Acid-catalysed Hydrolysis and Protonation Behaviour of *N*-Arylpropane-1,3-sultams

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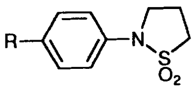
The acid-catalysed hydrolyses of some *N*-(*para*-substituted phenyl)propane-1,3-sultams have been studied in aqueous acidic solutions. The rate maxima observed are shown to be consistent with an A-2 mechanism in which extensive protonation of the substrate occurs. Values of pK_{BH^+} for the sultams have been determined.

Whilst the acid-catalysed hydrolysis of sulfonamides has been studied in some detail because of its relevance to the Hinsberg method for the separation of amines, very few studies of the hydrolyses of sultams (the corresponding cyclic sulfonamides) have been recorded.[1] Erman and Kretschmar reported that a number of five-membered *N*-alkyl sultams undergo hydrolysis in methanolic HCl or HBr or in glacial acetic acid.[2] They suggested that acid catalysed cleavage of the ring proceeds *via* an A-1 mechanism by analogy to the mechanism proposed earlier for the acid-catalysed hydrolysis of sulfonamides[3] although Klamann and his co-workers subsequently changed this view.[4] In order to clarify the situation for the hydrolysis of sultams, we now report a detailed study of the protonation behaviour and kinetics of hydrolysis of a series of five-membered *N*-arylpropane-1,3-sultams **1** in aqueous solutions of mineral acids.



1 R = **a**, MeO; **b**, Me; **c**, H; **d**, Cl; **e**, NO$_2$

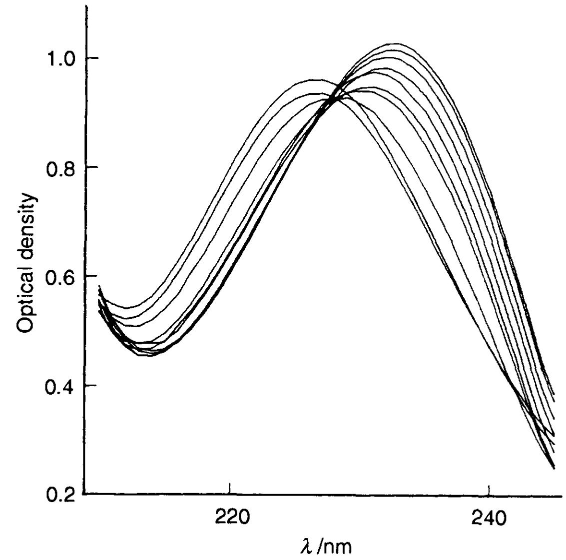


Fig. 1 Absorbance of the sultam **1b** as a function of sulfuric acid concentration. Solvent (top to bottom at right-hand margin): water, sulfuric acid 6.0, 8.0, 10.5, 11.0, 11.5, 12.5, 13.0, 13.5, 14.0 mol dm^{-3}.

Experimental

Materials.—Sultams were prepared *via* the corresponding sultaines as described by Erman and Kretschmar.[2] Sultam **1a** had m.p. 122–124 °C (white needles from methanol) (Found: C, 52.9; H, 5.8; N, 6.2. Calc. for $C_{10}H_{13}NO_3S$: C, 53.0; H, 6.0; N, 6.1%); ν_{max}/cm^{-1} 1130 and 1290. Sultam **1b** had m.p. 91–92 °C (lit.,[2] 91.4–92.0°); sultam **1c** had m.p. 120–121 °C (lit.,[2] 120–121 °C); sultam **1d** had m.p. 109–111 °C (from acetone) (Found, C,46.7;H,4.4.;N,6.0.Calc.for$C_9H_{10}ClNO_2S$;C,46.8;H,4.5;N, 6.0%), ν_{max}/cm^{-1} 1130 and 1300; sultam **1e** had m.p. 150–152 °C (lit.,[2] 152–154 °C).

Protonation Equilibria Measurements.—The absorbances at 1 nm intervals in the range 206–320 nm were recorded at 25 ± 0.2 °C for the sultams in both water and various concentrations of sulfuric acid in the concentration range 6–18 mol dm^{-3}. All spectra were recorded for ten minutes at one or two minute time intervals and the absorptions extrapolated to produce 'zero time' spectra.

Analysis of Spectra.—The spectra of all the sultams studied showed a large medium effect with no simple isobestic point as illustrated for *N*-*p*-tolylpropane-1,3-sultam in Fig. 1. In addition to this medium effect, however, at the higher acidities there is evidence of a further reaction whose effect on the spectra could be reduced but not eliminated by obtaining zero time spectra. Hence it was not possible to directly determine values of ε_{BH^+} which are needed for the calculation of log *I* values and the principal methods used to correct for medium effects.[5–7]

As one approach to the determination of pK_{BH^+} values, we have adopted the titration curve analysis (TCA) method described by Zalewski and Dunn.[8] The absorbance A_i at any part of the titration curve (a plot of absorbance *A* versus H_o) can be represented by eqn. (1); where $[C]$ is the total concentration of base, ε_B and ε_{BH^+} the extinction coefficients of the species B and BH$^+$ at a given wavelength. The values of ε_B, ε_{BH^+} and K_{BH^+} are disposable parameters which were determined by a least-squares computer fit of the data to eqn. (1). This procedure uses values of A_i in the region $pK_{BH^+} \pm 2H_o$ units and leads to calculated values of ε_B and ε_{BH^+} which are average values for the acidity range used. Values of pK_{BH^+} obtained by this method (Method A) are summarised for all the sultams studied in Tables 1 and 2.

$$A_i = [C]\frac{(\varepsilon_B K_{BH^+} + h_o\varepsilon_{BH^+})}{(K_{BH^+} + h_o)} \qquad (1)$$

The values of ε_B and ε_{BH^+} were also used to calculate A_B and A_{BH^+}. The ionization ratio *I* and alternative values of pK_{BH^+} (Method B) were calculated from eqn. (2) and the

Table 1 Spectral and pK_{BH^+} data for *N*-(*p*-substituted phenyl)propane-1,3-sultams[a,b]

Substituent	λ_B/nm	ε_B	ε_{BH^+}	λ_{BH^+}/nm	ε_B	ε_{BH^+}	pK_{BH^+}
MeO	233	12 729	10 846	—	—	—	−5.97
Me	235	10 594	7 659	223	8 352	10 225	−5.95
H	233	9 110	2 758	219	5 950	7 401	−6.52
Cl	235	14 204	11 698	225	8 238	11 653	−6.82
NO_2	323	8 807	5 246	258	1 324	4 952	−8.30

[a] Zalewski–Dunn method[8] at λ_B. [b] Units of ε, $dm^3\ cm^{-1}\ mol^{-1}$.

Table 2 Summary of pK_{BH^+} values for *N*-(*p*-substituted phenyl)propane-1,3-sultams

		Method A	Method B		Method C		Method D[b,c]	
Substituent	$(H_0)_{1/2}$[a]	pK_{BH^+}	pK_{BH^+}	d log I/dH_0	pK_{BH^+}	d log I/d H_0	pK_{BH^+}	m^*
MeO	−5.95	−5.97	−6.23	1.04	−6.59	0.97	−6.03	0.926
Me	−5.99	−5.95	−5.99	1.01	−6.20	1.01	−5.89	0.992
H	−6.57	−6.52	−6.66	1.00	−6.57	1.02	−6.19	0.969
Cl	−7.00	−6.82	−6.97	1.01	−6.81	1.02	−6.68	0.965
NO_2	−8.62	−8.30	−8.67	1.14	−8.76	0.80	−8.16	0.883

[a] H_0 Value corresponding to half-protonation. [b] Derived from CVA reconstituted spectra using eqn. (5). [c] Log C_{H^+} and X values from ref. 13.

Table 3 Hydrolysis of the sultam **1b** at different temperatures

Acid concentration ([H^+]/mol dm^{-3})		Rate (10^2k_1/min^{-1})				
		45.0 °C	50.0 °C	55.0 °C	60.0 °C	65.0 °C
H_2SO_4	4.00	0.82	1.32	—	3.14	4.98
H_2SO_4	8.00	8.11	12.1	18.3	27.8	—
HCl	4.00	0.42	0.66	1.07	1.64	—
HCl	8.00	1.16	1.85	2.81	3.98	6.10
$HClO_4$	4.00	—	0.65	0.99	1.54	2.20
$HClO_4$	8.00	3.89	—	8.86	12.4	17.9

$$I = \frac{(A_B - A)}{(A - A_{BH^+})} \qquad (2)$$

standard Hammett relationship [eqn. (3)].

$$\log I = -H_0 + pK_{BH^+} \qquad (3)$$

We have also used the recently described one-step computer method of combining principal component (characteristic vector) analysis of the spectra of sultams at various acidities with titration curve analysis to provide values of pK_{BH^+}.[9,10] Principal component analysis can be used to obtain an abstract solution where all data are expressed as linear sums of product terms. Thus any absorbance $A_{n,p}$ could be represented by eqn. (4); in which C represents the principal component for

$$A_{n.p} = A_{n,p} + C_{1,p}L_{n,1} + C_{2,p}L_{n,2} \qquad (4)$$

wavelength p, and L represents the loading for the nth spectrum, numerator 1 and 2 describe first and second components and finally p and n describe certain wavelengths and acidities, respectively. A is a value of mean absorbance at a given wavelength.

Principal component analysis procedures applied to the digitalised set of spectra of the sultams indicate one principal component accounting for more than 93% of total data variability and two principal components accounting for approximately 99%. The first principal component is associated predominately with protonation and the second reflects all side reactions (*e.g.* hydrogen bonding and solvation). The principle of highest dissimilarity of real spectra was used in converting the abstract mathematical solutions into reconstituted spectra of B and BH^+.[11,12] Ionization ratios and values of pK_{BH^+} calculated using eqn. (2) and either the Hammett Acidity Function Method (HAFM) [eqn. (3)] or the Excess Acidity Function Method[13] (EAM) [eqn. (5)] are summarised in Table 2 (Methods C and D respectively).

$$\log I - \log C_{H^+} = m^*X + pK_{BH^+} \qquad (5)$$

Kinetic Measurements.—The rates of hydrolysis of sultams were determined spectrophotometrically by following the decrease in their characteristic absorbtion spectra as follows: **1a**, 231; **1b**, 230; **1c**, 230; **1d**, 238 and **1e**, 330 nm. A Perkin Elmer Model 554 spectrometer fitted with a thermostatted cell block (± 0.03 °C) was used. Good isosbestic points were obtained and the final absorbances corresponded to the expected aminosulfonic acid products. Reactions were followed to at least three half-lives and gave good first-order plots. Values of the first-order rate-coefficients k_1 were calculated using the standard equation.

Discussion

Protonation Behaviour.—Values of pK_{BH^+} for the sultams studied are summarised in Table 2 together with the values of H_0 for half-protonation [$(H_0)_{1/2}$]. Consistently lower values of pK_{BH^+} estimated by the EAM procedure (Method D) were obtained compared to those estimated by the HAFM procedure including that derived *via* principal component analysis (Methods A–C). Similar differences have been observed for a variety of other very weak bases.[14–16] Such differences were originally attributed by Cox to the extrapolative nature of the EAM approach.[17] More recently Johnson and Stratton have suggested that the origin of the difference may lie in the unreliable behaviour of the Excess Acidity Scale X in regions of high acidity.[14]

With the exception of compound **1a**—the *N*-*p*-methoxy sultam—the variation of pK_{BH^+} with the series of sultams parallels the electronic properties of the substituent. As shown by the $(H_0)_{1/2}$ values the base strengths of sultams **1a** and **1b** are very similar. The value of $\lambda_{BH^+} - \lambda_B$ is very small for compound **1a** and this must throw some doubt on the accuracy of the spectroscopically determined value of pK_{BH^+} for this

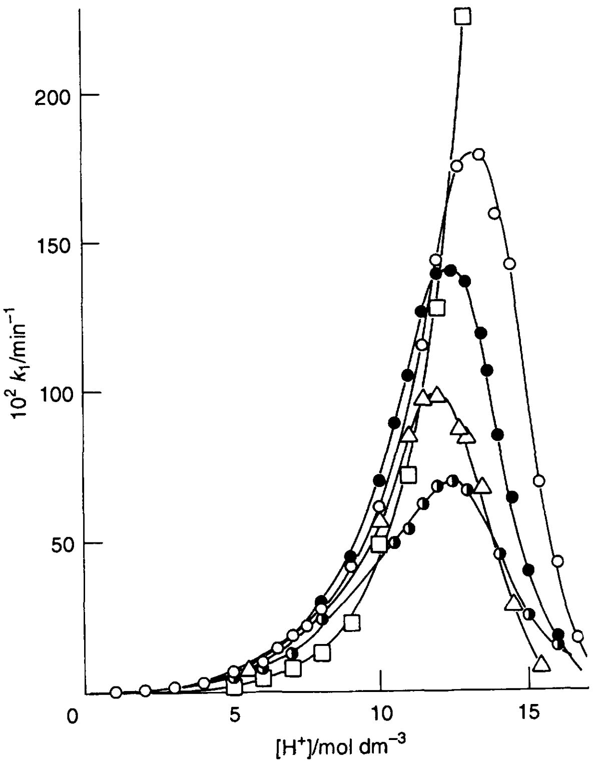


Fig. 2 Hydrolysis of sultams in aqueous sulfuric acid; □, **1e**; ○, **1d**; ●, **1c**; △, **1b**; ◑, **1a**

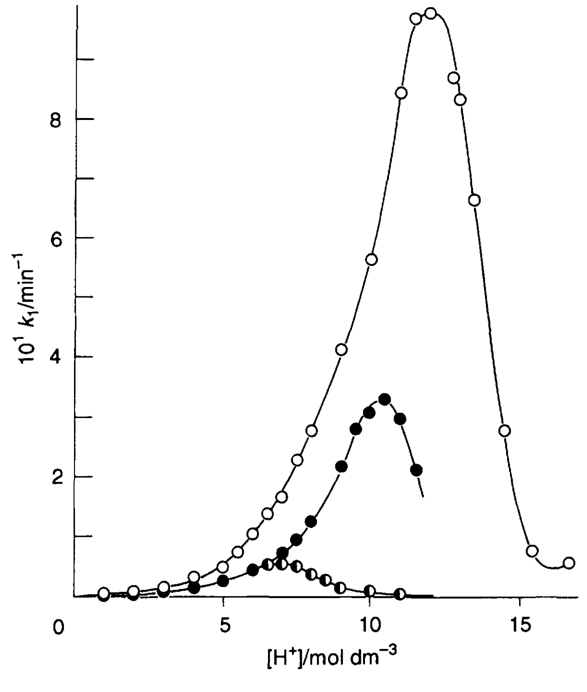
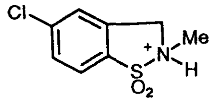


Fig. 3 Hydrolysis of **1b** in aqueous acidic solutions; ○, H_2SO_4; ●, $HClO_4$; ◐, HCl

sultam. A good straight line correlation (*r* 0.995) was obtained between values of $(H_0)_{1/2}$ and sigma suggesting that the former provide quite a good estimate of the relative basicities of sultams. Balon and his co-workers have recently observed a similar good correlation between $(H_I)_{1/2}$ values and the basicities of a series of substituted indoles.[18]

The general range of values of pK_{BH^+} for sultams obtained in the present study are consistent with the observations of King and his co-workers who reported an $(H_0)_{1/2}$ value of −4.0 for *N*-methylpropane-1,3-sultam and that *N*-arylsulfonamides were much less basic than the corresponding *N*-alkyl-system.[19,20]

NMR studies in fluorosulfonic acid have unequivocally established that protonation of the sultam *N*-methyl-5-chloro-1,2-benzisothiazoline-1,1-dioxide occurs on nitrogen and that its conjugate acid has the structure **2**.[21]



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The values of m^* obtained for the sultams **1a–e** obtained by the EAM fall into the range typically associated with protonation of a nitrogen base. The significantly lower value of m^* (0.926) for the methoxy system (**1a**) compared to that of the methyl system (**1b**) (0.992), reflecting the higher solvation requirement for the protonation of the former, may also account for the unexpected inversion of the relative pK_{BH^+} values. The need for two parameters to describe protonation equilibria of other weak bases has been recently proposed.[22]

Rate Dependence on Acidity.—Very similar kinetic behaviour was observed for the hydrolyses of sultams **1a–d** in sulfuric acid (Fig. 2). All show a clearly defined rate maximum. Because of its high reactivity, the hydrolysis of 4-nitrophenylpropane-1,3-sultam was studied only up to 12 mol dm^{-3} H_2SO_4 below which no maximum could be observed. A more detailed study of the hydrolyses of **1b** and **1d** revealed a rate maximum also for perchloric and hydrochloric acids (Fig. 3).

Similar rate maxima have been observed in the hydrolyses of other compounds *e.g.* amides[23] and hydroxamic acids[24] and were considered to arise from an A-2 reaction in which extensive protonation of the substrate occurs in regions of acidity in which the activity of water is falling. Such an explanation for the hydrolysis of sultams is supported by values of the kinetic deuterium solvent isotope effect (k^{D_2O}/k^{H_2O}) which are 1.37 and 0.51 for the hydrolysis of the sultam **1b** in 6.00 and 14.5 mol dm^{-3} sulfuric acid respectively. A similar fall in the kinetic solvent isotopic effect with increasing acidity observed for the hydrolysis of amides has been discussed by Bell[25] and by Wiberg[26] in terms of the increasing extent of protonation of the substrate and the weaker nucleophilic reactivity of D_2O compared to H_2O.

The kinetic data was analysed by the Excess Acidity treatment of Cox and Yates.[27] Their relationship for mainly unprotonated substrates [eqn. (6)] was used at acidities

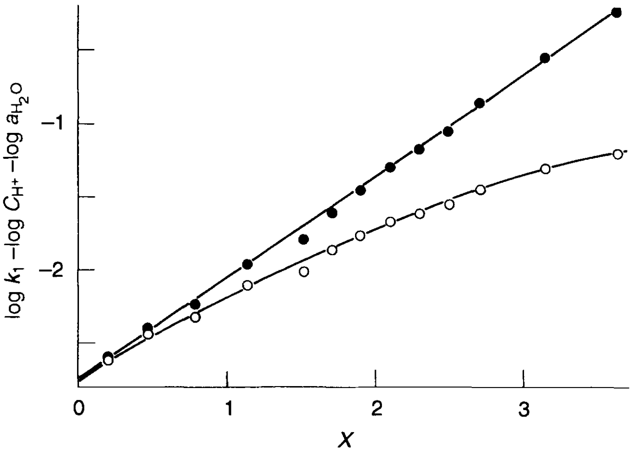


Fig. 4 Excess acidity plot for hydrolysis of the sultam **1b** in aqueous sulfuric acid; ○, no H_2O; ●, 1 H_2O

Table 4 Excess Acidity treatment of the hydrolysis of sultams **1a–e** in aqueous sulfuric acid

Sultam	Substituent	$m^*m^‡$	$\log(k_0/K_{SH^+})$	N^a	$m^‡$
1a	MeO	0.682 ± 0.011	−2.963	10	0.736
1b	Me	0.695 ± 0.009	−2.876	13	0.700
1c	H	0.706 ± 0.009	−2.849	11	0.728
1d	Cl	0.695 ± 0.009	−2.856	12	0.720
1e	NO_2	0.776 ± 0.016	−3.390	9	0.878

[a] Number of data points.

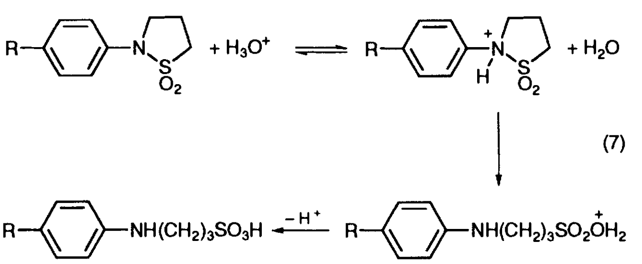
Table 5 Arrhenius parameters for the hydrolysis of the sultam **1b** in different acids

Acid	$[H^+]$/mol dm^{-3}	$\Delta H^‡$/kJ mol^{-1}	$-\Delta S^‡$/J K^{-1} mol^{-1}
H_2SO_4	4.00	76.4 ± 1.3	47.0 ± 3.8
H_2SO_4	8.00	68.0 ± 1.3	53.3 ± 3.8
HCl	4.00	81.5 ± 0.8	35.6 ± 2.5
HCl	10.00	70.6 ± 1.3	59.6 ± 4.6
$HClO_4$	4.00	73.1 ± 1.3	63.0 ± 3.4
$HClO_4$	10.00	66.8 ± 1.3	63.0 ± 4.2

sufficiently low to ensure that any correction introduced by the protonation term was negligible.

$$\log k_1 - \log C_S/(C_S + C_{SH^+}) - \log C_{H^+} = m^*m^‡X + \log a_{Nu} + \log(+k_0/K_{SH^+}) \quad (6)$$

A plot of $\log k_1 - \log C_{H^+}$ *versus* X is shown in Fig. 4 for the hydrolysis of **1b**. The resulting curved plot is typical of an A-2 reaction involving water in the rate-determining transition state. Subtraction of $\log a_{H_2O}$ from the left-hand side of eqn. (6) gives good straight lines in all cases from which values of $m^‡$ and k_0 were calculated. (Table 4) These observations are consistent with the A-2 mechanism shown in eqn. (7).



(7)

The UV spectra of the hydrolysis products were identical to those of the corresponding aminosulfonic acids throughout the range of concentrations of mineral acids studied. The bimolecular mechanism proposed is further supported by the values of the entropies of activation which lie in the range normally associated with an associative mechanism.[28] A detailed study of these values for the hydrolysis of the sultam **1b** (Table 5) shows that they are essentially independent of the acid catalyst used.

References

1 *cf.* S. Searles and S. Nukina, *Chem. Rev.*, 1959, **59**, 1077.
2 W. F. Erman and H. C. Kretschmar, *J. Am. Chem. Soc.*, 1961, **26**, 4841.
3 D. Klamann and G. Hofbauer, *Liebigs Ann. Chem.*, 1953, **581**, 182.
4 D. Klamann and E. Fabienka, *Chem. Ber.*, 1959, 712.
5 L. A. Flexer, L. P. Hammett and A. Dingwall, *J. Am. Chem. Soc.*, 1935, **57**, 2103.
6 R. Stewart and M. Granger, *Can. J. Chem.*, 1961, **39**, 2508.
7 *cf.* T. Davis and T. A. Geissman, *J. Am. Chem. Soc.*, 1959, **76**, 3507.
8 R. I. Zalewski and G. E. Dunn, *Can. J. Chem.*, 1969, **47**, 2263.
9 R. I. Zalewski, *J. Chem. Soc., Perkin Trans. 2*, 1979, 1637.
10 R. I. Zalewski and S. Garibaldi, *J. Chem. Soc., Perkin Trans. 2*, 1988, 113.
11 *cf.* E. R. Malinovsky and D. G. Hoovey, in *Factor Analysis in Chemistry*, Wiley, New York, 1980, Ch. 7.
12 R. I. Zalewski, unpublished work.
13 R. A. Cox and K. Yates, *J. Am. Chem. Soc.*, 1978, **100**, 3861.
14 C. D. Johnson and B. Stratton, *J. Org. Chem.*, 1986, **51**, 4100.
15 C. D. Johnson and B. Stratton, *J. Org. Chem.*, 1987, **52**, 4798.
16 R. Noyo, M. Gruttadauria, D. Spinelli and G. Consiglio, *J. Chem. Soc., Perkin Trans. 2*, 1990, 1975.
17 Private communication quoted in ref. 14.
18 M. Balon, J. Hidalgo, P. Guardado, M. A. Munoz and C. Carmona. *J. Chem. Soc., Perkin Trans.* 2, 1993, 91.
19 J. F. King, R. Rathore, J. H. Li and D. F. Klassen, unpublished results reported in ref. 20.
20 J. F. King, in *The Chemistry of Sulphonic Acids, Esters and their Derivatives*, ed. S. Patai, Wiley, Chichester, 1991, Ch. 6.
21 F. M. Menger and L. Mandell, *J. Am. Chem. Soc.*, 1967, **89**, 4424.
22 A. Bagno, G. Scorrano and R. A. More O'Ferrall, *Rev. Chem. Intermed.*, 1987, **7**, 313.
23 J. T. Edward and S. C. R. Meacork, *J. Chem. Soc.*, 1957, 2000.
24 A. J. Buglass, K. Hudson and J. G. Tillett, *J. Chem. Soc. (B)*, 1971, 123.
25 R. P. Bell, *Acid-Base Catalysis*, Oxford University Press, London, 1941.
26 K. R. Wiberg, *Chem. Rev.*, 1955, **55**, 713.
27 R. A. Cox and K. Yates, *Can. J. Chem.*, 1979, **57**, 2944.
28 L. L. Schaleger and F. A. Long, *Adv. Phys. Org. Chem.*, 1963, **1**, 1.

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