

ipso-Attack in the Nitration of Aromatic Amines. Part 4.¹ Rate Profiles and Isotope Effects for the Rearrangements of *ipso*-Intermediates

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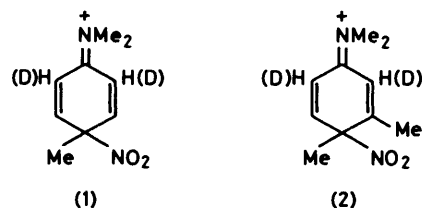
The conversion of the *ipso*-intermediates (1) and (2) into the corresponding *o*-nitroamines in aqueous sulphuric acid at 0 °C has been followed by u.v. spectrometry. The reactions are first-order and the form of the rate profile shows that either the 1,3-rearrangement of the nitro-group or the subsequent proton loss can be rate-determining depending on the acidity. This is confirmed by the isotope effect (k_H/k_D) which [for intermediate (1)] varies from 1.0 to 4.8 over the range 25.0–75.9% sulphuric acid. The rate of the 1,3-rearrangement is not very sensitive to the acidity but the rate of the subsequent proton loss varies with $h_0^{-0.7}$. A *meta*-methyl group slightly stabilises both the *ipso*-intermediate and the Wheland intermediate (3) relative to the transition state for the 1,3-rearrangement. With these *ipso*-intermediates, the rate of the rearrangement step is much faster than the corresponding step in the rearrangement of the cyclohexadienone intermediates derived from the nitration of phenols.

The work in Parts 1 and 3 of this series^{1,2} established that the nitration of a number of amines with *para*-alkyl groups in ca. 70% sulphuric acid occurs by *ipso*-attack followed by a 1,3-rearrangement of the nitro-group. Similar reactions have been observed in the nitration of certain *para*-substituted phenols.³ The rearrangement reactions of the amine intermediates, at least as exemplified by the *ipso*-intermediate (1), differ from those of the phenols in two respects; the reaction rate decreases with acidity and a hydrogen isotope effect (k_H/k_D ca. 5) is present when the positions *ortho* to the amino-group are deuteriated.² However, the earlier work² on the *ipso*-intermediate (1) provided a hint that both the slope of the rate profile and the isotope effect decreased as the acidity was lowered. In the present work, these changes are investigated in more detail using the *ipso*-intermediates (1) and (2).

For this work, the method of following the reactions has been changed from n.m.r. to u.v. spectrometry. This has several advantages; it increases the accuracy of the kinetics, it permits reactant concentrations to be changed by a factor of at least 3 without a significant change in the medium, and it increases the range of acidity over which the reactions can be followed. The last consequence arises because the formation of the *ipso*-intermediates requires concentrations of sulphuric acid >60% but, once formed, such solutions can be diluted as required and the use of u.v. spectrometry permits very dilute solutions to be studied.

One apparent disadvantage of the present method is that the initial concentrations of the *ipso*-intermediates are unknown. This arises partly because the reactions forming the *ipso*-intermediates are not quantitative (there are side-reactions including direct attack at the 2-position¹ and demethylation at the nitrogen atom particularly when an excess of amine is used²) and partly because the conversion of some of the *ipso*-intermediate into the 2-nitro-product occurs during the dilution of the reaction mixture. The presence of any initial side-reactions should be unimportant since the studies below suggest that there is no change in the u.v. spectra of the species formed over the period of a kinetic run, and knowledge of the initial concentration of the *ipso*-intermediate is unnecessary since first-order kinetics are observed for the rearrangement reaction.

The variation in the absorbance of the reaction mixture during the rearrangement of the *ipso*-intermediate (1) to the 2-nitro-product is shown for a typical kinetic run in Figure 1. Such runs give good isobestic points, excellent first-order kinetics, and final spectra that correspond closely to complete conversion into the 2-nitro-product (see Experimental section).



The resulting rate coefficients are in reasonable agreement with those obtained by n.m.r. spectroscopy over the region of acidity for which both methods can be used (see later). It appears therefore that the method based on u.v. spectrometry provides a valid measure of the rates of these rearrangement reactions.

Most of the reactions, including that in Figure 1, were carried out in the presence of a small amount of hydrazine (a scavenger for nitrous acid)⁴ for this was found to increase the stability of the rearranged product and facilitate the determination of infinity readings. Almost all of the rate coefficients were calculated using experimental infinity readings but the values for a few of the slower runs were based on Guggenheim plots⁵ or calculated infinity readings (see Experimental section). In most of the kinetic runs, the initial concentrations of the amine and nitric acid would correspond to concentrations of the *ipso*-intermediate of $(1.5\text{--}2.0) \times 10^{-4}$ mol dm⁻³ on the assumption of 100% reaction but in a few runs the concentrations were decreased by a factor of 2 or 3; the rate coefficient for the rearrangement was unchanged.

The effect of other species present on the rates of rearrangement of *ipso*-intermediates (1) and (2) is shown in Table 1. The first four runs show that the added hydrazine has no effect. The next seven runs show that the presence of an excess of the amine or nitric acid has no significant effect on the reaction rate. Since side-reactions become much more important when an excess of amine is used,² this result indicates that the products from such side-reactions do not influence the rate of rearrangement. The last group of runs show that the rate coefficient for the rearrangement is independent of the nominal concentration of the *ipso*-intermediate (the concentration that would result from 100% reaction combined with no rearrangement during dilution of the reaction mixture).

The rate coefficients for the rearrangement of the normal (k_H) and deuteriated (k_D) *ipso*-intermediates are compared for various acidities in Table 2. These reactions were carried out

Table 1. First-order rate coefficients (k_H) for the rearrangement of the *ipso*-intermediates (1) and (2) at 0 °C. Effect of other species present

Substrate	H ₂ SO ₄ / %	10 ⁵ [amine]/ mol dm ⁻³	10 ⁵ [HNO ₃]/ mol dm ⁻³	10 ³ [N ₂ H ₄]/ mol dm ⁻³	10 ⁴ k_H / s ⁻¹
(1)	54.9		4.0		30.2
(1)	54.9		4.0	1.0	31.1
(1)	65.8		4.0	1.0	12.7
(1)	65.8		4.0	2.0	12.8
(1)	65.8		21.0	1.0	13.2
(1)	65.8		4.0	1.0	12.7
(1)	65.8	2.0		1.0	13.1
(1)	65.8	12.0		1.0	13.8
(2)	50.7		21.0	1.0	7.47
(2)	50.7		2.7	1.0	7.43
(2)	50.7	12.0		1.0	7.67
(1)	69.7		4.0	1.0	7.21
(1)	69.7		4.0	1.0	7.24 ^a
(2)	24.9		4.0	1.0	10.62
(2)	24.9		2.0	1.0	10.45 ^b

^a Normal concentration of *ipso*-intermediate less than that in above run by a factor of 3. ^b As footnote (a), but with a factor of 2.

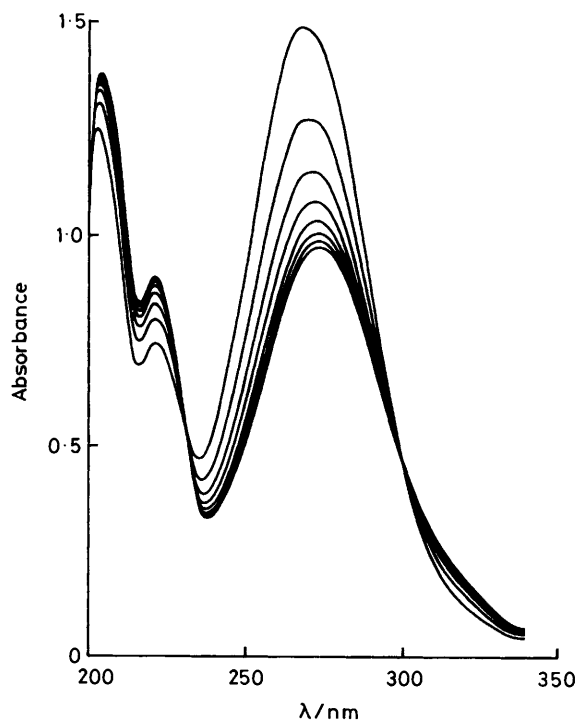


Figure 1. The variation in absorbance during the rearrangement of the *ipso*-intermediate (1) in 69.7% sulphuric acid at 0 °C. The nominal initial concentration of the *ipso*-intermediate was 1.5×10^{-4} mol dm⁻³ and the spectra were taken at 5 min intervals. For clarity, some of the later spectra have been omitted

with a slight excess of nitric acid (4×10^{-5} mol dm⁻³) and in the presence of hydrazine (1×10^{-3} mol dm⁻³).

Discussion

The rate profiles for the rearrangement of the normal and deuteriated forms of the *ipso*-intermediates (1) and (2) are shown in Figure 2 together with the earlier results^{1,2} obtained by n.m.r. spectroscopy over a more limited range of acidity. The agreement is satisfactory considering the marked difference in the reactant concentrations used in the two methods and the greater errors inherent in the n.m.r. method. The

Table 2. First-order rate coefficients at 0 °C for the rearrangement of the normal and deuteriated *ipso*-intermediates (1) and (2) at various acidities

Substrate	H ₂ SO ₄ / %	10 ⁴ k_H / s ⁻¹	10 ⁴ k_D / s ⁻¹	k_H/k_D
(1)	25.0	47.7	49.2	0.97
(1)	34.9	40.1	37.4	1.07
(1)	44.9	36.1	30.3	1.19
(1)	51.1	33.7	22.9	1.47
(1)	54.9	30.2	17.5	1.73
(1)	60.0	22.3	8.07	2.76
(1)	65.8	12.7	3.21	3.96
(1)	69.7	7.22	1.60	4.51
(1)	72.2	3.56 ^a	0.803 ^a	4.43
(1)	75.9	1.34 ^a	0.277 ^a	4.84
(2)	14.9	13.1		
(2)	24.9	10.5	10.6	0.99
(2)	34.8	9.42	8.84	1.07
(2)	45.0	8.35	7.46	1.12
(2)	50.7	7.47	6.71	1.11
(2)	55.0	7.07	5.60	1.26
(2)	59.7	6.62	4.07	1.63
(2)	65.8	4.58	1.87	2.45
(2)	71.5	2.34	0.575	4.07

Based on calculated infinity readings: see Experimental section.

present work confirms the curvature of the rate profile and shows that the isotope effect disappears as the acidity is decreased.

The form of the rate profiles can be understood in terms of the reactions in the Scheme. In the quantitative analysis of these results, it is helpful to assume initially that k_1 and k_{-1} are independent of acidity and isotopic composition and that the dependence of k_2 on the acidity is independent of the substrate and the isotopic composition. The best fit is then obtained for $k_2 \propto h_0^{-0.7}$ so that we can write equation (1). A

$$k_2 = k_2^L h_0^{-0.7} \quad (L = H \text{ or } D) \quad (1)$$

stationary-state treatment of the reactions in the Scheme then shows that the observed first-order rate coefficient should be given by equation (2).

$$k = \frac{k_1}{1 + (k_{-1}/k_2^L)h_0^{-0.7}} \quad (2)$$

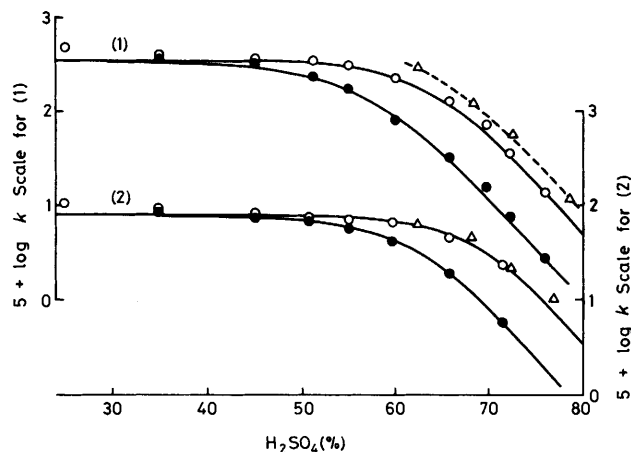


Figure 2. Rate profiles for the rearrangement of the *ipso*-intermediates (1) and (2) at 0 °C. Open circles, undeuterated compounds; dots, deuterated compounds; triangles, earlier results (refs. 1, 2) by ^1H n.m.r. spectroscopy. The lines are calculated from equation (2) using the values of the rate coefficients in Table 3

Table 3. Values of rate coefficients used for the calculated curves in Figure 2

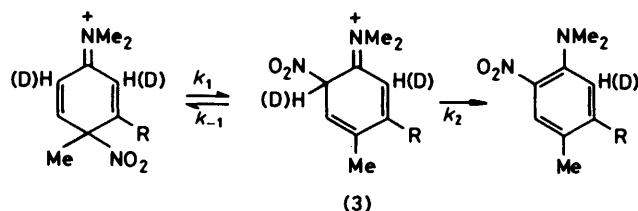
Substrate	$10^4 k_1/\text{s}^{-1}$	$10^4 k_{-1}/k_2^{\text{H}}$	$10^4 k_{-1}/k_2^{\text{D}}$
(1)	35	3.92	21.3
(2)	7.9	1.22	6.41

The complete set of four rate profiles should therefore be determined by six parameters [k_1 , (k_{-1}/k_2^{H}) , and (k_{-1}/k_2^{D}) for each substrate]. The curves in Figure 2 have been calculated by fitting equation (2) to the experimental results and the values of the resulting parameters are listed in Table 3. It is clear from Figure 2 that the experimental results can be represented in this way.

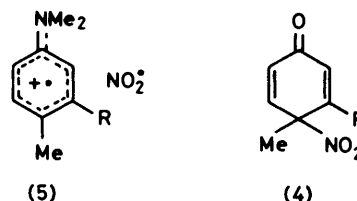
There is little direct evidence concerning the acidity dependence of proton loss from Wheland intermediates but the expected dependence can be deduced from the comparison of the kinetic acidity function (H_0^{\ddagger})⁶ for the rate of protonation of aromatic and unsaturated carbon atoms in aqueous sulphuric acid with the acidity function (H_0) for the equilibrium protonation of such systems. Since the former is very similar to H_0 and the latter has a slope⁷ of 1.6 against H_0 over the range 23–78% sulphuric acid, a plot of $\log k_2$ for proton loss from Wheland intermediates against H_0 in aqueous sulphuric acid should have a slope of *ca.* 0.6. This is very similar to the value of 0.7 implied by equation (1). The assumption that the rate of 1,3-migration (Scheme) is independent of acidity accords with the non-acid-catalysed pathway for such migrations in cyclohexadienones.³ Thus the assumptions underlying equation (2) are reasonable ones and the fit of the experimental rate profile to the calculated curves is unlikely to be accidental.

The assumption that k_1 and k_{-1} are independent of acidity may be an oversimplification, for the results for both substrates show a significant deviation from the theoretical curve at the lowest acidities (Figure 2). This presumably arises because k_1 increases slightly as the acidity is decreased (a slope of 0.08 for $\log k_1$ against H_0 would be sufficient). Such a variation could be a medium effect and does not require any change in the Scheme.

The quantitative analysis of the results in terms of equation



Scheme.



(2) has three main consequences. First, it confirms that the decrease in the reaction rate with acidity arises because the proton loss becomes rate determining and it permits the calculation of the isotope effect for this step [substrate (1), $k_2^{\text{H}}/k_2^{\text{D}}$ 5.4; substrate (2), $k_2^{\text{H}}/k_2^{\text{D}}$ 5.25]. Secondly, it permits the substituent effect of the 3-methyl group in (2) to be discussed in terms of the rate coefficients for the individual steps. From the values of k_1 for the two substrates, it is clear that the methyl group decreases the rate of the forward 1,3-rearrangement by a factor of 4.4.* The main effect of the methyl group on the $k_{-1}^{\text{H}}/k_2^{\text{H}}$ ratio (a decrease by a factor of 3.3) must come from the k_{-1}^{H} term: it would be unreasonable to assume that the methyl group increased the rate of proton loss from the Wheland intermediate (3). It follows that the methyl group decreases both the forward and reverse 1,3-rearrangements in the Scheme by a similar small factor. The methyl group appears therefore slightly to stabilise both the *ipso*-intermediate and the Wheland intermediate (3) in relation to the transition state for the 1,3-rearrangement.

Thirdly, the analysis permits the rates of 1,3-rearrangement of nitro-groups in the amine and phenol series to be compared without the complications arising from rate-determining proton loss. From the rate coefficient for the rearrangement of the cyclohexadienone (4; R = Me) in acetic acid at 30 °C ($1.6 \times 10^{-4} \text{ s}^{-1}$)⁸ and the corresponding activation energy ($25.8 \text{ kcal mol}^{-1}$),⁸ the rate coefficient at 0 °C can be calculated to be $1.45 \times 10^{-6} \text{ s}^{-1}$. This can be presumed to be the rate coefficient for the rearrangement itself since studies on the nitration of 2-deuterio-4-fluorophenol have shown that proton loss is not rate-determining in these reactions.^{3b} The corresponding rate coefficient in the amine series is k_1 for structure (2) ($7.9 \times 10^{-4} \text{ s}^{-1}$) (Table 3). The replacement of the C=O group by the C=NMe₂ group appears therefore to increase the rate of rearrangement by a factor of *ca.* 500.

In the previous work,² the 1,3-rearrangement was considered to occur *via* the radical pair (5) and it is interesting to consider to what extent the present results are consistent with this interpretation. There is considerable evidence that the non-acid-catalysed rearrangement of the cyclohexadienone (4; R = H) in acetic acid occurs *via* a radical pair⁸ and the

* This should include a statistical factor of 2 since the 3-methyl group blocks rearrangement to the 1-position, presumably by steric interaction. The very low rate of rearrangement of the *ipso*-intermediate with methyl groups in the 3, 4, and 5 positions (ref. 1) is consistent with this steric interaction.

Table 4. Absorption maxima and extinction coefficients in 76% sulphuric acid (unless specified otherwise) at 0 °C

Substrate	$\lambda_{\text{max.}}/\text{nm}$	$\epsilon/\text{dm}^3 \text{ mol}^{-1} \text{ cm}^{-1}$
4-MeC ₆ H ₄ NMe ₂ H ⁺	251, 257	215, 231
<i>ipso</i> -Intermediate (1) ⁺	ca. 267	
4-Me-2-NO ₂ C ₆ H ₃ NMe ₂ H ⁺	273 ^a	6 460
4-Me-3-NO ₂ C ₆ H ₃ NMe ₂ H ⁺	256	5 739
3,4-Me ₂ C ₆ H ₃ NMe ₂ H ^b	260, 278	373, 281
<i>ipso</i> -Intermediate (2) ⁺	ca. 272	
3,4-Me ₂ -6-NO ₂ C ₆ H ₂ NMe ₂ H ^b	291 ^c	7 686
Nitric acid	260	11.8
Hydrazine	252, 295	4.6, 5.2
Nitrous acid	240	16 190

^a Decreasing to 269 nm in 25% H₂SO₄. ^b In 65.8% sulphuric acid at 20 °C. ^c Decreasing to 286 nm in 14.9% sulphuric acid.

substituent effect of a 3-methyl group on this reaction is a factor of 2.9 on the overall reactions and 2.2 at a single 6-position.* This is identical to the substituent effect of the 3-methyl substituent in the intermediate (2) when a single 6-position is considered (see footnote p. 1193). This comparison is clearly consistent with the radical pathway for the rearrangement.

It is less clear why the *ipso*-intermediates from the amines should rearrange so much more rapidly than the related cyclohexadienones. The rate of rearrangement of the cyclohexadienones is greatly increased by protonation but the reaction mechanism is then considered to change to one involving a nitronium ion.³ There are difficulties in assuming that the rearrangement of the intermediates derived from the amines is analogous to that of the protonated cyclohexadienones partly because of the exchange experiments observed previously² and partly because of the weakly acidic media used in some of the rearrangements now reported. In such media, the lifetime of the nitronium ion is likely to be less than the lifetime of the encounter pair with the amine because of the very fast reaction of the nitronium ion with water.⁹ It appears unlikely therefore that a nitronium ion would have a sufficiently long lifetime to undergo 1,3-rearrangements in these media.

In some related work with Dr. J. P. B. Sandall, we have studied the rearrangements of the ¹⁵NO₂-labelled intermediate (1) in 60% sulphuric acid to determine whether the product shows ¹⁵N nuclear polarisation. Under these conditions, the rate profile (Figure 2) shows that the Wheland intermediate (3) reacts mainly by proton loss so, if nuclear polarisation were generated by the reactions of the radical pair (5), such nuclear polarisation should be detected in the product. Unfortunately no evidence for nuclear polarisation was found.¹⁰ This does not disprove the radical pair interpretation for the 1,3-rearrangements considered here but it implies that this interpretation cannot yet be considered as established.

Experimental

Materials.—The amines and the deuteriated amines were prepared as described previously.^{1,2} Studies of the deuteriated amines by n.m.r. spectroscopy and elemental analysis indi-

* The rearrangement of (4; R = Me) in acetic acid gives 66% of the corresponding 6-nitrophenol (ref. 8).

Table 5. Comparison of observed and calculated values of A_{∞} for the reactions of the intermediate (1)

H ₂ SO ₄ / %	10 ⁴ [intermediate] ^a / mol dm ⁻³	10 ³ [hydrazine]/ mol dm ⁻³	A_{∞}	
			Obs.	Calc. ^b
69.7	2.0		1.458	1.249
69.7	1.33	0.33	0.855	0.830
54.9	2.1		1.485	1.311
54.9	2.0	1.0	1.288	1.249

^a Assuming 100% reaction. ^b Taking ϵ 6 244 dm³ mol⁻¹ cm⁻¹ for the 2-nitro-product at 268 nm.

cated complete deuteration at the positions *ortho* to the amino-group. The ¹H n.m.r. spectra of the deuteriated amines dissolved in 72% sulphuric acid at 0 °C showed that no observable exchange occurred over a period of 24 h.¹⁰ The other reagents were as described.^{1,2}

***ipso*-Intermediates.**—The formation of the *ipso*-intermediates was carried out in the presence of nitrous acid to ensure complete reaction before dilution of the reaction mixtures. In the usual procedure for forming the intermediate from *NN*-dimethyl-*p*-toluidine, solutions of nitric acid (1 cm³, 0.6 mol dm⁻³), sodium nitrite (1 cm³, 0.025 mol dm⁻³), and the amine (1 cm³, 0.5 mol dm⁻³) in 72.6% sulphuric acid were brought to 0 °C, mixed, and kept for 15 min at 0 °C. The ¹H n.m.r. spectra of these mixtures showed that reaction to form the *ipso*-intermediate was effectively complete in ca. 10 min. The reaction mixtures were then diluted in several stages with more sulphuric acid at 0 °C and some hydrazine was added so that the final concentrations (assuming complete reaction) were (hydrazine) 10⁻³ mol dm⁻³ and (*ipso*-intermediate) 2 × 10⁻⁴ mol dm⁻³. Minor changes in this procedure were made to study the effect of changes in the initial concentrations of the reagents and in the formation of the intermediate from *NN*,3,4-tetramethylaniline.¹⁰

Kinetics.—The u.v. spectra of the reaction mixtures were determined using a Perkin-Elmer 554 spectrophotometer with the cells maintained at 0 °C and with a current of dry air passing through the cell compartment. The extent of reaction was calculated from the absorbance (A) at 280 nm (*NN*,3,4-tetramethylaniline) or 268–269 nm (*NN*-dimethyl-*p*-toluidine) (Figure 1), and the first-order rate coefficient k was calculated by Guggenheim's method⁵ or from the slope of a plot of $\ln(A_t - A_{\infty})$ against time where A_t and A_{∞} are the absorbance at time t and at the end of the run.

In most of the runs, the values of A_{∞} were determined directly and were compared with the calculated values using the extinction coefficients of the components (Table 4). The results showed that the contribution of hydrazine and the excess of nitric acid to the final absorbance was negligible; the contribution of the initial amines could be significant in those runs where an excess of amine was used; and the contribution of nitrous acid could be significant in those runs carried out without added hydrazine. Separate experiments showed that, in the presence of hydrazine, the contribution of the nitrous acid to the final absorption was negligible and the observed values of A_{∞} were then close to those calculated from the absorption of the product (Table 5).

The values of the rate coefficients in Table 2 are the mean of at least two kinetic runs for each substrate at each acidity. All of these runs gave correlation coefficients >0.999 and the differences in the values of k for a pair of runs under identical conditions was normally <2%. In two of the slowest runs

(footnote, Table 2), the rate coefficients were calculated on the assumption that the reaction was first-order by using the value of A_{∞} that gave the highest correlation coefficient.¹⁰ Some experiments were carried out on the temperature dependence of k for the rearrangement of the intermediate (1) giving for 74.4% sulphuric acid k $2.02 \times 10^{-4} \text{ s}^{-1}$ (0 °C) and $8.19 \times 10^{-4} \text{ s}^{-1}$ (15 °C); these values correspond to E 61.1 kJ mol⁻¹, log A 7.98. At the higher temperature the errors in the kinetics appeared somewhat greater.

Acknowledgements

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