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PAPER

Kinetic and computational evidence for an intermediate in the hydrolysis of sulfonate esters†

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The hydrolytic reactions of sulfonate esters have previously been considered to occur by concerted mechanisms. We now report the observation of a break in a Brønsted correlation for the alkaline hydrolysis of aryl benzenesulfonates. On either side of a break-point, $\beta_{leaving\ group}$ values of −0.27 ($pK_a < 8.5$) and −0.97 ($pK_a > 8.5$) are measured. These data are consistent with a two-step mechanism involving a pentavalent intermediate that is also supported by QM/MM calculations. The emerging scenario can be explained by the combined effect of a strong nucleophile with a poor leaving group that compel a usually concerted reaction to favour a stepwise process.

Introduction

Group transfer reactions play a central role in biology, encompassing the transfer of a range of ester and glycosyl groups to nucleophiles, including water. Phosphate transfer in particular is ubiquitous, from simple hydrolysis reactions to the processing of genetic information in DNA and RNA. Phosphate groups are used as energy transfer units in primary metabolism, but also in posttranslational modifications of peptides and proteins that trigger signalling pathways.[1] Sulfate groups are similarly transferred in the regulation of cellular communication events such as inflammation, cancer metastasis, microbial pathogenesis and hormone regulation.[2,3]

Enzymes catalyse these transfer reactions by stabilising their transition states, so the study of these high-energy species (including energetically similar intermediates) in simpler systems is important for understanding such reactions. Conventionally, significant rate accelerations have been thought to require highly specific interactions between the transition state and the enzyme, but many enzymes are now known to display "promiscuity".[4–8] This ability to catalyse a range of distinct reactions, often quite efficiently, raises questions about the molecular recognition mechanisms responsible for specificity and catalysis.

One enzyme that displays remarkable promiscuity is the phosphate diesterase/phosphonate monoesterase PMH, a member of the alkaline phosphatase superfamily.[9,10] Several members of this superfamily are able to hydrolyse a range of different esters and ester types (including phosphate mono- and diesters, and sulfate monoesters).[7,11–17] PMH not only catalyses these reactions, but also accepts sulfonate esters as substrates.[15] Sulfonate esters are close analogues of phosphate and sulfate esters, but do not appear to play a correspondingly vital role in nature. Many aerobic bacteria are able to use aromatic and aliphatic sulfonates ($R–SO_3^-$) as sulfur sources when inorganic sulfate is limited,[18,19] but the promiscuous activity of PMH is the first reported example of a natural enzyme able to catalyse sulfonyl group transfer. Bacteria that are able to use sulfonates rely on desulfonation reactions catalysed by α-ketoglutarate-dependent taurine dioxygenases or $FMNH_2$-dependent monooxygenases.[18,19] These enzymes catalyse the oxygen-dependent formation of α-hydroxysulfonate intermediates ($R–C(OH)–SO_3^-$) which are unstable and spontaneously decompose to an aldehyde and sulfite *via* C–S bond cleavage. In contrast, PMH catalyses hydrolysis of sulfonate esters *via* cleavage of the S–O bond to the leaving group[15] and this process has been studied mechanistically in this work.

Phosphate and sulfate group transfer reactions proceed *via* pentavalent transition states that can be classified as associative or dissociative, depending on whether formation of the transition state involves an increase or decrease, respectively, of the formal bond order. In solution, phosphate and sulfate monoesters react *via* dissociative transition states while reactions of phosphate di- and triesters are typically associative.[1,20–28] There is general agreement that phosphate transfer from monoester dianions does not involve pentavalent addition intermediates: such an intermediate was mistakenly identified in a crystal structure of the β-phosphoglucomutase active site,[29] but the structure was later shown to be a magnesium fluoride complex.[30–33]

Sulfonyl transfer reactions also proceed *via* pentacovalent species. In contrast to phosphate esters, sulfonate esters are

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uncharged, so that transition states and potential intermediates have less negative charge build-up compared to sulfate and phosphate group transfers. Nevertheless, so far no intermediate has been identified in any reaction involving sulfonate transfer between oxyanions[34–38] (although intermediates have been inferred in the related sultams).[39–41] We have revisited this reaction and report convincing kinetic and computational evidence for a reaction intermediate.

Results

We measured rates of alkaline hydrolysis for a series of benzenesulfonates in which the phenolate leaving group substituent was varied (Scheme 1). Reaction progress was measured by the increase in absorbance resulting from formation of the substituted phenolate products.

Hydrolysis of benzenesulfonates

The reaction of 4-nitrophenyl benzenesulfonate with hydroxide was followed in aqueous KOH solutions at 50 °C under pseudo-first-order conditions. The observed progress curves were fit to an exponential equation to give first order rate constants k_{obs} (Fig. S1†). To distinguish between hydroxide attack on the sulfonate group and the alternative mechanism in which the nucleophile attacks the activated 4-nitrophenyl ring, the reaction was carried out in the presence of ^{18}O-labelled water. Mass-spectrometric analysis (LC-MS, Fig. S2†) was used to distinguish between the two possible isotopically-labelled products: $PhSO_2{}^{18}O^-$ (generated by direct attack on sulfur) or $(O_2N)C_6H_4{}^{18}O^-$ (resulting from the displacement of the sulfonate anion by an S_NAr reaction). The exclusive product was $PhSO_2{}^{18}O^-$, establishing that direct nucleophilic attack on sulfonate sulfur is the predominant reaction pathway. The S_NAr mechanism is less likely for all other substrates (except 3-F-4-NO_2-phenyl benzenesulfonate, which shows no sign of special reactivity), so can safely be excluded for the entire group of compounds studied. The rate of hydrolysis of 4-nitrophenyl benzenesulfonate is first order with respect to both hydroxide and substrate concentrations (Fig. S3†), evidence that both species are involved in the rate determining transition state. The results of the following kinetic investigations are consistent with this assumption.

Thermodynamic parameters

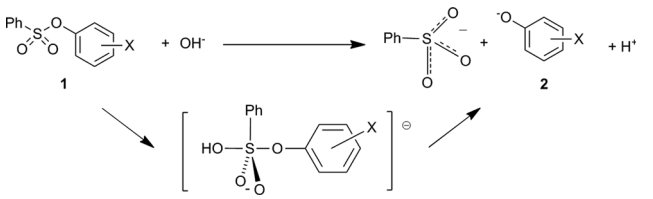
Activation parameters $\Delta S^‡$ and $\Delta H^‡$ were calculated from the temperature dependence of 4-nitrophenyl- and phenyl benzenesulfonate reaction rates (Table 1; Fig. S4†). The large negative entropies of activation are consistent with an associative mechanism, with bond making to the nucleophile under way and bond breaking to the leaving group incomplete in the rate determining transition state. The transition states are thus likely to involve a formal increase in bond order with charge accumulation on the sulfonate oxygen atoms.

Brønsted correlations

Details of the bond making and breaking processes that occur during the reaction can be derived from linear free energy relationships, and expressed as the coefficients of the relevant Brønsted correlations.[42,43] Substituents **X** on the phenolate anion leaving group were varied to determine the β_{LG} value for the reactions of phenyl benzenesulfonates with hydroxide. The sensitivity of reaction rate to the leaving group pK_a gives a quantitative measure of charge change at the leaving group oxygen on formation of the transition state, and thus an indication of the extent of bond cleavage.[43] Eight benzenesulfonates with substituted phenols as leaving groups were synthesised, and clean first order rate constants k_{obs} observed for the hydrolysis of each compound in 0.1 M KOH solutions. Fig. 1 shows the Brønsted correlation of the observed rate constants k_{obs} with the pK_a values of the leaving groups.

The plot exhibits two well-defined linear regions: a shallow gradient (β_{LG} = −0.27 ± 0.05) is observed for sulfonates with leaving groups of lower pK_a (<8.5) but the slope is much steeper (β_{LG} = −0.97 ± 0.03) for compounds with leaving groups with higher pK_a values (>8.5). Such a break in a Brønsted plot is typically caused by a change in the rate-determining step of a multi-step reaction: a change to an alternative mechanism as the leaving group pK_a is varied requires the reaction post-break to be faster.[42–45] For the hydrolytic reaction studied here, a two-step mechanism involving a pentavalent intermediate (Scheme 2, eqn (i)) is the obvious starting point.

Although in principle either formation or breakdown of the pentacovalent intermediate **INT** (Scheme 2) could be rate determining, the alkaline hydrolysis of esters is a special case. Hydroxide, because it is more basic, is a poorer leaving group than any aryloxide anion so the addition step must be rate determining (*i.e.* $k_{-1} < k_2$) for a two-step mechanism, for all eight esters **1**. Since the break in the Brønsted plot of Fig. 1 cannot be the result of a change to an alternative mechanism over the series of compounds tested, it must signal a change of the rate determining transition state on a common reaction coordinate. The only feasible alternative TS for this simple reaction is the concerted displacement of aryloxide by hydroxide. The lifetime of



Scheme 1 Alkaline hydrolysis of benzenesulfonates. The hydrolysis of sulfonate esters **1** in water involves hydroxide ion as the nucleophile and leads to sulfonate and phenolate anions **2**, by way of a pentacovalent species that may be a full intermediate.

Table 1 Activation parameters for hydrolysis of phenyl benzenesulfonates **1**

	1, X = 4-NO_2	**1**, X = H
E_a/kJ mol^{-1}	58 ± 1	71 ± 2
$\Delta H^‡$ (25 °C)/kJ mol^{-1}	55 ± 1	68 ± 2
$\Delta S^‡$ (25 °C)/J mol^{-1} K^{-1}	−113 ± 3	−104 ± 5

Conditions: [phenyl benzenesulfonate] = 300 μM; [4-nitrophenyl benzenesulfonate] = 40 μM; 0.1 M KOH; T = 30–60 °C.

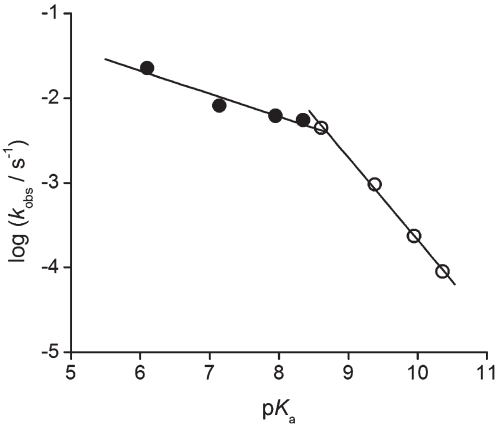
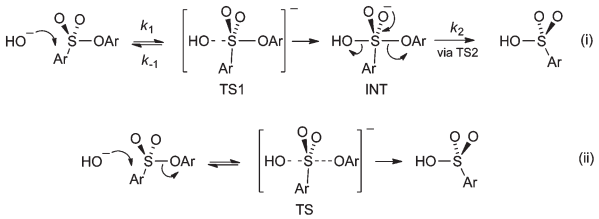


Fig. 1 Brønsted correlation for the alkaline hydrolysis of benzenesulfonates. Compounds studied (in order of increasing leaving group pK_a): 3-fluoro-4-nitrophenyl, 4-nitrophenyl, 4-cyanophenyl, 3-nitrophenyl, 4-chlorophenyl, 3-cyanophenyl, phenyl, and 3,4-dimethylphenyl benzenesulfonates. *Conditions*: 0.1 M KOH; T = 50 °C. The gradients of the two lines are: −0.27 ± 0.05 (R^2 = 0.96) and −0.97 ± 0.03 (R^2 = 0.99).



Scheme 2 Alternative pathways for the alkaline hydrolysis of aryl benzenesulfonates **1**. Both involve rate-determining attack of hydroxide on the central sulfur atom: to form a pentavalent intermediate in a two-step mechanism (i), and in a concerted $S_N2(S)$ process (ii).

the intermediate (**INT**, Scheme 2) is determined primarily by k_2, the greater of the two rate constants for its decomposition, which will be particularly sensitive to the leaving group pK_a. Evidently this lifetime becomes insignificant when pK_a < 8.5, so the reaction becomes concerted. Thus the common pathway (Scheme 2) involves formation of the pentacovalent species in both cases, but this has a significant lifetime only when the leaving group pK_a > 8.5. The different β_{LG} values determined from the Brønsted plot indicate that the transition state for the formation of the intermediate during the two-step process (Scheme 2, eqn (i)) is very close in structure to the high-energy intermediate, while that for the concerted process (Scheme 2, eqn (ii)) must be considerably earlier.

A concerted reaction with a shifting TS structure would yield a curved plot with a rather less pronounced break (analogous to those seen for stepwise reactions involving a change in the rate determining step).[46–48] A fit to this model is possible based on our data (see ESI, Fig. S7†), but is ultimately discounted based on the computational results described in the next paragraph.

Confirmation and characterisation of the intermediate by *ab initio* molecular orbital calculations

The structure of the potential intermediate was probed by *ab initio* molecular orbital calculations performed using the

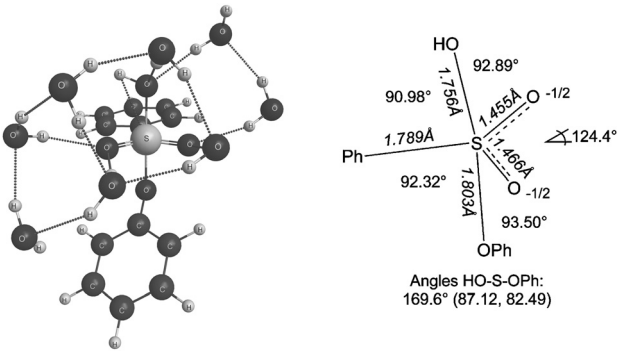


Fig. 2 Calculated structure of the proposed pentacovalent intermediate **INT** resulting from the attack of a hydroxide anion on the sulfur centre of phenyl benzenesulfonate, with selected bond lengths and angles at the central sulfur.

Effective Fragment Potential (EFP) method and the Conductor-like Polarizable Continuum Model (C-PCM).[49,50] This QM/MM technique was used to model solvation in a cluster with eight water molecules. In the EFP approach the solute is considered at the full *ab initio* level, and the solvent cluster allows a set of non-bonding interactions such as Coulomb interactions, dipole polarizability, and repulsive potential to be included. In addition long-range interactions and dielectric stability are taken into account by point charges generated by the C-PCM method. Optimization should identify any stable intermediate structure for the reaction between hydroxide and phenyl benzenesulfonate.

Fig. 2 shows the structure of the pentacovalent species to which calculations converge (RMS gradient 2.481.70 × 10^{-5} Hartree $Bohr^{-1}$), where the EFP/C-PCM approach introduces an extra stability of −57.61 kcal mol^{-1}. The axis of the pentacoordinate species shows significant deviation from linearity (approximately 170° rather than 180°), perhaps as the result of steric interactions between the sulfonyl group oxygens and the aromatic rings. The apical S–O bond length to the hydroxide nucleophile is significantly shorter (1.756 Å) than that to the leaving group oxygen (1.803 Å), consistent with an intermediate structure closer to products. This conclusion is amply confirmed by the remarkable extension of this bond when compared with the starting material, as discussed below.

The introduction of discrete water molecules into the calculation proved to be crucial. Without hydrogen bonding between the solvent and the sulfonate the intermediate shown in Fig. 2 was found not to be stable. In the absence of water no stationary point could be identified using the continuous model C-PCM,[51] or under gas phase conditions. These observations indicate that, at least in this case, continuous models for solvation do not themselves account adequately for the experimental evidence.[52] If the continuous-medium approach fails for calculation of this simple species in solution, it is unlikely to be reliable in an enzyme active site, where the local environment cannot be reliably predicted and individual hydrogen bonding interactions are likely to play an even greater role.

Identical calculations to those used for phenyl benzenesulfonate also predicted an intermediate to form during the reaction of the 3,4-dimethylphenyl derivative with hydroxide. However, no stable intermediate could be found at this level of theory for the reaction of hydroxide with 4-nitro or 4-cyanophenyl

benzenesulfonates, consistent with the absence of INT for the substrates falling to the left of the break in the Brønsted plot. Calculations using these substrates converged at species close to the stable products with S–O bond lengths to the leaving group that are too long to be considered bonded (1.94 and 1.92 Å for 4-nitro- and 4-cyanosulfonate, respectively).

In the calculated cluster-structure for **INT** (Fig. 2) the water molecules form a hydrogen bonding network, interacting with the negatively charged oxygen atoms of the intermediate and each other. The distances between the substrate backbone and the first solvation shell range from 2.89 to 4.30 Å. Two hydrogen bonds are observed to each of the two sulfuryl oxygens, which show high sp^2 character and are in hydrogen bonding contact, almost in the plane of the sulfonyl group. Six further water molecules provide additional stabilization for those in direct contact with the sulfuryl oxygens.

Most significant for the discussion of the mechanism are the S–O bond lengths to the incoming nucleophile (1.756 Å) and to the leaving group (1.803 Å). The relative lengths of these two bonds are consistent with bond-breaking to, and thus the development of negative charge on, the leaving group, being well-advanced in the intermediate and thus in the transition state leading to it. Consistent with this conclusion is the increase in the absolute length of the S–OAr bond compared with that predicted for the reactant. High quality crystal structures are available for aryl benzenesulfonate esters.[53–56] Closest in reactivity to the phenyl ester **1** (R = Ph) is the *p*-acetylaminophenyl derivative (σ_p for NHAc is close to zero) for which the length of the S–OAr bond to the leaving group is 1.586 Å[57] (compared with 1.606 Å for the *p*-nitrophenyl derivative, with the best leaving group of the set).[54,55,57] The bond-length extension from the starting material to intermediate **INT** – and by a short extrapolation to the transition state leading to it – is a substantial 14%. These observations are entirely consistent with the large Brønsted value observed for the loss of higher pK_a leaving groups, which indicates a more product-like transition state compared with the concerted process.

Discussion

Two new pieces of evidence support the existence of an intermediate during the hydrolysis of benzenesulfonate esters **1** with poor leaving groups:

(i) The break in the linear free energy relationship (Fig. 1) at leaving group pK_a ~ 8.5 is evidence for a change in the rate-determining transition state as the leaving group is varied: different degrees of charge accumulation on the leaving group result in the two distinct slopes in Fig. 1. Fig. 3 shows simplified free energy profiles for the two mechanisms operating on either side of the break-point in the Brønsted plot. Hydroxide attack is rate determining in both cases. For poor leaving groups the reaction is stepwise, with substantial development of negative charge on the leaving group oxygen in **TS1**: consistent with it being close in structure to the intermediate **INT** (where the bond to the nucleophile is fully formed). For better leaving groups the pentacovalent **INT** becomes too short-lived to be a kinetically significant intermediate. The observed values of β_{LG} reflect the difference in effective charge on the leaving group oxygen between the ground and the transition state: the increase in β_{LG} from −0.97 to −0.27 marking a change to an early transition state for the most reactive systems.

(ii) Calculations of the possible intermediate structure find a stable energy minimum for the addition of hydroxide to phenyl benzenesulfonate (**1**, X = H: leaving group pK_a > 8.5). The significant asymmetry in the bonds that are made and broken (Fig. 2) is consistent with the observed Brønsted values. The calculated extension of the bond to the leaving group is consistent with the negative β_{LG} value of −0.97. A recent theoretical analysis of the alkaline hydrolysis of a series of alkyl and aryl dimethyl phosphate triesters arrives at almost identical conclusions: that "for esters with poor leaving groups (pK_{LG} > 8) the reaction occurs *via* a stepwise mechanism, whereas for good leaving groups, it occurs *via* a concerted mechanism".[58]

The distinction between the two pathways is illustrated in more detail in Scheme 3.

Williams and his co-workers studied sulfonyl transfer from a series of aryl 4-nitrobenzenesulfonates to the phenolate anion, and from 4-nitrophenyl 4-nitrobenzenesulfonate to a broad range of oxygen nucleophiles (but not hydroxide).[38] Brønsted plots were linear throughout the pK_a ranges studied, the absence of the

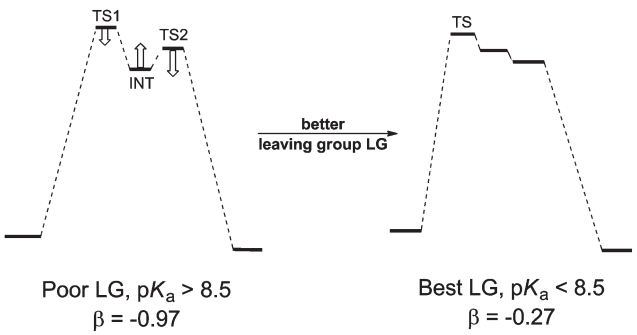
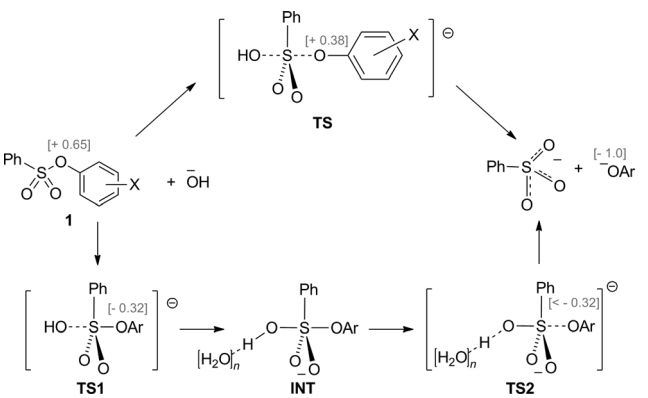


Fig. 3 Free-energy diagrams for the hydrolysis of sulfonate esters in water by hydroxide (Scheme 2). **TS2** never becomes rate determining because hydroxide is always a poorer leaving group than ArO^-. The intermediate **INT** is kinetically significant only for leaving groups of relatively high pK_a (LG: leaving group).



Scheme 3 Concerted and stepwise pathways compared for the reaction of Scheme 1 and the free energy profiles of Fig. 3. Effective charges on the leaving group oxygen are based on the $\beta_{equilibrium}$ of 1.6 ± 0.2 estimated for the reactions of aryl *p*-nitrobenzene sulfonates with substituted phenolates.[38]

break expected for a two-step mechanism indicating that the reactions are concerted. Values of 0.64 and −0.91 for β_{nuc} and β_{LG}, respectively, allowed an estimate of 1.6 ± 0.2 for $\beta_{equilibrium}$.

There is a big difference in the β_{LG} values determined for the concerted mechanism in this work, and by D'Rozario *et al.*[38] for the concerted sulfonyl group transfer from aryl 4-nitrobenzenesulfonates to phenoxide. A similar range of leaving group pK_a values was used in both investigations, but the observed β_{LG} changes from −0.27 to −0.91 with the change of nucleophile from hydroxide (this work) to phenolate.[38] This change must be due to the weaker phenolate nucleophile shifting the transition state to a more product-like structure, with greater cleavage of the bond to and charge accumulation on the leaving group oxygen during the reaction. Sensitivity of β_{LG} values to the basicity of the nucleophile has also been observed for reactions of dialkyl aryl phosphate triesters where a β_{LG} of −0.36 was measured for the hydroxide reaction and −0.99 for attack by water:[23] as the more reactive species hydroxide promotes a much earlier transition state. Zalatan *et al.*[11] found a similar β_{LG} (−0.97) for the alkaline hydrolysis of ethyl aryl phosphate diesters. Interestingly the Brønsted plot in this work showed signs of a break (similar to that of Fig. 1) for the 4-nitrophenyl ester (the best leaving group used), although this deviation was explained in terms of a "resonance effect".

The available data suggest that the viability of an addition intermediate (like **INT** in this work) depends on the electrophilicity of the reacting ester and the nucleophilicity/leaving group ability of the incoming and the departing group. Most favourable is the combination of a strong nucleophile with a (similarly) poor leaving group. Sulfonates **1**, like phosphodiesters,[43] can be expected to undergo concerted displacements if both the nucleophile and the leaving group are weakly nucleophilic.

Experimental

Materials

Chemicals were purchased from Sigma-Aldrich, Fluka and Breckland Scientific Supplies. ^{1}H NMR spectra were obtained on a Bruker Avance 500 Dual Cryo spectrometer. Mass spectra of benzenesulfonates were recorded on a Micromass Quattro II triple quadrupole instrument by the EPSRC National Mass Spectrometry Service Centre (University of Wales Swansea). Mass spectra of the hydrolysis products from the isotope labelling experiment were recorded on a Waters ZQ instrument.

Synthesis of phenyl sulfonates

Benzylsulfonylchloride (2.81 ml, 22 mmol) was added dropwise to a solution of 3- or 4-nitrophenol (2.78 g, 20 mmol) in pyridine (50 ml) to prepare 3- and 4-nitrophenyl benzenesulfonates. The other benzenesulfonates were prepared by adding benzylsulfonylchloride (1.28 ml, 10 mmol) dropwise to a solution of the appropriate phenol (10 mmol) in tetrahydrofuran (20 ml) with triethylamine (1.67 ml, 12 mmol). All reactions were stirred overnight at room temperature and then filtered to remove the precipitate. The solvent was evaporated, and the crude product redissolved in dichloromethane. The organic phase was washed with saturated $NaHCO_3$ solution and water, and dried with anhydrous sodium sulfate. The solvent was removed under reduced pressure, and the product purified by column chromatography on silica (cyclohexane–ethyl acetate, varying ratios) where necessary.

Product characterisation

^{1}H NMR (500 MHz, $CDCl_3$, Ar–H unless stated otherwise) and mass spectrometry results for substituted phenyl benzenesulfonates (X = phenyl substitution):

X	Yield	^{1}H NMR shifts, δ/ppm	MS m/z [M^+]
3-F-4-NO_2	0.97 g, 3.3 mmol, 33%	8.04 (1H, m), 7.89–7.86 (2H, m), 7.76–7.72 (1H, m), 7.61–7.57 (2H, m), 7.05–6.95 (2H, m)	Calculated 297.0 found 297.1
4-NO_2	4.10 g, 15 mmol, 75%	8.18–8.13 (2H, m), 7.85–7.81 (2H, m), 7.72–7.67 (1H, m), 7.57–7.53 (2H, m), 7.18–7.13 (2H, m)	Calculated 279.0 found 279.3
4-CN	1.84 g, 7.1 mmol, 71%	7.85–7.82 (2H, m), 7.73–7.68 (1H, m), 7.63–7.59 (2H, m), 7.58–7.53 (2H, m), 7.14–7.10 (2H, m)	Calculated 259.0 found 259.3
3-NO_2	2.93 g, 10.5 mmol, 53%	8.15–8.12 (1H, m), 7.88–7.84 (2H, m), 7.79 (1H, t, J = 2.23 Hz), 7.74–7.70 (1H, m), 7.60–7.55 (2H, m), 7.52 (1H, t, J = 8.20 Hz), 7.43–7.39 (1H, m)	Calculated 279.0 found 279.3
3-CN	0.46 g, 1.8 mmol, 18%	7.85–7.81 (2H, m), 7.73–7.69 (1H, m), 7.59–7.54 (3H, m), 7.43 (1H, t, J = 8.04 Hz), 7.31–7.28 (1H, m), 7.25–7.23 (1H, m)	Calculated 259.0 found 259.0
4-Cl	0.85 g, 3.2 mmol, 32%	7.83–7.80 (2H, m), 7.70–7.65 (1H, m), 7.55–7.51 (2H, m), 7.26–7.22 (2H, m), 6.93–6.89 (2H, m)	Calculated 268.0 found 268.0
H	0.87 g, 4 mmol, 37%	7.84–7.80 (2H, m), 7.67–7.63 (1H, m), 7.54–7.49 (2H, m), 7.30–7.21 (3H, m), 6.98–6.95 (2H, m)	Calculated 234.0 found 234.1
3,4-diMe	0.93 g, 3.6 mmol, 36%	7.85–7.81 (2H, m), 7.67–7.62 (1H, m), 7.54–7.49 (2H, m), 6.98 (1H, d, J = 8.25 Hz), 6.78 (1H, d, J = 2.50 Hz), 6.62 (1H, dd, J = 8.23, 2.53 Hz), 2.19 (3H, s, Me–H), 2.17 (3H, s, Me–H)	Calculated 262.1 found 262.0

Kinetic measurements

A Varian Cary 100 Scan UV-visible spectrophotometer was used to follow kinetic runs, and the Cary WINUV kinetics application was used for analysis. The optimal wavelength to monitor each reaction was determined by repetitive wavelength scans. Product formation was followed by measuring the increase in absorbance

due to the phenolate ion at the following wavelengths: 4-nitro (400, 440 or 442 nm), 3-nitro (395 nm), 3-fluoro-4-nitro (440 nm), 4-chloro (299 nm), 3-cyano (291 nm), 4-cyano (276 nm), 3,4-dimethyl (237 nm), and unsubstituted (280 nm). Reactions were initiated by adding 10–50 μl of the sulfonate dissolved in acetonitrile to preheated aqueous solutions in quartz cuvettes (final volume of 1 ml).

Hydroxide ion concentrations were much greater (>300-fold) than sulfonate concentrations to obtain pseudo-first-order conditions. Origin 6.0 (Microcal Software) was used for non-linear fitting of the absorbance *vs.* time data to determine the observed first order rate constant, k, from the equation

$$A_t = A_\infty - (A_\infty - A_0)e^{-kt}$$

where A_t, A_0, and A_∞ are the absorbances at times t, 0, and ∞ respectively. Correlation coefficients (r-values) were greater than 0.99 for all reactions.

k_{obs} values were related linearly to hydroxide concentration, indicating that the reaction is first order with respect to hydroxide. A linear dependence is also observed with sulfonate concentration (using initial rates), indicating a first order relationship for sulfonate also.

pH Dependence

The pH-rate profile for the hydrolysis of 4-nitrophenyl benzenesulfonate was determined from initial rates measurements (sulfonate concentration 0.01–0.05 mM) at 50 °C. 100 mM CAPS (pH 9.7–11.4), CHES (pH 8.5–10.8) and HEPES (pH 7.3–8.1) buffers with KOH were used to maintain pH during the reactions, and the ionic strength was adjusted to 0.5 M with KCl.

Activation parameters

Thermodynamic parameters were calculated, using the Arrhenius equation,[59] for the hydrolysis of 4-nitrophenyl benzenesulfonate and phenyl benzenesulfonate in 0.1 M KOH. Measurements were performed at five different temperatures in the range 30–60 °C, and mean values from 2–3 readings are plotted. Individual readings are within 1.2% of the mean value, and correlation coefficients for the Arrhenius plots are ≥0.999.

Brønsted parameters

The hydroxide-catalysed hydrolysis of eight benzenesulfonates with different leaving groups was followed in 0.1 M KOH at 50 °C. The mean values from 2–4 measurements of the observed rate constant, k_{obs}, were used for the Brønsted plot (correlation coefficients for both lines are greater than 0.999; standard deviations were all less than 2% of the mean value of k_{obs}).

Published pK_a values[60] (at T = 25 °C) were used for all phenols except 3-fluoro-4-nitrophenol. This value was determined by measuring $A^{390\ nm}$ of an aqueous solution of 30 μM 3-fluoro-4-nitrophenol as a function of pH and determining the inflection point of this curve (Fig. S5†). This method was also used to confirm the literature pK_a values; all pK_a values are listed in Table S1.†

Isotope labeling

4-Nitrophenyl benzenesulfonate (0.25 mM) was hydrolysed (50 °C, 2 h) in an aqueous solution of 0.1 M KOH containing 38% ^{18}O-labelled H_2O (Isotec). The hydrolysis products were analysed by LC-MS to determine which product contained ^{18}O (Fig. S2†).

Theoretical structure of the intermediate

Calculations to optimize the geometry of the intermediate shown in Fig. 2 were performed using the GAMESS package[61] through a hybrid EFP[62] plus C-PCM calculation method (QM/EFP/PCM)[49,50] for the solute coupled with H_2ORHF pre-parameterized water as the solvent in an HF/6-31++G* level of theory. The Cartesian coordinates of the intermediates are listed in the ESI.†

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