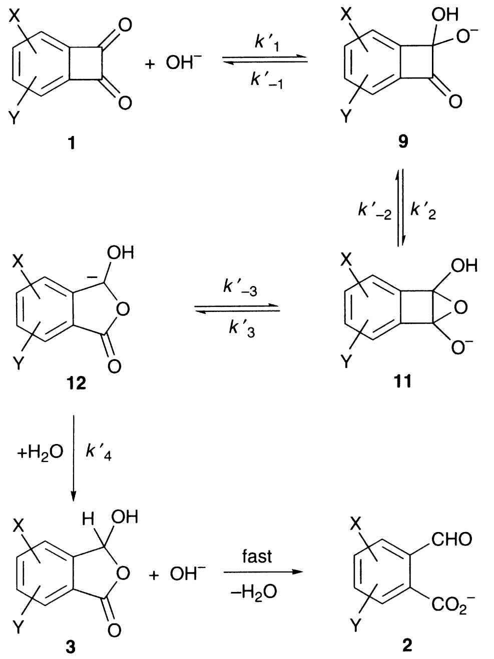
When the base-catalysed ring fission was studied in ^{18}O-enriched water, the product of the ring fission, 2-formylbenzoic acid **3a**/**4a** showed *three* enrichments; whereas the exchange of the latter acid itself studied under identical base-catalysed conditions gave *only* one enrichment.

Discussion

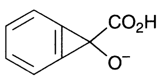
The two likely mechanisms for the base-catalysed ring fission are shown in Schemes 1 and 2. Both schemes involve initial formation of the tetrahedral adduct **9**. The studies of hydrolysis in ^{18}O-enriched water clearly indicate rapid, reversible hydration with equilibration of the adduct. A similar situation exists for benzil in the benzilic acid rearrangement.[8] The solvent kinetic isotope effect, $k_2^{D_2O}/k_2^{H_2O}$, was found to be 1.7$_3$ at 25 °C. This is in agreement with formation of the adduct in a rapid pre-equilibrium, arising from the greater nucleophilicity of OD$^-$ in D$_2$O than OH$^-$ in H$_2$O, *cf.* ref. 9. In Scheme 1, the adduct breaks down with ring fission to give the anion of benzaldehyde **10**. The formation of the adduct **9** will involve ring angle strain, but this will be less severe than in the starting compound **1**. However, the adduct **9** does not break down by fission of the aryl carbon–carbonyl carbon bond. Thus, an energetically preferable route for fission must exist. The collapse of the adduct **9** to a 1-hydroxybenzocyclopropene-1-carboxylic acid anion **13** is blocked because of excessive ring angle strain in the fused bicyclo system. Such a reaction pathway occurs for the related 3,4-diphenylcyclobutene-1,2-diones **14** that do not have a fused ring system.[4] The latter is a benzilic acid-type rearrangement.[5] The efficacy of a leaving group has been considered to be a function of the stability of anion formed.[10] The pK_a of benzaldehyde acting as a Brønsted acid to form **10** has not been measured; but must be very large, *cf.* ref. 11. Aryl carbon–carbonyl carbon bond fission of the adduct **9** would appear to be more favourable. Thus, the route shown in Scheme 1 seems unlikely.



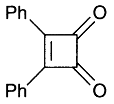
Scheme 1



Scheme 2

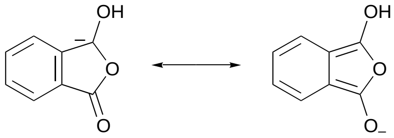


13



14

In Scheme 2, the adduct **9** effects intramolecular nucleophilic attack on the second carbonyl group. Such a process is analogous to the occurrence of neighbouring group participation by a proximate keto– or formyl–carbonyl group in the alkaline hydrolysis of esters.[12] The intermediate **11** is a fused tricyclic system and will be highly strained. This intermediate is a dehydro derivative of the known cyclic hydrate of *o*-phthalaldehyde.[13] However, the carbanionic intermediate **12** could be formed directly from **9**. Furthermore, the intermediate **12** could be stabilised by resonance, as shown in **15** below. This process is analogous to the formation of a carbanion in the reaction of benzil with cyanide anion,[14] *i.e.* the benzoin condensation.



15

Substituent effects

Non-proximate substituent effects in aryl systems can be correlated by use of the Hammett equation (1).[15] The rates of the

$$\log (k/k_o) = \rho\sigma \qquad (1)$$

base-catalysed fission of the 4-substituted benzocyclobutenes-1,2-diones can only be successfully correlated using σ_p as shown in Table 4. The symmetrical 4,5-disubstituent effect can be correlated almost as successfully using $2\sigma_p$ or $\sigma_m + \sigma_p$ as shown in Table 4. The three 4-mono-substituted substrates, using σ_p values, can be combined with the 4,5-di-substituted substrates, using either $2\sigma_p$ or $\sigma_m + \sigma_p$, to give very good linear relations, as shown in Table 4. The ρ value obtained is *ca.* 3.8 at 25 °C. Other correlations have been attempted using a statistical correction for the rate of 0.5 for the symmetrical di-substituted substrates or σ_m for the 4-substituents. These all gave very much poorer correlations. The use of σ_p for the mono-substituents and $2\sigma_p$ for the di-substituents was found in our studies of the reactivity of similarly substituted indane-1,2,3-triones[16] and 2,2-dihydroxyindane-1,3-diones.[1] A possible explanation for this behaviour has been discussed.[16] Furthermore, Jaffé-type treatments[17] for the mono-substituted substrates were not justified because results were only available for three mono-substituted substrates, as well as for the parent compound. It is clear that the observed ρ value is significantly greater than observed for the equilibria addition of hydroxide anion to benzaldehydes at 25 °C in water (2.24 or 2.76),[18] the base-catalysed rearrangement of symmetrically disubstituted benzils at 30 °C in 70% (v/v) aqueous DMSO (2.8)[6] and the alkaline hydrolysis of ethyl benzoates at 25 °C in water (1.33).[19]

The 3,6-dimethyl substrate reacts very much slower than 4,5-dimethyl compound. Steric retardation of the process appears to be the cause. Proximate substituent effects are more difficult to evaluate quantitatively. The ratio of the rate coefficient for the 3,6- to that of the 4,5-dimethyl substrate is *ca.* 2.9×10^{-3} at 25 °C and can be considered to be a measure of the steric effect alone. This effect is much greater than that of an *ortho*-methyl substituent on the alkaline hydrolysis of alkyl benzoates.[20] The ratio of the rate coefficient for the alkaline hydrolysis of the 2-dimethylaminoethyl 2-methylbenzoate to that benzoate of the 4-methylbenzoate is *ca.* 0.27 at 37 °C in water.[21] It seems very likely that, in the present study, both the formation of the adduct and the fission process are significantly more crowded than the initial state. Formation of the carbonionic intermediate **12** will be particularly demanding of space and thus strongly by steric bulk effect of the 3,6-dimethyl groups.

Product studies

A significant difference in the mechanistic Schemes 1 and 2 is that the formyl group forms on the carbonyl group not suffering initial attack by hydroxide anion in Scheme 1, whereas, in Scheme 2, the formyl group forms on the carbonyl group suffering initial attack. However, the hydroxy groups on **11** could rapidly equilibriate by a prototropic shift. As such, the product studies do not allow differentiation between Scheme 1 and 2.

Solvent effects

The effects of solvent on the rates of base-catalysed fission of the parent dione are shown in Table 3. The present results can be compared with the effects of solvent composition on the base-catalysed rearrangement of benzil[6] and the alkaline hydrolysis of methyl benzoate.[22] The rates of reaction increase markedly with increasing DMSO content which is considered to arise mainly from the increased activity of hydroxide. DMSO is also known to stabilise charge delocalised structures. However, the effect of increasing dioxane content on the rates of similar reactions has been found to be comparatively minor, but appears to be discriminating with both increases and decreases in rates observed.[22] The behaviour observed for the ring-fission of benzocyclobutene-1,2-dione is very similar to that of the alkaline hydrolysis of methyl benzoate, particularly the modest decrease in rate with increasing dioxane content. This evidence appears to favour the occurrence of charge-localised intermediates like **11**, rather than a charge-delocalised intermediate like **12**.

Mechanistic pathway

The evidence indicates that the reaction proceeds by the pathway shown in Scheme 2. The rate-determining step could be either the formation of the carbanionic intermediate **12**, following the pre-equilibrium formation of the adduct **9** and the oxirane **11**, or the formation of the oxirane **11**, following the pre-equilibrium formation of the adduct **9**.

Experimental

Materials

Benzocyclobutene-1,2-dione itself was prepared by two methods. The first was by the method of Cava *et al.*[23] in which 1,1,2,2-tetrabromobenzocyclobutene was reacted with silver trifluoroacetate in aqueous acetonitrile. The second was the general method developed by McOmie's group.[24] Cyclic hydrazines, 2,3-dihydrophthalazines, are prepared from phthalic anhydrides and oxidized in the presence of anthracene to give the corresponding Diels–Alder adducts. The latter were submitted to vacuum pyrolysis to give the benzocyclobutene-1,2-diones. Thus, the unsubstituted, 4-methoxy, 4-chloro, 3,6- and 4,5-dimethyl and 4,5-dichlorobenzocyclobutene-1,2-diones were prepared.[24] The purity of these compounds was monitored by IR and ^{1}H and ^{13}C NMR spectroscopy, as well as by elemental analysis. Their mps after repeated recrystallization and

Table 4 Hammett reaction constants (ρ) for the base-catalysed ring fission of the substituted benzocyclobutenediones in water ($\mu = 0.1$ mol dm^{-3})[a]

	ρ	$\log k_o$	r	s	n
4-Substituents with σ_p	3.937	2.598	0.994	0.32	4
4,5-Di-substituents with ($\sigma_m + \sigma_p$)	3.745	2.363	0.999	0.18	3
4,5-Di-substituents with $2\sigma_p$	4.017	2.652	0.994	0.43	3
4-Substituents and 4,5-di-substituents with σ_p and ($\sigma_m + \sigma_p$)	3.675	2.500	0.992	0.24	6
4-Substituents and 4,5-di-substituents with σ_p and $2\sigma_p$	3.912	2.501	0.987	0.31	6

[a] *r* is the correlation coefficient, *s* the standard deviation and *n* the number of substituents studied.

drying under reduced pressure (P_2O_5), were in agreement with literature values,[24] except for the previously unreported 4-methyl compound which was prepared by the same route.

Anthracene adduct of 6-methylphthalazine-1,4-dione

This was prepared by the method of Gould *et al.*[24] from the corresponding dione[25] and was recrystallised from toluene as colourless needles, mp 300–303 °C (decomp.) (Found: C, 78.2; H, 4.4; N, 7.5. $C_{23}H_{16}N_2O_2$ requires: C, 78.4; H, 4.6; N, 7.9%).

4-Methylbenzocyclobutene-1,2-dione

The pyrolysis[24] of the anthracene adduct described above gave the dione which was recrystallised from dichloromethane as yellow needles, mp 110–111 °C (Found: C, 74.0; H, 4.1. $C_9H_6O_2$ requires C, 73.8; H, 4.0%).

The solvents for the kinetic studies were purified as described previously.[26]

Measurements

Rate coefficients for the base catalysed ring fission of the substituted benzocyclobutenediones were determined spectrophotometrically by use of a Perkin-Elmer lambda 5 UV–VIS spectrometer. A Haake thermostatted water circulatory bath was used to control the temperature of the cell to ± 0.05 °C. The reactions were followed at the wavelengths shown in Table 1. The procedure was that described previously.[27] Buffers were prepared from AnalaR grade chemicals and distilled water (freshly boiled and cooled under N_2 bubbling). The ionic strength was maintained at 0.1 mol dm^{-3} with sodium chloride. The pH of the buffers solutions was measured with a Pye-Unicam model PW9409 direct reading pH meter with glass combination electrode, calibrated with standard buffers at 25 °C. Buffer solution pH was measured using a thermostatted glass vessel at the reaction temperatures. The pD values were obtained by adding 0.40 to the pH meter readings.[28] Both phosphate and borate buffers (pH 7.4 to 9.2 at 25 °C) were used and no buffer catalysis was observed.

Product studies

The products of base-catalysed ring fission of the substituted benzocyclobutenediones were found to be the anions of the corresponding substituted 2-formylbenzoic acids. For the parent dione, the product was isolated in quantitative yield and was confirmed spectrophotometrically by comparison of the spectrum of the acid in base with that of the reaction product. In general, the products of the kinetic runs were isolated by acidification and extraction with diethyl ether. The products were recrystallised from methanol and had mps in good agreement with literature values.[29] The extracts were also treated with diazomethane in diethyl ether. The products were then isolated and examined by ^{1}H and ^{13}C NMR spectroscopy, as well as mass spectrometery and GLC. The structures of the products of the ring-fission of the mono-substituted benzocyclobutene-1,2-diones were confirmed or established by their ^{1}H and ^{13}C NMR spectra, but the quantitative evaluation of the product ratio for the 4-methyl substrate was completed by GLC.

Hydrolysis using ^{18}O-enriched water

The base-catalysed fission of benzocyclobutene-1,2-dione was studied by use of ^{18}O-enriched water (4.5 atom%). The reaction was under normal kinetic conditions in excess of base for approximately ten 'half-lives' of the dione. After neutralisation and extraction with diethyl ether, the acid was esterified with diazomethane in diethyl ether. The chain (normal) methyl ester of 2-formylbenzoic acid was isolated and purified by flash distillation at reduced pressure. The same procedure was followed using 2-formylbenzoic acid itself as substrate. The mass spectra of the samples and control (using dione and ordinary water) were recorded on an AEI MS12 spectrometer. The enrichment was calculated from the peak areas due to M^+ and $M^+ + 2$.

References

1 K. Bowden and S. Rumpal, Part 23, *J. Chem. Soc., Perkin Trans. 2*, 1997, 983.
2 A. H. Schmidt and W. Ried, *Synthesis*, 1978, 649.
3 M. P. Cava and D. R. Napier, *J. Am. Chem. Soc.*, 1957, **79**, 3606.
4 A. Al-Najjar, K. Bowden and M. V. Horri, *J. Chem. Soc., Perkin Trans. 2*, 1997, 993.
5 S. Selman and J. F. Eastham, *Quart. Rev.*, 1960, **14**, 221.
6 K. Bowden and K. D. Williams, *J. Chem. Soc., Perkin Trans. 2*, 1994, 77.
7 J. C. Bradley and T. Durst, *Can. J. Chem.*, 1995, **73**, 1660.
8 I. Roberts and H. C. Urey, *J. Am. Chem. Soc.*, 1938, **60**, 880.
9 J. Hine and H. W. Haworth, *J. Am. Chem. Soc.*, 1958, **80**, 2274.
10 S. L. Johnson, *Adv. Phys. Org. Chem.*, 1967, **5**, 237.
11 J. Chandrasekhar, J. G. Andrade and P. v. R. Schleyer, *J. Am. Chem. Soc.*, 1981, **103**, 5612; J. C. Kleingeld and N. M. M. Nibbering, *Tetrahedron*, 1984, **40**, 2789.
12 K. Bowden, *Adv. Phys. Org. Chem.*, 1993, **28**, 171.
13 K. Bowden, F. A. El-Kaissi and N. S. Nadvi, *J. Chem. Soc., Perkin Trans. 2*, 1977, 1799.
14 J. P. Kuebrich and R. L. Schowen, *J. Am. Chem. Soc.*, 1971, **93**, 1220; and references therein.
15 C. D. Johnson, *The Hammett Equation*, Cambridge University Press, Cambridge, 1973.
16 K. Bowden and S. Rumpal, *J. Chem. Res.*, 1997, 35 (*S*); 0355 (*M*).
17 H. H. Jaffé, *J. Am. Chem. Soc.*, 1954, **76**, 4261; A. R. Fersht and A. J. Kirby, *J. Am. Chem. Soc.*, 1967, **89**, 4853.
18 P. Greenzaid, *J. Org. Chem.*, 1973, **38**, 3164; W. J. Bover and P. Zuman, *J. Chem. Soc., Perkin Trans. 2*, 1973, 786.
19 M. Hojo, M. Utaka and Z. Yoshida, *Tetrahedron Lett.*, 1966, 19.
20 N. B. Chapman, J. Shorter and J. H. P. Utley, *J. Chem. Soc.*, 1963, 1291.
21 J. J. Zimmerman and J. E. Goyan, *J. Med. Chem.*, 1970, **13**, 492.
22 K. Bowden and M. J. Price, *J. Chem. Soc.* (*B*), 1971, 1748.
23 M. P. Cava, D. R. Napier and R. J. Pohl, *J. Am. Chem. Soc.*, 1963, **85**, 2076.
24 K. J. Gould, N. P. Hacker, J. F. W. McOmie and D. H. Perry, *J. Chem. Soc., Perkin Trans. 1*, 1980, 1834; O. Abou-Teim, R. B. Jansen, J. F. W. McOmie and D. H. Perry, *J. Chem. Soc., Perkin Trans. 1*, 1980, 1841.
25 E. H. White, D. F. Roswell and O. C. Zafiriou, *J. Org. Chem.*, 1962, **34**, 2462.
26 D. D. Perrin and W. L. F. Amarego, *Purification of Laboratory Chemicals*, Pergamon Press, Oxford, 3rd edn., 1988.
27 K. Bowden and A. M. Last, *J. Chem. Soc., Perkin Trans. 2*, 1973, 345.
28 L. Pentz and E. R. Thornton, *J. Am. Chem. Soc*, 1967, **89**, 6931; P. K. Glasoe and F. A. Long, *J. Phys. Chem.*, 1960, **64**, 188; B. Zerner and M. L. Bender, *J. Am. Chem. Soc.*, 1961, **83**, 2267.
29 C. Donati, R. H. Prager and B. Weber, *Aust. J. Chem.*, 1989, **42**, 787; M. D. Gaul, G. A. Junk and H. J. Svec, *Environ. Sci. Technol.*, 1987, **21**, 777 (see *Chem. Abstr.*, 1987, **107**, 77406x); K. Krohn, H. Rieger, E. Broser, P. Schiess, S. Chen and T. Strubin, *Liebigs Ann. Chem.*, 1988, 943; and references therein.

Paper 6/06310A
Received 13*th September* 1996
Accepted 23*rd December* 1996