Nature of nitrenium: carboxylate ion pair intermediates in the hydrolysis of *O*-aroyl-*N*-acetyl-*N*-(2,6-dimethylphenyl)-hydroxylamines

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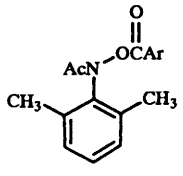
O-Aroyl-*N*-acetyl-*N*-(2,6-dimethylphenyl)hydroxylamines [aroyl = benzoyl (**1a**), 3-nitrobenzoyl (**1b**), and pentafluorobenzoyl (**1c**)] are solvolysed in aqueous solutions by rate-limiting ionization to nitrenium:carboxylate ion pair intermediates. These in part collapse at the *ortho* position to give unstable 1,5-dimethyl-5-aroyloxy-6-acetyliminocyclohexa-1,3-dienes **2** that react further as described in the previous paper. The ion pairs from **1** also proceed directly to products of substitution *para* to the acetylamino group—4-aroyloxy-2,6-dimethylacetanilide **5**, a product of internal return, and 4-hydroxy-2,6-dimethylacetanilide **6**, a product of water addition. These same products also arise *via* ionization of **2**. The ratio **5**:**6** obtained directly from **1** is significantly lower than that from **2**, demonstrating that **1** and **2** do not ionize to exactly the same ion pairs. Experiments with **1a** in the presence of bromide show that the yield of the cyclohexadiene is unaffected, while the yields of **5** and **6** are decreased, albeit to different amounts. Two new products, 4-bromo-2,6-dimethylacetanilide and 2,6-dimethylacetanilide, are observed in their places. Experiments with **1c** in acid solutions demonstrate that the yield of cyclohexadiene can be decreased by H^+, by protonation of the carboxylate ion in the ion pair. Using the H^+ reaction as a clock, the lifetime of this ion pair, the initial ion pair in the ionization of **1**, is calculated as *ca.* 10 ps. Thus this ion pair is too short-lived to react with external nucleophiles, and probably also with solvent. The trapping data for the *p*-ester **5** are shown to be inconsistent with a mechanism where a single ion pair serves as precursor, and this product is proposed to arise in part from a short-lived ion pair, and in part from a longer-lived one. The latter ion pair is probably also the species that gives rise to the *p*-phenol **6** by reaction with water. Using the bromide reaction as the clock, this ion pair is shown to have a lifetime of 0.25–0.50 ns. A number of mechanistic models incorporating these features are consistent with the experimental results, and two of these are discussed. Whatever the mechanism a minimum of three short-lived ion pair intermediates is required.

In the preceding paper, we presented an analysis of the behaviour of the cyclohexadienes **2** in aqueous solution.[1] We initially encountered these compounds as intermediates in a study of the hydroxylamine esters **1**, and were able to establish conditions where samples of **2** could be isolated and their chemistry directly examined. In this paper we turn to the hydroxylamine derivatives themselves, and present an analysis of their considerably more complex behaviour.



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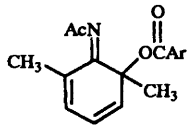
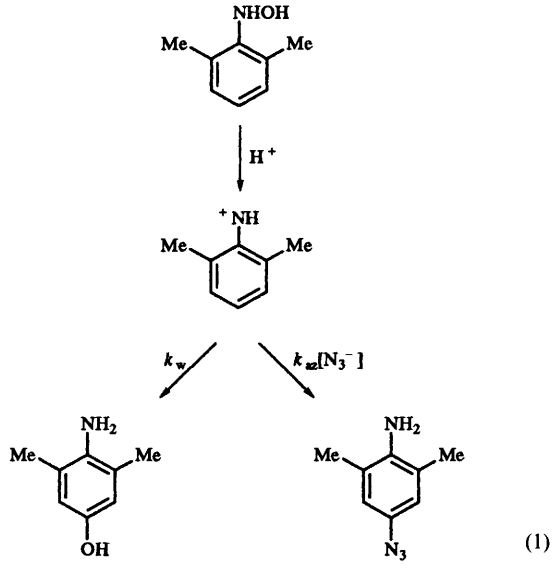


2

a Ar = C_6H_5
b Ar = 3-$NO_2C_6H_4$
c Ar = C_6F_5

This investigation was driven by previous work with *N*-(2,6-dimethylphenyl)hydroxylamine itself.[2] Under weakly acidic conditions, this compound undergoes a Bamberger rearrangement producing the *para*-substituted phenol. The addition of azide results in a *para*-azido adduct, but causes no acceleration in the rate of decay of the hydroxylamine. This is classic evidence for the involvement of an intermediate, in this case an arylnitrenium ion. The product selectivity ratio $k_{Az}:k_w$ is 7.4 $dm^3\ mol^{-1}$, which, with a value of $k_{Az} \approx 5 \times 10^9\ dm^3\ mol^{-1}\ s^{-1}$,[3-5] gives a lifetime ($1:k_w$) of 1.4 ns for the 2,6-dimethylphenylnitrenium ion in water.



(1)

Nitrenium ions are the proposed ultimate carcinogens arising from aromatic amines.[6] The formation of these cations requires a twofold activation process, oxidation to the hydroxylamine followed by esterification of the hydroxy group to acetate[7-10] or sulfate[11-13] esters. The latter step results in a better leaving group, but it also means that the cation forms initially as an ion

pair, rather than as an ion–molecule pair as in the Bamberger rearrangement. With the known lifetime of the nitrenium ion in the 2,6-dimethyl system, we felt it of interest to examine ester precursors to this type of cation. The three derivatives were chosen so as to provide leaving groups of substantially different stability. The chemistry of these compounds proves to be more complicated than that exhibited by the parent hydroxylamine in acid. Products of substitution both *meta* and *para* to the nitrogen are observed, with the substituting groups being derived from the solvent, the leaving group and external nucleophiles. The rearranged species **2** is a precursor of some, but not all of these products. Experiments have also been carried out with bromide and hydronium ion as trapping reagents. Overall, the conclusion is reached that at least three different ion pair intermediates are responsible for the products.

Results

Kinetics

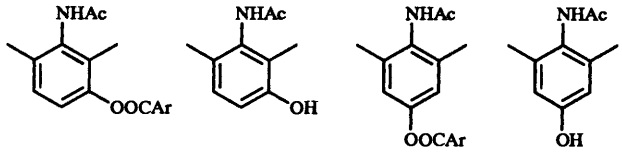
Unless otherwise specified, kinetic and product studies were carried out under the same conditions as employed in the study of the cyclohexadienes **2**, 8.3% by volume acetonitrile, 40 °C and 1 mol dm^{-3} ionic strength maintained with $NaClO_4$. In the case of the pentafluoro derivative **1c**, kinetics could be conveniently followed spectroscopically from a change in absorbance at 240 nm. With the esters **1a** and **1b**, the disappearance of the starting material was monitored by HPLC. In every case, excellent exponential behaviour was followed. The observed first-order rate constants were independent of pH over the range examined, from pH = 8 to 1 mol dm^{-3} $HClO_4$. Experiments with different buffer concentrations revealed that there was no effect of the buffer. Thus the reaction of each compound is characterized by a single first-order rate constant. These values are given in Table 1.

Table 1 Rate constants for the disappearance of *O*-aroyl-*N*-acetyl-*N*-(2,6-dimethylphenyl)hydroxylamines in aqueous solutions; conditions: 40 °C and ionic strength 1 mol dm^{-3} in 8.3% by volume acetonitrile

Aroyl	k/s^{-1}
C_6H_5CO–	2.05×10^{-5}
3-$NO_2C_6H_4CO$–	2.98×10^{-4}
C_6F_5CO–	9.67×10^{-3}

Products

Products observed with **1** proved to be qualitatively the same as those identified in the reaction of the cyclohexadienes **2** in aqueous solution, comprising *m*-aroyloxy- and *m*-hydroxy-2,6-dimethylacetanilides **3a**, **b**, **c** and **4**, and the *p*-aroyloxy- and *p*-hydroxy isomers **5a**, **b**, **c** and **6**. The appropriate benzoic acid was also formed. Control experiments demonstrated that the phenols and benzoic acid did not arise from further hydrolysis of the esters. Quantitative results are summarized in Table 2. As shown in this table, the four acetanilides in total quantitatively account for starting **1**, and the yields of the two phenols **4** and **6** taken together are equal to the yield of the benzoic acid.



3a; Ar = C_6H_5 **4** **5a, b, c** **6**
b; Ar = 3-$NO_2C_6H_4$
c; Ar = C_6F_5

Products in the presence of bromide

The reaction of the benzoate **1a** was examined in solutions with varying concentrations of sodium bromide. Conditions were identical with the above, except that the ionic strength was 2 mol dm^{-3}. The results are given in Table 3. At zero bromide concentration, there is no significant difference from the products at ionic strength 1 mol dm^{-3}. Two new products are observed with bromide present, 4-bromo-2,6-dimethylacetanilide **7** and 2,6-dimethylacetanilide **8**. Good mass balance is observed, the products in all cases amounting to 90–105% of the starting material. The products **7** and **8** form at the expense of

Table 2 Products obtained in the reaction of *O*-aroyl-*N*-acetyl-*N*-(2,6-dimethylphenyl)hydroxylamines **1** in aqueous solutions[a]

Product	C_6H_5COO– (**1a**)[b] pH = 3.6	3-$NO_2C_6H_4COO$– (**1b**)[c] pH = 3.6	3-$NO_2C_6H_4COO$– (**1b**)[c] pH = 1.9	C_6F_5COO– (**1c**)[d] pH = 2.2	C_6F_5COO– (**1c**)[d] pH = 6.7
m-OOCAr **3**	0.381 ± 0.002	0.266 ± 0.002	0.264 ± 0.001	0.092 ± 0.001	0.0
m-OH **4**	0.017 ± 0.001	0.067 ± 0.001	0.064 ± 0.001	0.120 ± 0.004	0.0
p-OOCAr **5**	0.216 ± 0.003	0.212 ± 0.001	0.206 ± 0.003	0.216 ± 0.002	0.333 ± 0.014
p-OH **6**	0.379 ± 0.002	0.455 ± 0.003	0.465 ± 0.003	0.572 ± 0.005	0.693 ± 0.014
ArCOOH	0.406 ± 0.003	0.563 ± 0.002	0.565 ± 0.003	0.698 ± 0.014	0.693 ± 0.005
4 + **6**	0.396	0.522	0.529	0.692	0.693
3 + **4** + **5** + **6**	0.993	1.000	0.999	1.000	1.026
$k(2):k(1)$[e]	3.6×10^4	4.5×10^2	2.1×10^5	9.8×10^1	1.6
$F_{meta}(2)$[f]	1.000	1.00	1.00	0.98	0.002
$\frac{3}{3+4}$ from **1**[g]	0.96	0.80	0.80	0.43	
$\frac{3}{3+4}$ from **2**[h]	0.94	0.82	0.82	0.43	
% **2** from **1**[i]	39.8	33.3	32.8	21.2	

[a] Conditions: 40 °C, 1 mol dm^{-3} ionic strength ($NaClO_4$) in 8.3% by volume acetonitrile. Yields were determined by HPLC analysis after 10 half-lives of reaction and are reported as fractions based upon the number of moles of starting material. Errors represent one standard deviation, based upon replicate measurements. [b] 0.016 mol dm^{-3} acetate buffer, 10% acetate, pH = 3.6. Doubling the acetate concentration has no effect. [c] First column, 0.016 mol dm^{-3} acetate buffer, 10% acetate, pH = 3.6. Second column, 0.0114 mol dm^{-3} $HClO_4$. [d] First column, 0.006 mol dm^{-3} $HClO_4$. Second column, 0.006 mol dm^{-3} phosphate buffer, 50% HPO_4^{2-}, pH = 6.7. [e] Ratio of first-order rate constants for the reactions of **2** and **1** at the pH of the product analysis. [f] Fraction of the reaction of the cyclohexadiene **2** that results in *meta* products at the pH of the experiment. [g] Fraction *m*-ester **3** of total *meta*-substituted products [**3**:(**3** + **4**)], in the experiment starting with **1**. [h] Fraction *m*-ester **3** of total *meta*-substituted products [**3**:(**3** + **4**)], in experiment starting with an isolated sample of **2**. [i] Percentage of the reaction of **1** proceeding *via* the rearranged **2** = 100 × (**3** + **4**):(**3** + **4** + **5** + **6**).

Table 3 Products obtained in the reaction of *O*-benzoyloxy-*N*-acetyl-*N*-(2,6-dimethylphenyl)hydroxylamine **1a** in aqueous solutions containing sodium bromide[a]

[NaBr]	*m*-OOCPh **3**	*p*-OOCPh **5**	*p*-OH **6**	PhCOOH	*p*-Br **7**	Anilide **8**
0	0.340	0.206	0.369	0.391	0	0
0	0.360	0.215	0.372	0.403	0	0
0.202	0.353	0.196	0.312	0.428	0.057	0.012
0.253	0.352	0.195	0.299	0.430	0.075	0.016
0.354	0.360	0.188	0.285	0.445	0.096	0.030
0.455	0.352	0.179	0.240	0.452	0.110	0.042
0.556	0.361	0.173	0.238	0.471	0.126	0.066
0.657	0.362	0.172	0.216	0.490	0.139	0.080
0.758	0.341	0.154	0.193	0.470	0.144	0.081
0.859	0.343	0.150	0.180	0.482	0.152	0.086
0.960	0.335	0.150	0.156	0.502	0.159	0.119
0.960	0.337	0.147	0.139	0.486	0.154	0.123

[a] See footnote *a* of Table 2 for conditions. The ionic strength was maintained at 2 mol dm^{-3} with $NaClO_4$. All experiments were conducted in 0.016 mol dm^{-3} acetate buffer, 10% acetate, pH = 3.6. The *m*-phenol **4** was also present, but its amount in all cases was less than 2% of the starting **1a**.

Table 4 Products obtained from the reaction of *O*-pentafluorobenzoyloxy-*N*-acetyl-*N*-(2,6-dimethylphenyl)hydroxylamine **1c** in aqueous solutions containing perchloric acid[a]

[$HClO_4$]	*m*-OOCAr **3**	*m*-OH **4**	*p*-OOCAr **5**	*p*-OH **6**	ArCOOH
0.008	0.091	0.118	0.216	0.575	0.702
0.010	0.092	0.122	0.216	0.568	0.689
0.050	0.092	0.119	0.206	0.582	0.690
0.171	0.085	0.107	0.176	0.631	0.740
0.205	0.083	0.114	0.170	0.634	0.742
0.228	0.085	0.110	0.165	0.638	0.739
0.285	0.081	0.106	0.163	0.646	0.751
0.342	0.079	0.106	0.144	0.672	0.756
0.398	0.079	0.104	0.142	0.677	0.766
0.456	0.079	0.099	0.132	0.688	0.777
0.510	0.078	0.098	0.128	0.696	0.765
0.570	0.076	0.097	0.121	0.705	0.790
0.682	0.074	0.092	0.112	0.722	0.790
0.798	0.075	0.086	0.103	0.736	0.809
0.910	0.066	0.082	0.096	0.756	0.832
1.000	0.068	0.078	0.097	0.768	0.825

[a] See footnote *a* of Table 2 for conditions.

the *para* products **5a** and **6**, the *meta*-ester **3a** being essentially unchanged up to 1 mol dm^{-3} bromide. [The *meta*-phenol **4** was formed in only small amounts (< 2%) in these experiments and was not quantitatively analysed in this part of the study.] Kinetic experiments were carried out by measuring the disappearance of **1a** with HPLC. These showed no effect of the added bromide, the rate constant at the highest sodium bromide concentration, for example, being less than 4% different from one obtained with no bromide present.

Products in the presence of perchloric acid

Table 4 summarizes products obtained with the pentafluoro derivative **5c** in solutions with varying concentrations of perchloric acid. Yields of the two *meta* products **7c** and **8** and the *para* ester **9c** decrease with increasing acid concentration, while yields of the *para*-phenol **10** and pentafluorobenzoic acid show corresponding increases. Kinetic studies conducted in these same solutions reveal that there is little effect of the acid, the rate constant increasing by 7% on proceeding from the most dilute to the most concentrated acid in this series. This small increase likely represents a specific salt effect as the medium is changed from 1 mol dm^{-3} $NaClO_4$ to 1 mol dm^{-3} $HClO_4$.

Discussion

Nitrenium ion intermediates

Previous studies of esters of *N*-arylhydroxylamines have concluded that their solvolysis reactions proceed by N–O ionization producing intermediate nitrenium ions.[14-19] That this is also the case with **1** is indicated by the lack of dependence of the rate constants on pH and buffer concentration, coupled with a strong dependence on the carboxylate leaving group. The plot of log *k* *versus* pK_a(ArCOOH) has a slope, β_{lg}, of −1.06, clearly consistent with a transition state with extensive carboxylate ion character. The requirement for a mechanistic scheme where products at least in part derive from an ion pair is also clearly demonstrated, through the observation of the esters **7** and **9**. Since there is no added benzoate such products must be obtained from internal return within some ion pair. It can be noted that there was a significant amount of acetate present in some of the experiments reported in Table 2, and yet there were no products derived from this anion.

These observations do not distinguish a mechanism where ionization is rate-limiting and one involving rate-limiting capture of an ion pair forming in a pre-equilibrium step. The latter, however, can be excluded, since the products are affected by added reagents such as bromide and perchloric acid, but these have little effect on the rate. Thus the product-determining steps must come after the rate-limiting ionization.

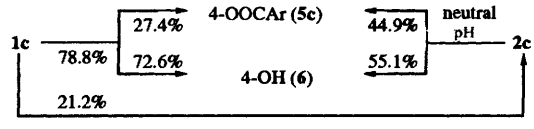
Cyclohexadiene intermediate

The experiments with isolated **2** show that under acidic conditions these compounds are converted exclusively into the *meta*-substituted products **3** and **4**. As shown by the entry F_{meta}(**2**) in Table 2, four of the analyses with **1** were performed

under such conditions, and indeed the *meta* products are observed. More importantly, as seen by comparing the two entries **3**:(**3** + **4**), these are formed in exactly the same relative amounts whether **1** or **2** is the precursor. The cyclohexadienes cannot be observed in these experiments, since, as demonstrated by the entry $k(2):k(1)$, these react more rapidly than **1** undergoes ionization. The conclusion, however, is that the cyclohexadienes do form from the hydroxylamine esters, and it is their further reaction that results in **3** and **4**.

However, not all of the products from **1** can be explained as arising from **2**. If this were the case, the acid experiments with the former would have resulted in almost exclusively *meta* products. Thus two reaction channels must be invoked starting with **1**, one that forms **2** and a second that leads to the *para* products. The percentage of the former reaction, as calculated from the total yield of the two *meta* products, is provided in the last row of Table 2. In all cases, less than 50% of the cyclohexadiene is actually formed. There is a dependence on the leaving group, the poorer the leaving group, the greater the fraction of **2**.

Only *para* products were observed in the one study conducted at neutral pH. This is expected, since under these conditions the cyclohexadiene (**2c**) is also converted into the *para*-acetanilides. In this experiment a peak corresponding to **2c** could actually be observed in HPLC traces at intermediate reaction times, since in this case the rate of reaction of **2c** is comparable to the rate of ionization of **1c**. The cyclohexadiene **6c** can in fact be demonstrated to form to the same extent in this experiment as in acid. As shown in Scheme 1, the *para*-



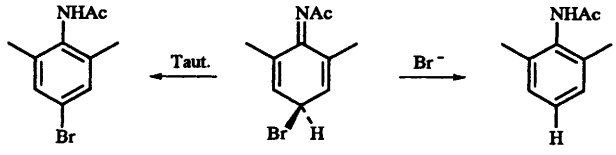
Scheme 1

acetanilides form at neutral pH in two ways, directly from **1c** and indirectly by way of **2c**. Based upon experiments starting with isolated **2c**, the indirect route results in a 55.1:44.9 phenol:ester ratio. The ratio for the direct route is 72.6:27.4, as determined from the analysis in acids, where **2c** leads to *meta*-acetanilides. The acid result also provides the information on the initial partitioning, 78.8% of **1c** reacting directly to the *para* products. With these three ratios, the overall *p*-phenol:*p*-ester product ratio from **1c** is calculated as 68.9:31.1. The observed ratio is 68.2:31.8, within experimental error the same.

The reaction of the cyclohexadiene that results in the *para*-acetanilides is an ionization,[1] in fact with a β_{lg} of -1.1 similar to the value obtained with the hydroxylamine derivatives. An important observation when it comes to considering the mechanism is that the *p*-phenol:*p*-ester ratio is different when the products form directly from **1** or from isolated **2**. The ratios for the pentafluoro derivative are given in Scheme 1. The data for the *m*-nitro compound are 68.6% *p*-phenol:31.4% *p*-ester from **1b** and 33.5% *p*-phenol:66.5% *p*-ester from **2b**. In each case there is relatively more phenol when **1** is the starting material.

Trapping experiments

Bromide and hydronium ion have a significant effect on the product distribution, without changing the rate. In the former case bromide diverts the products by reacting with the nitrenium ion. This trapping results in an adduct **9**, which proceeds to *p*-bromoacetanilide **7** by tautomerization, or reacts with a second equivalent of bromide to give the acetanilide **8** and Br_2. This mechanism for the formal reduction of



7 **9** **8** (2)

hydroxylamine derivatives by halides has been proposed by Pelecanou and Novak.[16] Consistent with the mechanism is the observation in the present study that **7** is the major product at low bromide concentration, while **8** increases more rapidly at higher concentration.

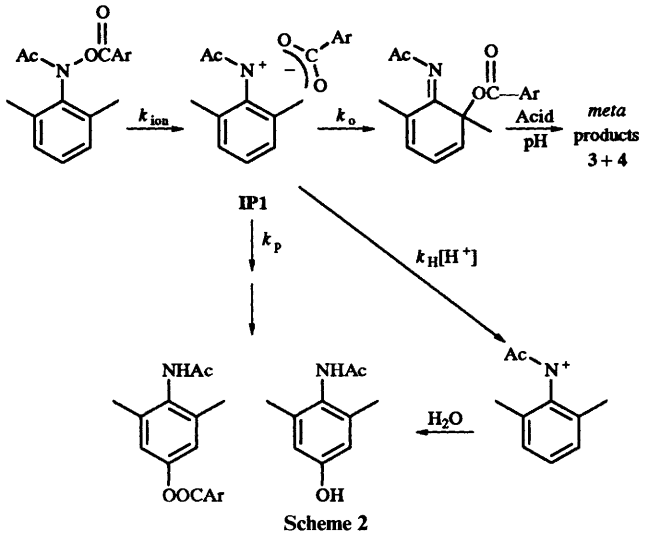
In the case of perchloric acid, our proposal is that hydronium ion traps the carboxylate counter-ion in the ion pair. Protonation prior to the formation of the ion pair is ruled out by the observation that there is no change in the rate constant. Protonation in the ion pair prevents internal return, and thus decreases the yields of the *p*-ester product and the *meta* products derived from the cyclohexadiene, and increases the yields of the *p*-phenol and ArCOOH. The effect of acid on the two *meta* products is about the same, although there is a slightly greater inhibition of the *m*-phenol at higher acidity. As discussed in the previous paper, the ratio of these products is determined by a competition in the protonated cyclohexadiene between the intramolecular carboxylate and water. The small change in the product ratio with increasing acidity is likely caused by a specific salt effect on the activity of water, decreasing the rate of its reaction.

A key observation is that the effect of bromide differs with the various products. For example, 1 mol dm^{-3} bromide reduces the yields of the *p*-phenol and *p*-ester to different extents, 38% and 70%, respectively, of the amounts obtained in the absence of bromide. At the same time, bromide has essentially no effect on the *meta*-ester, and thus its precursor, the cyclohexadiene. This observation, coupled with others, requires a scheme involving several ion pair intermediates. A mechanism with a single common intermediate as a precursor for all three products is clearly ruled out, as is a mechanism where the same ion pair serves as the precursor for two of the products. In the former case, all three products would have been equally affected by bromide, and, in the latter case, two of the products. As will be seen in the following, several mechanistic variations can be written that are reasonably consistent with the experimental data. However, whatever the mechanism, we will argue that a minimum of three ion pairs are required.

The initial ion pair

One ion pair that is common to all mechanistic schemes, and is well defined in terms of lifetime, is the initially formed one, the ion pair that undergoes internal return at the *ortho* position to form the cyclohexadiene. This trapping appears in the form of the *meta* products observed under acidic conditions. Since these *meta* products are not the sole products, the initial ion pair does not just collapse, but there must be other channels leading from it to the *para* products. This situation is summarized in Scheme 2, where for the purpose of discussion of the initial ion pair, designated **IP1**, processes leading to the *para* products are grouped together as k_p.

The fact that bromide has a negligible effect on the products derived from the cyclohexadiene implies that **IP1** is too short-lived to be trapped by this external nucleophile. This is not a



Scheme 2

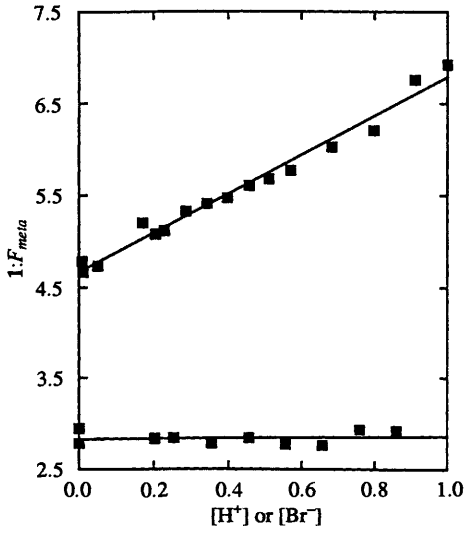


Fig. 1 Plots of $1:F_{meta}$ *versus* concentration of trapping reagent: top, data for pentafluorobenzoyloxy derivative **1c** in the presence of H^+; bottom, data for benzoyloxy derivative **1a** in the presence of Br^-

new observation; several previous studies of reactions implicating nitrenium ion intermediates have found that added nucleophiles have little effect on a product that is derived from internal return at an *ortho* position.[15,17,18,20,21]

The observation that is new is that return at the *ortho* position can be diverted by the hydronium ion. The H^+-reaction can therefore be used as a clock to provide an estimate of the lifetime of the ion pair. In terms of Scheme 2, the eqn. (2) can be written for the fraction of *meta* products. This predicts a

$$\frac{1}{F_{meta}} = \left(\frac{k_o + k_p}{k_o}\right) + \left(\frac{k_H}{k_o}\right)[H^+] \qquad (3)$$

linear relation between $1:F_{meta}$ and $[H^+]$, with the slope equal to the ratio $k_H:k_o$, and the slope:intercept ratio equal to $k_H:(k_o + k_p)$. The latter supplies the lifetime of **IP1** $\{1:(k_o + k_p)\}$ referenced to k_H. Rate constants for protonation of carboxylate ions by the hydronium ion fall in the range 3–5 × 10^{10} dm^3 mol^{-1} s^{-1};[22] we will use the mean in our calculations. (The actual number may be somewhat smaller owing to the occluded collision cross-section resulting from the presence of the nitrenium counter-ion.)

The plot for **1c** (Fig. 1) has a slope of 2.1 ± 0.1, an intercept of 4.7 ± 0.1, and a slope:intercept ratio of 0.45 ± 0.02. Using 4 × 10^{10} dm^3 mol^{-1} s^{-1} for k_H, the rate constant k_o is 2 × 10^{10} s^{-1}, and the lifetime for **IP1** is 11 ps. This obviously corresponds to a very short lifetime for this ion pair. Interestingly, the almost doubling in F_{meta} in changing from **1c** to **1a** means that despite the high reactivity of **IP1**, partitioning within the ion pair does show some dependence on leaving group. If the assumption is made that the change occurs in k_o, with k_p being relatively insensitive to leaving group, k_o for the benzoyloxy compound is calculated as 4.5 × 10^{10} s^{-1}. This is approximately double the rate constant for pentafluoro, and corresponds to a β_{nuc} value of 0.1.

The short lifetime for **IP1** is obviously consistent with the inability of added nucleophiles, like bromide, to react at this stage. That this is indeed the case can be demonstrated quantitatively by the following analysis. With bromide as the trapping reagent, the dependence of F_{meta} takes the same form as eqn. (3), with $[H^+]$ replaced by $[Br^-]$, and k_H by k_{Br}, the rate constant for reaction of the ion pair with bromide. A plot of $1:F_{meta}$ *versus* $[Br^-]$ is also provided in Fig. 1. This obviously shows little dependence on the nucleophile. The intercept of this plot is well defined as 2.8 ± 0.07, but the slope, 0.03 ± 0.12, is not statistically different from zero. Taking one standard deviation, the upper limit on the slope is 0.15, so that the upper limit for $k_{Br}:(k_o + k_p)$ is 0.05. With the lifetime of *ca.* 10 ps calculated from the H^+-trapping experiments, this places an upper limit on k_{Br} of 5 × 10^9 dm^3 mol^{-1} s^{-1}. The latter value is of course very near the diffusion limit for a cation:anion combination reaction in aqueous solution.[4]

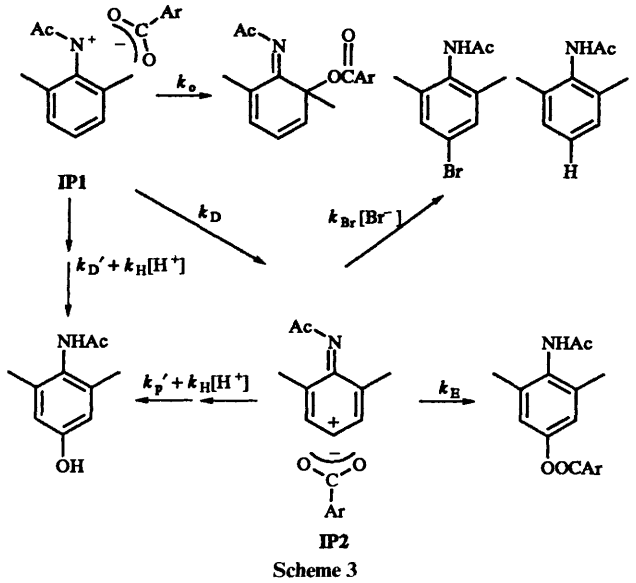
The question can also be addressed as to whether solvent can react at the stage of **IP1** to give the *p*-phenol product. In other words, is one of the processes grouped together as k_p in Scheme 1 a reaction with water? As discussed in the introduction, the solvent traps the free 2,6-dimethylnitrenium ion with a rate constant slightly less than 10^9 s^{-1};[2] a calculation based on the bromide effect on the *p*-phenol (see later) implies that with the *N*-acyl substituent, the value may be 2–4 times larger, but no more. Thus water reacts with the nitrenium counter-ion in **IP1** with a rate constant of the order of 10^9 s^{-1}, certainly smaller than 5 × 10^9 s^{-1}. Since the overall rate constant for the reactions of this ion pair is 10^{11} s^{-1}, direct reaction with water can make only a small contribution, at most a few percent.

A single ion pair precursor for the *p*-ester?

The above analyses show that the very different trapping effects of H^+ and Br^- on the *meta* products are consistent with rate constants expected for these two ions. With the *p*-ester, the effects of H^+ and Br^- are more similar, 1 mol dm^{-3} concentrations of the two reducing the yield by 55% and 30%, respectively. This produces an inconsistency in a mechanism where a single ion pair serves as the precursor for this product. Scheme 3 provides a general model for such a mechanism. In this scheme **IP1** is the same as in Scheme 2; the pathways k_D and k_D' represent, respectively, diffusional movement of the counter-ion to a second ion pair **IP2**, and some unspecified pathway that leads to *p*-phenol. The sum $k_D + k_D'$ is equal to k_p of Scheme 2. The ion pair **IP2** is the precursor of the *p*-ester, and can also react to give *p*-phenol by an unspecified pathway or pathways k_P'.

For the experiments with added acid, this scheme results in expression (4), where the first term in parentheses represents the

$$F_{p\text{-ester}} = \left(\frac{k_D}{k_o + k_D + k_D' + k_H[H^+]}\right) \times \left(\frac{k_E}{k_E + k_p' + k_H[H^+]}\right) \qquad (4)$$



Scheme 3

fraction of **IP1** that is converted into **IP2**, and the second term represents the fraction of **IP2** that collapses to *p*-ester. Since H^+ can react with both **IP1** and **IP2**, there is a term in $k_H[H^+]$ in the denominator of each expression. Substituting the expression for F_{meta} [eqn. (3)], with some algebraic manipulation, results in eqn. (5). Thus a plot of $F_{meta}:F_{p\text{-ester}}$

$$\frac{F_{meta}}{F_{p\text{-ester}}} = \left(\frac{k_o}{k_D}\right)\left(\frac{k_E + k_p'}{k_E}\right) + \left(\frac{k_o}{k_D}\right)\left(\frac{k_H}{k_E}\right)[H^+] \quad (5)$$

versus $[H^+]$ has a slope:intercept ratio equal to $k_H:(k_E + k_p')$, and the lifetime of **IP2** $\{1:(k_E + k_p')\}$ is obtained using H^+ as a clock, without knowing the $k_D:k_D'$ and $k_E:k_p'$ ratios. For the data in Table 4, such a plot (not shown) provides a slope:intercept ratio of 0.81 ± 0.07. With the assumption that $k_H = 4 \times 10^{10}$ dm^3 mol^{-1} s^{-1}, the lifetime of **IP2** is calculated as 21 ps, approximately double the lifetime of **IP1**.

The expression for bromide takes a form similar to that of eqn. (5), with a plot of $F_{meta}:F_{p\text{-ester}}$ *versus* $[Br^-]$ having a slope:

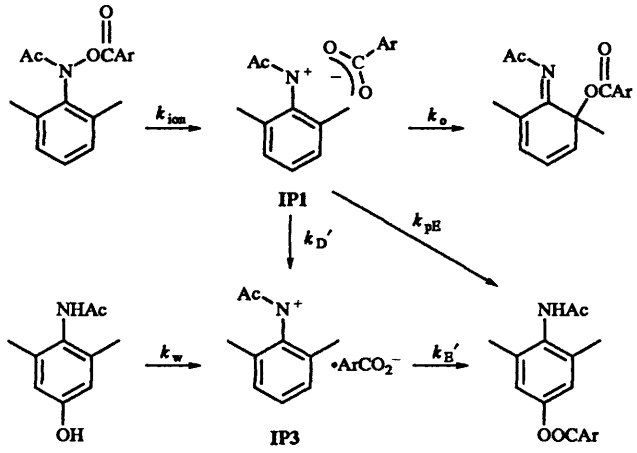
$$\frac{F_{meta}}{F_{p\text{-ester}}} = \left(\frac{k_o}{k_D}\right)\left(\frac{k_E + k_p'}{k_E}\right) + \left(\frac{k_o}{k_D}\right)\left(\frac{k_{Br}}{k_E}\right)[Br^-] \quad (6)$$

intercept ratio of $k_{Br}:(k_E + k_p')$. In this case, for the data in Table 3, the value so obtained is 0.44 ± 0.05.

It is this result that creates a problem. Using the value for $1:(k_E + k_p')$ estimated from the H^+ trapping, k_{Br} must be 2×10^{10} dm^3 mol^{-1} s^{-1}, four times greater than the upper limit calculated above, and above the diffusion limit for this type of reaction. One could argue that this inconsistency arises because of a wrong estimate for k_H. However, if there is a single ion pair leading to the *p*-ester, then the bromide data imply that this ion pair must have a very different lifetime from the ion pair leading to the *meta* products, since bromide has virtually no effect on the latter, but can affect the *p*-ester. The data for acid trapping however show that the *p*-ester is decreased by only about a factor of two more rapidly than the *meta* products, implying that the two precursor ion pairs have lifetimes that differ only by a factor of about two. In our opinion this cannot be reconciled by a single ion pair precursor to the *p*-ester.

A common intermediate for cyclohexadiene and the *p*-ester

To overcome this problem we propose that there are two different ion pairs that serve as the precursor for the *p*-ester, one that can be trapped by bromide and one that cannot be trapped One example of such a mechanism is given in Scheme 4. This ha the short-lived **IP1** collapsing not only at the *ortho* position, bu also at the *para* position by the route k_{pE}. A third pathway k_D involves diffusional movement to a longer-lived ion pai designated **IP3**. This ion pair can react with water to give the *p*-phenol and also collapse at the *para* position providing the second route to the *p*-ester. The sum $k_{pE} + k_D'$ is the same as k_p of Scheme 2.



Scheme 4

In terms of this mechanism, the fraction of *p*-phenol product is given by eqn. (7), where the first term in parentheses

$$F_{p\text{-Phenol}} = \left(\frac{k_D'}{k_o + k_D' + k_{pE}}\right)\left(\frac{k_w}{k_w + k_E' + k_{Br}[Br^-]}\right) \quad (7)$$

represents the fraction of **IP1** that goes to **IP3**, and the second term the fraction of **IP3** that reacts with water to give the *p*-phenol. Only the latter contains a term in bromide. Taking the reciprocal of this equation, [eqn. (8)], a plot of $1:F_{p\text{-phenol}}$ *versus*

$$\frac{1}{F_{p\text{-phenol}}} = \left(\frac{k_o + k_D' + k_{pE}}{k_D'}\right)\left\{\left(\frac{k_w + k_E'}{k_w}\right) + \left(\frac{k_{Br}}{k_w}\right)[Br^-]\right\} \quad (8)$$

$[Br^-]$ has a slope:intercept ratio of $k_{Br}:(k_E' + k_w)$. Thus the lifetime of **IP3** can be estimated relative to the bromide reaction, *without* knowledge of the various partitioning fractions. The plot (not shown) for the benzoyloxy data is linear, with the slope:intercept ratio equal to 1.32 ± 0.07. The value for k_{Br} is not known, but can be estimated, since, in general, ratios $k_{Hal}:k_{Az}$ for reactive carbocations are only slightly smaller than unity.[23,24] This implies that bromide, like azide, is reacting at close to the diffusion limit. We assume therefore that k_{Br} lies within the range (2.5–5) $\times 10^9$ dm^3 mol^{-1} s^{-1}, and calculate that the sum $(k_E' + k_w)$ lies within the range (2–4) $\times 10^9$ s^{-1}. Thus the lifetime of **IP3** is of the order of 0.25–0.5 ns. This is a not unreasonable value, considering that the free 2,6-dimethylnitrenium ion has a lifetime $(1:k_w)$ of 1.4 ns.[2] The nitrenium ion in **IP3** of course has an *N*-acetyl substituent, not N–H, and this will increase k_w. Judging from data for other arylnitrenium ions, an effect of the order of 2–3 is expected.[19,25] The ion pair **IP3** can also react by the internal return pathway k_E', although as will be seen in later analyses, this likely only represents about 20% of the fate of **IP3**.

The expression for the bromide dependence of the *p*-ester is more complex, where the two terms on the right hand side

$$F_{p\text{-ester}} = \left(\frac{k_{pE}}{k_o + k_D' + k_{pE}}\right) + \left(\frac{k_D'}{k_o + k_D' + k_{pE}}\right)\left(\frac{k_E'}{k_w + k_E' + k_{Br}[Br^-]}\right) \quad (9)$$

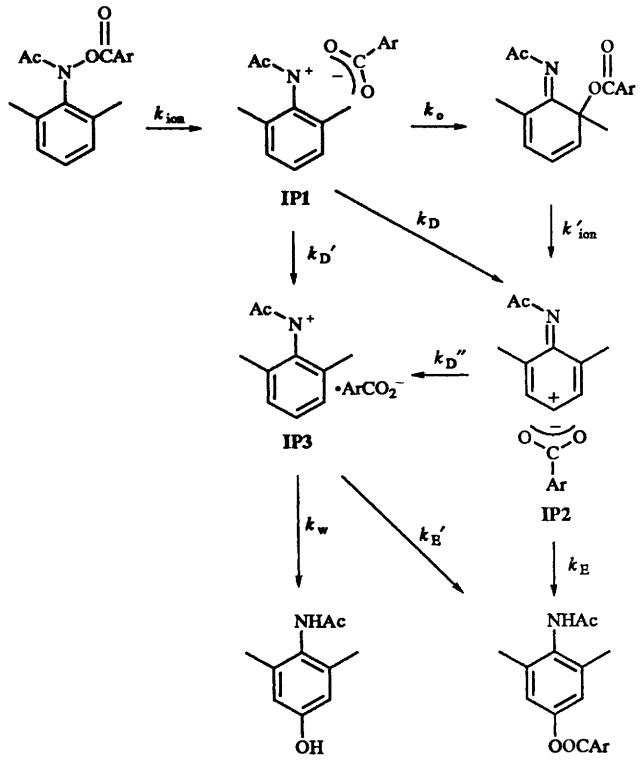
represent *p*-ester arising directly from **IP1** and indirectly from **IP3**. This equation has three independent terms, $k_{Br}:(k_w + k_E')$, $k_E:(k_w + k_E')$, and $k_D':(k_o + k_D' + k_{pE})$. The fraction $k_{pE}:(k_o + k_D' + k_{pE})$ is not independent, being equal to $1 - k_D':(k_o + k_D' + k_{pE}) - k_o:(k_o + k_D' + k_{pE})$, where the latter fraction is known since this is just F_{meta} (0.40 for the benzoyloxy compound). Using the value of $k_{Br}:(k_w + k_E')$ obtained from the *p*-phenol data, an iterative procedure was carried out, varying the two other fractions until the best fit of eqn. (9) to the experimental data was obtained. This provided values of $k_{pE}:(k_o + k_D' + k_{pE}) = 0.10$, $k_D':(k_o + k_D' + k_{pE}) = 0.50$ and $k_E':(k_w + k_E') = 0.22$. Thus for the benzoyloxy system, the mechanism of Scheme 4 has **IP1** partitioning 40% to cyclohexadiene, 10% to the *p*-ester and 50% to **IP3**. The latter in turn partitions 78% to *p*-phenol and 22% to the *p*-ester. The total yield of *p*-ester in the absence of bromide is 21%, 10% coming directly from **IP1** and 11% from **IP3**. In the presence of bromide, the *p*-ester arising from **IP3** is decreased at the same rate as the *p*-phenol, while the fraction arising from **IP1** is unaffected. With the approximately 50:50 breakdown between these two routes, the overall result is that bromide has about half the effect on the *p*-ester as on the *p*-phenol.

A similar argument explains the differential effects of H^+. The *p*-ester that arises from **IP1** is obviously affected to the same extent as the cyclohexadiene, but the *p*-ester from the longer-lived **IP3** is reduced much more. Overall therefore, H^+ has a greater effect on the yield of *p*-ester.

Scheme 4, with its two ion pairs, does explain qualitatively and quantitatively the results starting with hydroxylamine ester. However, a third ion pair is now required to account for the ionization reaction of the cyclohexadiene resulting in a greater *p*-ester:*p*-phenol ratio than obtained with the hydroxylamine. A mechanism where the cyclohexadiene ionizes only through **IP1** would result in the same ratio independent of starting state, since the various partitionings that give rise to the *para* products would then be identical. A mechanism where the cyclohexadiene ionizes to **IP3** would result in relatively more *p*-phenol than obtained from the hydroxylamine derivative, since the latter has the additional route to *p*-ester *via* **IP1**. Mechanisms that involve ionization to both **IP1** and **IP3** would result in some intermediate situation, but always with more phenol from the cyclohexadiene than from the hydroxylamine. The only way to reconcile this is to have the cyclohexadiene ionize, at least in part, to an ion pair that is different from **IP1** and **IP3**, an ion pair that results in the greater amount of *p*-ester.

Three ion pair intermediates

Scheme 5 provides a mechanism incorporating features of the previous ones, and that avoids the problem of having the cyclohexadiene ionize to a different ion pair. In this mechanism, the initial ion pair partitions between collapse to the *meta* products and rearrangement to two new ion pairs **IP2** and **IP3**. The sum $k_D + k_D'$ is equal to k_p of Scheme 2. The ion pair **IP2** is also short-lived, and cannot be trapped by bromide. The fate of **IP2** is internal return and diffusional separation to **IP3**. The ion pair **IP3** is identical with the same ion pair in Scheme 4, being a longer-lived ion pair producing both *p*-phenol and *p*-ester, and capable of reaction with bromide. The difference between Schemes 4 and 5 is that the short-lived ion pair providing *p*-ester in Scheme 5 is not the same as the one that collapses to cyclohexadiene.



Scheme 5

For this mechanism, **IP3** forms directly from **IP1** and indirectly from **IP2**. With **IP1** and **IP2** being unaffected by bromide, the fraction of *p*-phenol forming with bromide present is given by expression (10).

$$F_{p\text{-phenol}} = \left[\left(\frac{k_D'}{k_D + k_D' + k_p}\right) + \left(\frac{k_D}{k_D + k_D' + k_p}\right) \times \left(\frac{k_D''}{k_E + k_D''}\right)\right]\left(\frac{k_w}{k_E' + k_w + k_{Br}[Br^-]}\right) \quad (10)$$

This equation contains three independent partitioning fractions, [eqns. (11)–(13)]. As in a previous analysis, the

$$x = \left(\frac{k_D}{k_o + k_D + k_D'}\right) \quad (11)$$

$$y = \left(\frac{k_E}{k_E + k_D''}\right) \quad (12)$$

$$z = \left(\frac{k_E'}{k_E' + k_w}\right) \quad (13)$$

fraction $k_o:(k_o + k_D + k_D')$ is known, since this is simply F_{meta} in the absence of any trapping agent, and therefore the fraction $k_D':(k_o + k_D + k_D')$ can be expressed in terms of x as $(1 - x - F_{meta})$.

With the appropriate substitutions of x, y and z, eqn. (10) can be rewritten as eqn. (14). Thus a plot of $1:F_{p\text{-phenol}}$ *versus* $[Br^-]$

$$\frac{1}{F_{p\text{-phenol}}} = \left(\frac{1}{(1 - F_{meta} - xy)(1 - z)}\right) \times \left(1 + \frac{k_{Br}}{k_E' + k_w}[Br^-]\right) \quad (14)$$

has a slope:intercept ratio of $k_{Br}:(k_E' + k_w)$, providing the lifetime of **IP3** relative to the bromide reaction, without knowledge of the partitioning fractions. This of course is exactly the same situation as arose in the analysis of Scheme 4. The ion pairs designated **IP3** in Schemes 4 and 5 are the same, with lifetimes in the range 0.25–0.5 ns.

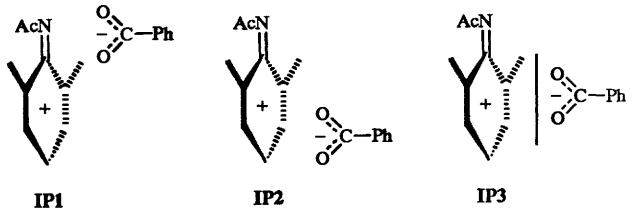
In terms of Scheme 5, the yield of *p*-ester is given by expression (15) where *x*, *y* and *z* are defined as in eqns. (11)–(13).

$$F_{p\text{-ester}} = xy + z(1 - F_{meta} - xy) \times \left(\frac{1}{1 - \frac{k_{Br}}{k_E' + k_w}[Br^-]}\right) \quad (15)$$

The analysis of the data for the *p*-phenol has provided the value of $k_{Br}:(k_E' + k_w)$, and we can therefore plot $F_{p\text{-ester}}$ *versus* the entire quantity in brackets containing $[Br^-]$. Such a plot (not shown) is linear; the slope and intercept are 0.112 ± 0.009 and 0.100 ± 0.007, respectively. The latter is equal to *xy*, the fraction of **IP1** that is converted into **IP2** times the fraction of the latter that collapses to give *p*-ester. The individual values of *x* and *y* cannot be obtained; their product however does represent the yield of *p*-ester that cannot be changed by added bromide. The slope is equal to $z(1 - F_{meta} - xy)$, and since *xy* and F_{meta} are known, *z* can be calculated as 0.22. This is the fraction of **IP3** that reacts by internal return to give *p*-ester. It can be seen that the numbers here are the same as obtained in the analysis of Scheme 4, the ion pair **IP3** reacting about 20% by internal return, and a 10% yield of *p*-ester (*ca.* half the total yield) that cannot be trapped by bromide.

The explanations behind the differential effects of bromide and acid apply equally as well to Scheme 5 as to Scheme 4. Bromide can decrease the yield of the *p*-ester that comes from **IP3**, but not the quantity derived from **IP2**, so that the overall decrease is not as great as observed with the *p*-phenol. Similarly acid will have a much greater effect on **IP3** than **IP2**, and thus *p*-ester will fall off more rapidly than the cyclohexadiene-derived products. Unfortunately, the expression for the effect of H^+ on the yield of *p*-ester is intractable, and only this qualitative statement can be made.

In terms of the structures of the ion pairs, both **IP1** and **IP2** can be regarded as tight ion pairs. We can speculate that the former has the carboxylate still associated with the nitrogen to which it had been attached prior to the N–O heterolysis, while the carboxylate in the latter has moved over the aromatic ring. The longer-lived **IP3** could be regarded as a solvent-separated ion pair.



IP1 **IP2** **IP3**

The mechanism of Scheme 5 has the feature that it is not necessary to invoke another ion pair to explain the results for the cyclohexadiene, since these can be explained by incorporating a pathway in which this species ionizes directly to **IP2**. In this way, the pathway **IP1** ⟶ **IP3** ⟶ phenol leading to *p*-phenol does not occur when the cyclohexadiene is the precursor, so that this compound will produce a greater *p*-ester:*p*-phenol ratio than the hydroxylamine ester. The ionization of the cyclohexadiene obviously need not go totally to **IP2**. A pathway *via* **IP1** is also allowed, provided there is some fraction proceeding to **IP2**, enough to account for the different products. The ion pair **IP2** could conceivably also be converted back into **IP1**. However, it is important to note that complete equilibration between **IP1** and **IP2** is not allowed, since this would mean that the cyclohexadiene and the hydroxylamine ester would give the same *p*-ester:*p*-phenol ratio. Conversion of **IP3** back into **IP1** is not allowed, at least not in significant amounts. If this were to occur, bromide would reduce the yield of cyclohexadiene-derived products by intercepting **IP3** and preventing the return to **IP1**.

Conclusions

The models presented in Schemes 4 and 5 both satisfy the experimental data, although the latter seems more reasonable since it incorporates in the same mechanism the results for the cyclohexadiene. These are not the only mechanisms and we do not wish to claim that they are. Other mechanisms that would satisfy the experimental data also exist, and particularly if interconversions of ion pairs are considered, the analysis is indeed complicated. Overall, no single mechanism provides an unambiguous fit to the data. However, whatever the mechanism, the analysis presented above shows that there must be three cationic intermediates in the product-determining steps. Some of these are extremely short-lived, and cannot be trapped by external nucleophiles. Other intermediates, on the other hand, are capable of reaction with added nucleophiles. However, even here, the most long-lived ion pair (or free cation) has a lifetime of less than a nanosecond.

Experimental

The hydroxylamine esters **1**, products **3**–**6**, and HPLC conditions for the quantitative analysis of these reactions are described in the preceding paper.[1] 2,6-Dimethylacetanilide was prepared by acetylating 2,6-dimethylaniline, and 4-bromo-2,6-dimethylacetanilide was prepared by aqueous bromination of 2,6-dimethylacetanilide.

Kinetic analyses for the benzoate **1a** and the *m*-nitrobenzoate **1b** were performed following the disappearance of the peak for the compound with HPLC. The pentafluoro compound **1c** was studied following a change in the UV spectrum at 240 nm.

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