Ground state structures of sulfate monoesters and sulfamates reveal similar reaction coordinates for sulfuryl and sulfamyl transfer†

Emma Denehy,[ab] Jonathan M. White[ab] and Spencer J. Williams*[ab]

Received (in Cambridge, UK) 28th September 2005, Accepted 4th November 2005
First published as an Advance Article on the web 21st November 2005
DOI: 10.1039/b513712h

Structure/reactivity and structure/structure correlations of 5 sulfate monoesters and 11 sulfamate esters determined by low temperature X-ray crystallography reveal similar ground state deformations that suggest similar reaction coordinates for sulfuryl and sulfamyl group transfer.

It is increasingly emerging that sulfate monoesters ($ROSO_3^-$) fulfil a regulatory role in the extracellular domain that parallels the role played by phosphate esters in the intracellular domain.[1,2] In tandem, there has been a renewed interest in the reactions of sulfamate esters, $ROSO_2NH_2$, due to their ability to act as irreversible inactivators of arylsulfatases, a class of enzymes responsible for the catalysis of sulfate monoester hydrolysis.[3–5] Here, we report structure/reactivity and structure/structure correlations for the solvolysis of sulfate monoesters and sulfamate esters that provide evidence for geometric changes that occur at the transition state of sulfuryl and sulfamyl transfer.

Studies of effective charge for sulfuryl group (SO_3) transfer between nitrogens reveal significant reduction in charge on the acceptor nitrogen with little corresponding development on the donor nitrogen.[6] $^{18}O/^{16}O$ non-bridging kinetic isotope effects measured for pH independent solvolysis of 4-nitrophenyl sulfate indicate a trigonal bipyramidal geometry about sulfur in the transition state (Fig. 1a, X = O^-).[7] Together these and other studies point to a concerted reaction for sulfuryl group transfer proceeding through an exploded sulfur trioxide-like transition state with bond cleavage from the leaving group being highly advanced relative to bond formation to the nucleophile. The solvolysis of sulfamate esters presents a more complex mechanistic picture. *N*,*N*-Disubstituted sulfamates may only solvolyse through a bimolecular mechanism (Fig. 1a, X = NR_2).[8] At low pH this pathway has also been proposed for solvolysis of sulfamates that bear an acidic proton,[9] however, when deprotonation may occur an alternative elimination mechanism dominates that proceeds through a sulfeneimine intermediate (SO_2=NH or SO_2=NR; Fig. 1b).[10]

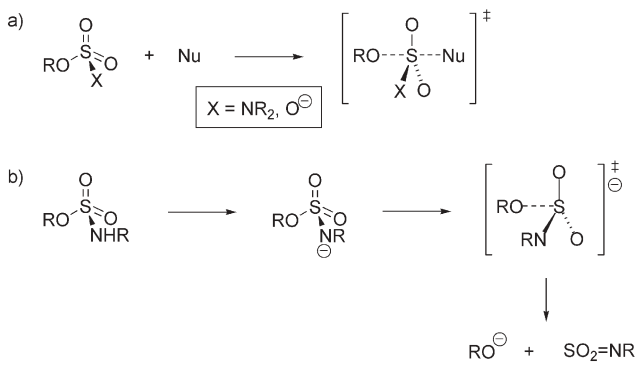

Fig. 1 Proposed mechanisms of sulfuryl and sulfamyl transfer for sulfate monoesters and sulfamates: a) bimolecular pathway, b) stepwise pathway.

Structure/reactivity and structure/structure correlations provide a powerful means of revealing important geometric changes manifested along the reaction coordinate upon approach to the transition state. To date no studies have been published on structure/reactivity or structure/structure correlations of sulfamate esters and only recently has a preliminary study been reported on structure/structure and structure/reactivity of sulfate monoesters.‡[11]

Here a series of sulfate monoesters ($ROSO_3^-{}^+K$) and corresponding sulfamate esters were prepared. Sulfate monoesters were synthesized by reaction of sulfur trioxide–pyridine complex with alcohols or, unexpectedly, by methanolysis of potassium 2,4-dinitrophenyl sulfate. Sulfamates were prepared by reaction of phenols with chlorosulfonyl isocyanate and aliphatic alcohols with sulfamoyl chloride. Accurate structures of 5 sulfates and 11 sulfamates were determined by low temperature X-ray crystallography.§ Thermal ellipsoid plots for representative structures of 4-methoxyphenyl sulfate **1** and 4-methoxyphenyl sulfamate **2** are

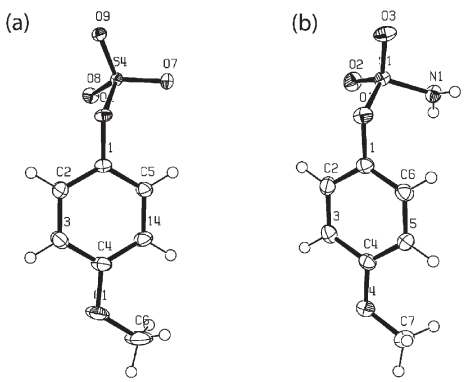

Fig. 2 Representative thermal ellipsoid plots of (a) one of two independent molecules of 4-methoxyphenyl sulfate **1** (excluding potassium for clarity) and (b) 4-methoxyphenyl sulfamate **2**. Ellipsoids are at the 50% probability level.

[a]*School of Chemistry, University of Melbourne, Parkville, Australia*
[b]*Bio21 Biotechnology and Molecular Science Institute, University of Melbourne, Parkville, Australia. E-mail: sjwill@unimelb.edu.au; Fax: +61 3 9347 8124; Tel: 61 3 8344 2422*

† Electronic supplementary information (ESI) available: synthesis and characterization of sulfates and sulfamates, ^1H and ^{13}C NMR spectral data of new compounds and crystallographic data. See DOI: 10.1039/b513712h

presented in Fig. 2. A plot of the sulfur-bridging oxygen bond distance *vs.* the pK_a value of the parent alcohol is presented in Fig. 3a. In each case there are good correlations that yield the following equations:

$$r_{S-O}/\text{Å} = 1.67 - 4.7 \times 10^{-3} \text{p}K_a(\text{ROH});\ R^2 = 0.95 \quad (1)$$

$$r_{S-O}/\text{Å} = 1.63 - 3.8 \times 10^{-3} \text{p}K_a(\text{ROH});\ R^2 = 0.85 \quad (2)$$

These structural data report upon ground state structural manifestations of the sulfuryl and sulfamyl transfer reactions of sulfate monoesters in the pH-independent region (Eqn 1) and of the neutral sulfamate species (Eqn 2). Bimolecular attack at sulfur in the neutral sulfamate ester is proposed as the major hydrolytic pathway at low pH,[9] but has yet to be studied in detail. These data provide structural insight into this pathway, analogous to the solvolysis of *N*,*N*-disubstituted sulfamates (Fig. 1a, X = NR_2).[8]

The data in Fig. 3a have two striking features, namely the similarity in slope between the two series and the longer S–O_b bond lengths of the sulfate monoester series. Both series display similar sensitivity of S–O_b bond distance to leaving group ability as measured by leaving group pK_a value. This relationship is consistent with kinetic data, where the sensitivity of leaving group dependence of arylsulfate monoester hydrolysis in the pH-independent region ($\beta_{lg} = -1.2$)[12] is comparable to that seen for reaction of *N*,*N*-dialkyl arylsulfamate esters with hydroxide ($\beta_{lg} = -1.1$).[8] Together, the structure/reactivity correlations seen here and β_{lg} values for nucleophilic substitution of aryl sulfates and *N*,*N*-dialkyl arylsulfamates provide strong evidence for qualitative similarity in the reaction coordinates of bimolecular sulfuryl and sulfamyl transfer reactions of sulfate monoesters and sulfamate esters.

The longer S–O_b bond distances of the sulfate monoester series over the sulfamate ester analogues cast light on the relative reactivity of these compounds. Kirby and coworkers' first cardinal rule of structure–reactivity correlations states "the longer the bond, in a given system, the faster it breaks".[13] As discussed above, the similarity of the slope of the structure/reactivity correlations suggests these reactions are qualitatively similar and share similar reaction coordinates. Thus, the longer S–O_b bonds seen in sulfate monoesters suggest a lower activation energy for sulfuryl transfer relative to sulfamyl transfer in sulfamate esters.

Close examination of the structures of the sulfate monoesters reveals that the average length of the *anti* S–O_{nb} bonds is 0.03 Å smaller than that seen for the *gauche* O_b–S–O_{nb} and the average *anti* O_b–S–O_{nb} angle is 5.7° smaller than the *gauche* O_b–S–O_{nb} angle. A similar effect has been noted in theoretical and structural analyses of sulfate esters[14,15] and Brandão and coworkers attribute the contraction of the *anti* O_b–S–O_{nb} angle to a simple steric effect.[11]

Similar geometric features are manifested in the sulfamate series. All sulfamate esters display the same conformation around the sulfur–nitrogen bond (Fig. 2b), with electron density about nitrogen consistent with the hydrogens being positioned *gauche* to the S–O_b bond. Here, however, this effect can also be explained by an anomeric effect arising from n → σ* orbital overlap of the nitrogen lone pair with the σ* antibonding orbital of the antiperiplanar S–O_b bond.

A well-defined increase in the sum of the O_{nb}–S–O_{nb} angles for the non-bridging angles in the sulfate monoester series correlates with an increase in S–O_b bond lengths [Σ(O_{nb}–S–O_{nb} angles) = 49.3(r_{S-O}/Å) + 262 (degrees), R^2 = 0.86] (Fig. 3b).¶ Although modest, this structure/structure relationship gives evidence for ground state deviations from a distorted tetrahedral geometry about sulfur in the ground state to a trigonal planar arrangement at the transition state, consistent with kinetic studies of sulfuryl transfer reactions that point to a sulfur trioxide-like transition state.[6,7]

Sulfuryl and phosphoryl transfer reactions are both of significant interest in biological systems.[16] Kirby has reported structure/reactivity correlations for phosphate triesters and monoesters that show a significant difference in sensitivity to the leaving group.[17] The sensitivity of the phosphate monoester to leaving group ability was estimated to be at least two-fold greater than the corresponding triesters, which was attributed to the powerful internal electron donation by the monoester dianion relative to the neutral triester.[17] Solvolysis of phosphate

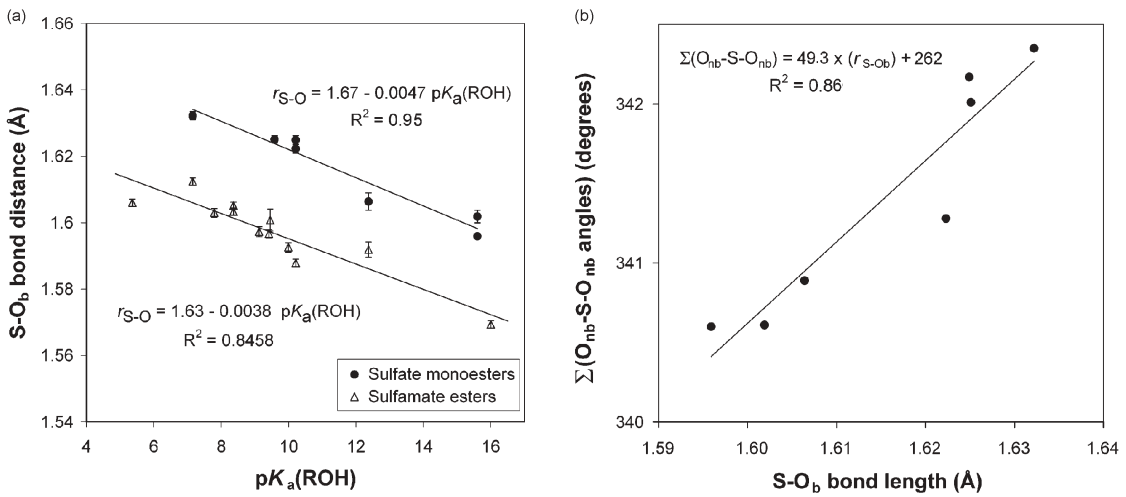

Fig. 3 (a) Structure/reactivity plot of r_{S-O} *vs.* pK_a (ROH) for sulfate monoesters (●) and sulfamates (△) and (b) structure/structure correlation plot of r_{S-O} *vs.* Σ(O_{nb}–S–O_{nb} angles) for sulfate monoesters. The two points for compound **1** (pK_a = 10.21) represent two independent molecules in the crystal structure.

monoesters is proposed to proceed *via* a metaphosphate-like transition state whilst the triesters must proceed through an associative mechanism. The sulfate esters described here provide an interesting contrast. The slope of the structure/reactivity correlation for the sulfate monoester series, -4.7×10^{-3}, is equivalent to 435 kcal mol^{-1} Å^{-1} (calculated from $\beta_{lg} = -1.2$)[12] whereas Kirby calculated the corresponding slope in the phosphate monoester series to be -8×10^{-3}, equivalent to 230 kcal mol^{-1} Å^{-1}, indicating it is energetically more expensive to stretch an S–OR bond relative to a P–OR bond.

Williams[18] has proposed that the degree of nucleophile participation in sulfonyl (SO_2) transfer mechanisms is inversely related to the ability of the system to internally donate electron density into sulfur, and Kirby[17] has made similar comments for phosphate mono- and triester solvolysis. Williams has studied sulfuryl and phosphoryl transfer between nitrogen nucleophiles and calculated rate constants where the entering and leaving group are identical.[19] The Brønsted relationships of these identity reactions predict that at the transition state the bond orders of the fissile bonds of sulfuryl transfer are greater than for phosphoryl transfer and that a sulfuryl group surrenders less negative charge than a phosphoryl group.[19] The structural data reported here provide strong evidence that internal electron donation into sulfur during sulfuryl transfer is far less pronounced than the corresponding electron donation into phosphorus during phosphoryl transfer. Internal electron donation to the central atom may be effected by rearrangement of electron density at the nonbridging oxygens, reflecting a shift from a polarized bonding interaction with the central atom to a more covalent-type bonding interaction. Thus, a more dramatic shift in X–O_{nb} bond polarity is expected along the phosphoryl transfer reaction coordinate (X = P) than along the sulfuryl transfer (X = S) reaction coordinate.

This reasoning is consistent with the striking difference in the magnitude of solvent effects observed for sulfuryl and phosphoryl transfer, which both exhibit an acceleration of solvolysis rates in solvents of reduced polarity. For phosphate monoesters the rate acceleration is dramatic, being as high as 10^6 in DMSO/water. For sulfate monoesters the effect is much more modest; under similar conditions a 50-fold rate acceleration is observed.[7] Solvents of reduced polarity will afford greater transition state stabilization to phosphoryl transfer relative to sulfuryl transfer if a more significant shift in the X–O_{nb} bond polarity occurs along the reaction coordinate, resulting in greater acceleration of phosphoryl transfer.

Structure/reactivity and structure/structure correlations of sulfate monoesters and sulfamate esters support a mechanism that proceeds through significant bond lengthening of the scissile S–O_b bond and a dissociative, sulfur trioxide-like transition state. The similarity of the slope of the structure/reactivity plots suggests that pH independent solvolysis of sulfate monoesters and neutral sulfamate solvolysis proceed through qualitatively similar reaction profiles. These correlations provide a powerful view of the sensitivity of the ground state structures of these species to leaving group ability and provide strong evidence for a sulfur trioxide-like transition state in both reactions with minimal internal electron donation from the non-bridging oxygens. This work suggests a close mechanistic relationship of sulfamyl and sulfuryl group transfer that is similar to but distinct from phosphoryl group transfer.

This work was supported by a University of Melbourne Early Researcher Grant, the Australian Research Council (DP0449625) and a Sir John and Lady Higgins Research Scholarship to ED. Jeremy Paige is thanked for synthetic assistance.

Notes and references

‡ Brandão and co-workers studied the structure of potassium 4-nitrophenyl sulfate and 9 other structures taken from the Cambridge Crystallographic Database (CCD) and identified a tentative correlation of increasing S–O bond length and reactivity; however, this study was limited by the uncertainty of assigning reliable pK_a values to many of the leaving groups, and the effects of libration on data collected at room temperature. A personal communication with one of the authors of that paper (AJK) revealed several errors in reporting their data apparently arising from a vertical translation of data in Table 3 and from an incorrect pK_a value for 4-nitrocatechol. These errors affect the slope of the correlations observed but do not materially affect any conclusions presented.

§ Structures determined herein: potassium 4-methoxyphenylsulfate monoester **1** (2 independent molecules in unit cell), potassium 4-acetamidophenylsulfate monoester **3**, potassium 4-nitrophenylsulfate monoester **4**, potassium 2,2,2-trifluoroethylsulfate monoester **5**, potassium methyl sulfate **6**, 4-methoxyphenylsulfamate ester **2**, 4-nitrophenylsulfamate ester **7**, 3-nitrophenylsulfamate ester **8**, 4-iodophenylsulfamate ester **9**, 4-cyanophenylsulfamate ester **10**, 4-chlorophenylsulfamate ester **11**, 3-chlorophenylsulfamate ester **12**, phenylsulfamate ester **13**, 3,4-dinitrophenylsulfamate ester **14**, ethylsulfamate ester **15**, and 2,2,2-trifluoroethylsulfamate ester **16**. CCDC 285416–285431. For crystallographic data in CIF or other electronic format see DOI: 10.1039/b513712h The low temperature X-ray structure of potassium 4-nitrophenyl sulfate was reported by Sieroslawski *et al.* whilst this work was in progress.[20]

¶ The same general trend is evident in the sulfamate ester data, however, a quantitative relationship between sulfur geometry and S–O_b bond distance or pK_a(ROH) is ill-defined for the sulfamate series; this may be attributed to geometric distortions around sulfur caused by random variations in the intermolecular hydrogen bonding in the crystal network.

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