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Klaudia Szeler, [Nicholas Williams](#), Alvan C. Hengge, [Shina Caroline Lynn Kamerlin](#)

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Modeling the Alkaline Hydrolysis of Diaryl Sulfate Diesters: A Mechanistic Study

Klaudia Szeler,¹ Nicholas H. Williams,² Alvan C. Hengge,^{3,*} Shina C. L. Kamerlin^{1,*}

1. Department of Chemistry – BMC, Uppsala University, BMC Box 576, S-751 23 Uppsala, Sweden. 2. Department of Chemistry, University of Sheffield, Sheffield, S3 7HF, UK. 3. Department of Chemistry and Biochemistry, Utah State University, Logan, UT 84322-0300, USA.

Corresponding author email addresses: alvan.hengge@usu.edu and lynn.kamerlin@kemi.uu.se

Abstract

Phosphate and sulfate esters have important roles as biological building blocks and in regulating cellular processes. However, while there has been substantial experimental and computational investigation of the mechanisms and the transition states involved in phosphate ester hydrolysis, there is far less (in particular computational) work on sulfate ester hydrolysis. Here, we report a detailed computational study of the alkaline hydrolysis of diaryl sulfate diesters, using different DFT functionals and both pure implicit solvation as well as mixed implicit/explicit solvation with varying numbers of explicit water molecules. We consider both the impact of how the system is modeled on computed linear free energy relationships (LFER) and the nature of the transition states. Although our calculations consistently underestimate the absolute activation free energies, we obtain good agreement with experimental LFER data when using pure implicit solvent, and excellent agreement with experimental kinetic isotope effects for all models used. Our calculations suggest that the hydrolysis of sulfate diesters proceeds through loose transition states, with minimal bond formation to the nucleophile and with bond cleavage to the leaving group already initiated. Comparison to prior work indicates that these transition states are similar in nature to those of analogous reactions such as the alkaline hydrolysis of neutral arylsulfonate monoesters or charged phosphate diesters and fluorophosphates. Obtaining more detailed insight into the transition states involved assists in understanding the selectivity of enzymes that hydrolyze these reactions; however, this work also highlights the methodological challenges involved in reliably modeling sulfate ester hydrolysis.

Keywords: sulfate diester hydrolysis • reaction mechanisms • density functional theory • linear free energy relationships • mixed implicit/explicit solvation

Introduction

The hydrolysis of both phosphate and sulfate esters is ubiquitous in biology, and plays important roles in numerous cellular processes, including in particular the regulation of cellular signaling processes.¹⁻³ Therefore, unsurprisingly, the enzymes that catalyze these reactions are involved in a range of human diseases, making them important drug targets.⁴⁻⁶ In addition, many phosphatases also possess promiscuous sulfatase activity,^{7, 8} and such promiscuity is likely to be of evolutionary significance for these enzymes.⁹⁻¹³ While there has been substantial research focus on understanding enzymatic phosphate and sulfate hydrolysis (for reviews, see *e.g.* refs. 2, 3, 7, 8, 14 and references cited therein), understanding the corresponding non-enzymatic hydrolyses of these compounds is also important, in order to provide insight into the fundamental chemistry and the nature of the transition states involved. Here, the lion's share of research has focused on understanding phosphoryl transfer reactions using both experimental and computational approaches, and studies of linear free energy relationships (LFER), kinetic isotope effects (KIE), and activation entropies, complemented by computational modeling, has provided significant insight into the reactivity of these compounds (for detailed reviews see *e.g.* ^{2, 3}).

In contrast, there has been far less research effort invested into studying non-enzymatic sulfate hydrolysis, and, in particular, while there have been a number of elegant experimental studies of sulfate ester hydrolysis, corresponding computational studies have been very limited. Both experimental^{13, 15-24} and computational²⁵⁻²⁷ studies of sulfate monoester hydrolysis suggest that the transition states for these reactions are mechanistically similar to those of their corresponding phosphate monoesters, proceeding through concerted pathways with loose (concerted but dissociative in character) transition states, with little bond formation to the nucleophile and advanced bond cleavage to the leaving group, resulting in an SO₃-like sulfonyl group. This is

supported by the similar kinetic parameters,^{16, 20} linear free energy relationships,¹⁵⁻¹⁹ and kinetic isotope effects^{20, 21} for the hydrolysis of sulfate and phosphate monoesters. In addition, studies of the pH-dependence of these reactions show a broad pH-independent region between pH 4 and 12^{15, 16, 21, 28} (where hydrolysis likely proceeds by S-O rather than C-O bond cleavage), and a hydrolysis rate that is accelerated under strongly acidic or basic conditions.^{16, 29} Computational comparison of the hydrolysis of *p*-nitrophenyl phosphate and sulfate monoesters provide a similar mechanistic picture for these reactions,²⁷ although the transition state for the hydrolysis of the sulfate monoester was calculated to be slightly more compact than that for the corresponding phosphate monoester. This is likely due to the fact that in contrast to the phosphate monoester dianion, the sulfate monoester is monoanionic.

In the case of sulfate diester hydrolysis, the majority of reported studies involve the reactivity of either dialkyl or aryl alkyl sulfate diesters, in which the reaction proceeds by attack at carbon with C-O rather than S-O bond cleavage.^{30, 31} In contrast, experimental work indicates that the alkaline hydrolysis of diaryl sulfate diesters proceeds through nucleophilic attack at sulfur (**Figure 1**),³² making it possible to compare the transition states for these reactions to those obtained in our prior work on the alkaline hydrolysis of related compounds such as sulfate and phosphate monoesters, aryl phosphate diesters, fluorophosphates, pyridinio-N-phosphonates and neutral sulfonate monoesters.^{27, 33-37} In all three cases, both experimental and computational work suggests that these reactions still proceed through concerted but tighter transition states than those observed in the case of phosphate and sulfate monoesters, and it would therefore not be implausible to assume the same holds true also for neutral diaryl sulfate diesters (**Figure 1**). This would also be supported by experimental data³² which provides a slope, β_{lg} , of -0.7 ± 0.2 for the alkaline hydrolysis of a series of diaryl sulfate diesters (compared to a reported value of -1.81 ± 0.09 for

aryl sulfate monoesters²⁴), and ^{15}k and $^{18}k_{\text{lg}}$ KIE of 1.0000 ± 0.0005 and 1.003 ± 0.002 , respectively, for hydroxide attack on *p*-nitrophenyl sulfate.

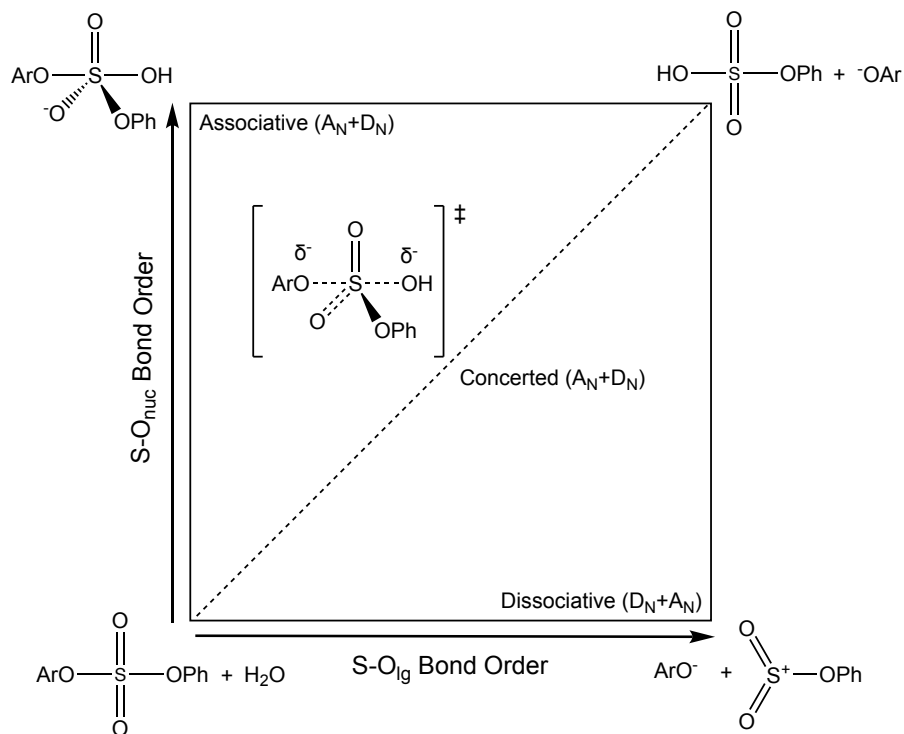


Figure 1. An overview of different mechanistic possibilities for the alkaline hydrolysis of the arylsulfate diesters studied in this work, as illustrated on a More-O’Ferrall Jencks plot.^{38, 39} Shown here are both the mechanistic extremes of fully associative (A_N+D_N , top left) and fully dissociative (D_N+A_N , bottom right) pathways. The dashed line indicates a concerted (A_ND_N , center) pathway with concomitant bond formation to the nucleophile and bond cleavage to the leaving group; note that although we have drawn the line through the center of the plot, these transition states can potentially be either dissociative or associative in nature, depending on whether bond formation to the nucleophile precedes or follows bond formation to the leaving group. In addition, the “products” (top right) would be expected to rapidly undergo proton transfer to form PhOSO_3^- and ArOH . Adapted with permission from ref. ³² (direct link: <https://pubs.acs.org/doi/abs/10.1021/jo0488309>). Copyright 2004 American Chemical Society.

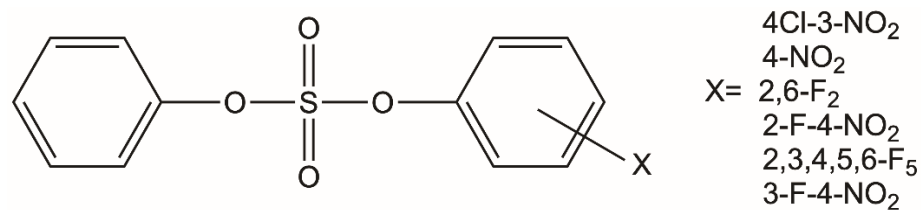


Figure 2. Overview of the compounds studied in this work, based on the experimental work presented in ref. ³².

In the present work, we perform a detailed comparison of the alkaline hydrolysis of a series of diaryl sulfate diesters with leaving groups of varying pK_a (**Figure 2**),³² using three different density functionals, and comparing both pure implicit solvent and mixed implicit/explicit solvation, for comparison to our prior work.^{27, 36, 40} We show that the slope of the calculated LFER is highly dependent both on the functional used, and on the number of explicit water molecules introduced into the system, but that in all cases, we are able to obtain good agreement with experimental KIE irrespective of the functional used or the number of water molecules. We also compare our calculated transition states to those obtained in our previous computational studies of related compounds,^{27, 33-37} and confirm that like other analogous compounds, the alkaline hydrolyses of sulfate diesters proceeds through tighter concerted transition states than those obtained for the corresponding monoesters.

Methodology

In the present, we have performed density functional theory (DFT) calculations of the alkaline hydrolysis of diaryl sulfate diesters shown in **Figure 2**, using the M11L,⁴¹ M062X⁴² and ω B97X-D.⁴³ All transition states were initially optimized using the M11L functional, with the final optimized structures being reoptimized using either the M062X or the ω B97X-D functionals. We note that in a small number of cases, direct re-optimization was not possible, as the transition state optimization never converged. These optimizations were therefore initiated from different starting

points. Specifically, the starting structure for the final transition state for 2,3,4,5,6-pentafluoro sulfate in the presence of 2 explicit water molecules, optimized using the M062X functional, was the ω B97X-D optimized transition state rather than the M11L optimized state. In the case of the transition states for the hydrolysis of 2,6-difluoro and 2-fluoro-4-nitrophenyl sulfate, optimized with the M11L functional in the presence of 8 water molecules, these structures were optimized using the transition states for 2-fluoro-4-nitrophenyl and 3-fluoro-4-nitrophenyl sulfate as starting structures, respectively. All other structures converged normally and were therefore obtained as initially described above.

Initial transition state optimizations were performed using the 6-31+G* basis set and the SMD solvation model, with the addition of between 0 and 8 explicit water molecules to the system. The water molecules were added to the system one by one in a symmetrical fashion (*i.e.* adding an additional water molecule to either side of each optimized transition state and reoptimizing the new transition state). The water molecules were added in such a way as to saturate all possible hydrogen bonding interactions with the sulfate diester. The resulting transition states were characterized both by frequency calculations at the same level of theory, as well as by following the intrinsic reaction coordinate (IRC)^{44, 45} in both the reactant and product directions followed by optimization to the actual reactant and product. These structures were first optimized using an UltraFine integration grid, and the optimized stationary points were re-optimized using a SuperFine integration grid. The resulting absolute energies and Cartesian coordinates of all optimized stationary points are provided in the **Supporting Information**.

Bond orders, frequencies, zero-point energies and entropies were all calculated at 313.15K from the final optimized structures at the same level of theory, whereas the electronic energies were obtained by performing single point calculations using the larger 6-311+G** basis set. The

partial charges were obtained using the CHarges from ELeCtrostatic Potentials using a Grid-based method (CHELPG) charge calculation scheme⁴⁶ using the 6-31G* basis set, and bond orders were calculated based on the Wiberg bond index⁴⁷ using natural bond orbital (NBO) analysis.⁴⁸ All quantum chemical calculations were performed using Gaussian 16, Rev. B01.⁴⁹ Finally, kinetic isotope effects were calculated using the Biegeleisen-Mayer equation⁵⁰ using the frequencies in the Gaussian output files and Kinisot (“Kinetic Isotope Effects with Python”, developed by the Paton lab and available for open source download from Zenodo, DOI: 10.5281/zenodo.60082), with the ¹⁵N/¹⁴N isotopic replacement manually added to the code.

Results and Discussion

Exploring the Impact of Including Explicit Water Molecules in the Simulations

In prior work on the hydrolysis of phosphate monoester dianions and sulfate monoester monoanions, we demonstrated that the inclusion of explicit water molecules into the system (in addition to the implicit solvent model) can have substantial impact on the energies and geometries of the resulting optimized structures and the ability to reproduce all the experimental data, including isotope effects.²⁷ To assess whether that is also the case for neutral diaryl sulfate diesters, we performed geometry optimizations of key stationary points for the alkaline hydrolysis of 4-nitrophenyl sulfate in the presence of 0 to 8 explicit water molecules and using three different DFT functionals, and examined the impact of inclusion of these water molecules on the resulting activation free energies, charge distributions, and geometries. The resulting data are shown in **Figures 3, S1-S3, and Tables S1 to S21**.

From these data, it can be seen that all three functionals grossly underestimate the activation free energy to the hydrolysis reaction, with the lowest energies provided by the M062X functional, the highest by the ω B97X-D functional, and the M11L functional being intermediary between the

other two functionals. This underestimation is to be expected when modeling systems involving hydroxide as a nucleophile, as discussed at length by both ourselves and others elsewhere.^{35, 51-54} Therefore, our focus is not on whether a functional does a good job of reproducing *absolute* experimental activation free energies, but rather whether our models can reproduce *trends* in experimental observables (such as the slope of an LFER).

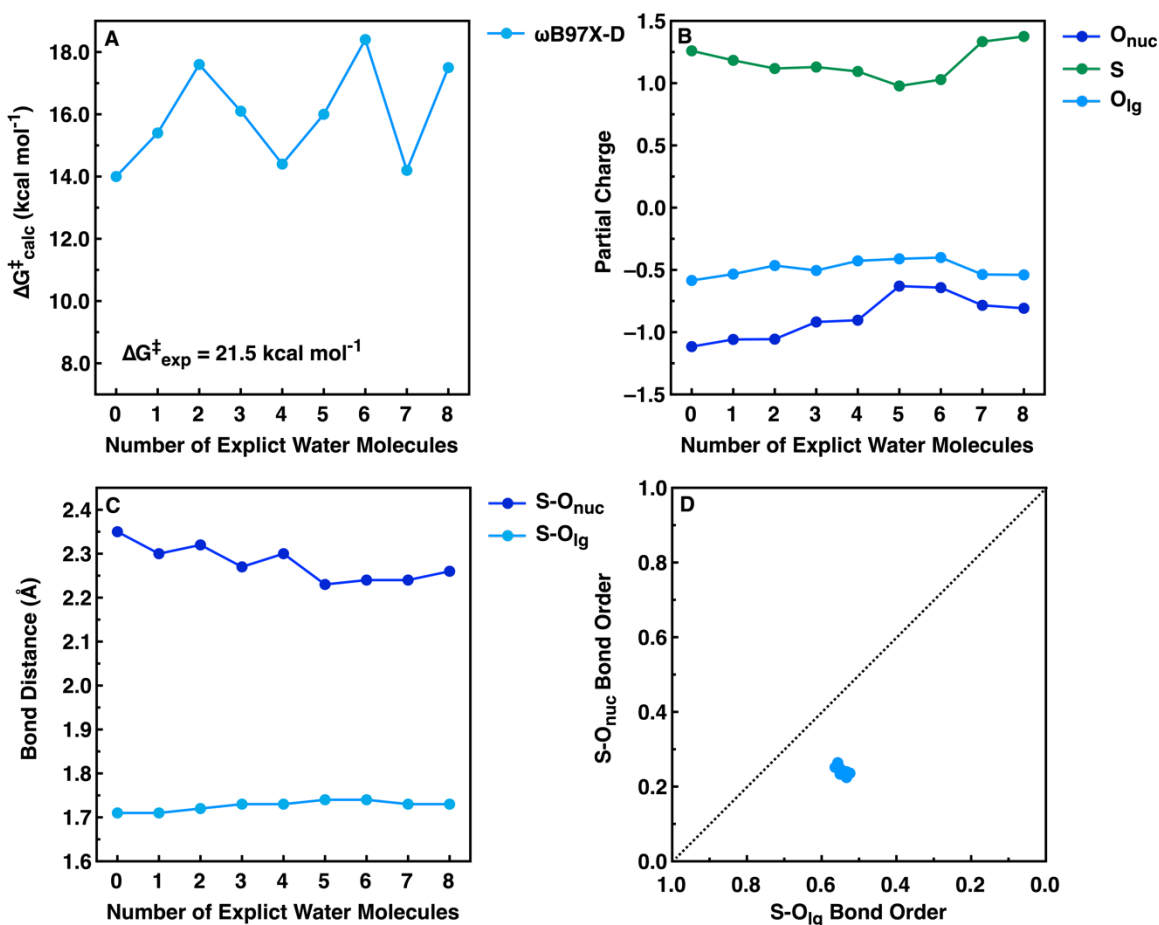


Figure 3. Overview of the (A) activation free energies, (B) partial charges at the transition state, (C) S-O_{nuc} and S-O_{lg} distances at the transition state and (D) S-O_{nuc} and S-O_{lg} bond orders at the transition state for the alkaline hydrolysis of 4-nitrophenyl sulfate with varying numbers of water molecules, obtained using the ω B97X-D⁴³ functional, as described in the **Methodology** section. The calculated activation free energy was obtained using transition state theory at 313.15 K, based on kinetic data provided in ref. ³². For the corresponding data obtained using the M11L⁴¹ and M062X⁴² functionals, see **Figures S1** and **S2**, and for the corresponding raw data see **Tables S1 to S21**.

In terms of trends, it can be seen that there is considerable oscillation in the calculated activation free energies, depending on the number of explicit water molecules included in the system. This largely has to do with the positioning of the explicit water molecules: it is critical to introduce these water molecules symmetrically into the system, saturating all available hydrogen bond donors/acceptors to avoid accidentally over-stabilizing part of the system and obtaining potentially spurious intermediates, as discussed in detail in ref. ^{35, 55}. However, unlike in the case of the charged species studied in most of our previous work,^{27, 33, 34, 36, 37, 40} the diaryl sulfate diesters being studied in the present work are neutral species. This means that while the explicit water molecules interact quite nicely with the polarized transition state, the orientation of the water molecules at the reactant and product states can be quite “distorted” (for example all water molecules clustering together and away from the sulfate diester), suggesting that the sulfate oxygen atoms are poorer hydrogen bond acceptors than the water oxygen atoms. This then leads also to a distortion in the position of the nucleophilic hydroxide ion relative to the sulfur atom, moving it away from an ideal position for in-line attack on the sulfur atom (see *e.g.* **Figures 4, S4 and S5**), which in turn impacts the calculated activation free energies. That is, we obtain average $\Delta G^\ddagger_{\text{calc}}$ of 12.8 ± 1.3 , 10.3 ± 1.6 and 16.0 ± 1.6 using each of the M11L, M062X and ω B97X-D functionals, indicating that our calculated energies are less sensitive to the number of explicit water molecules included in the system. Similarly, the calculated geometries are also largely independent of number of water molecules included in the system – as can be seen from **Figure S3**, while there are small differences between the different density functionals, the data clusters around each functional irrespectively of the number of explicit water molecules included in the system.

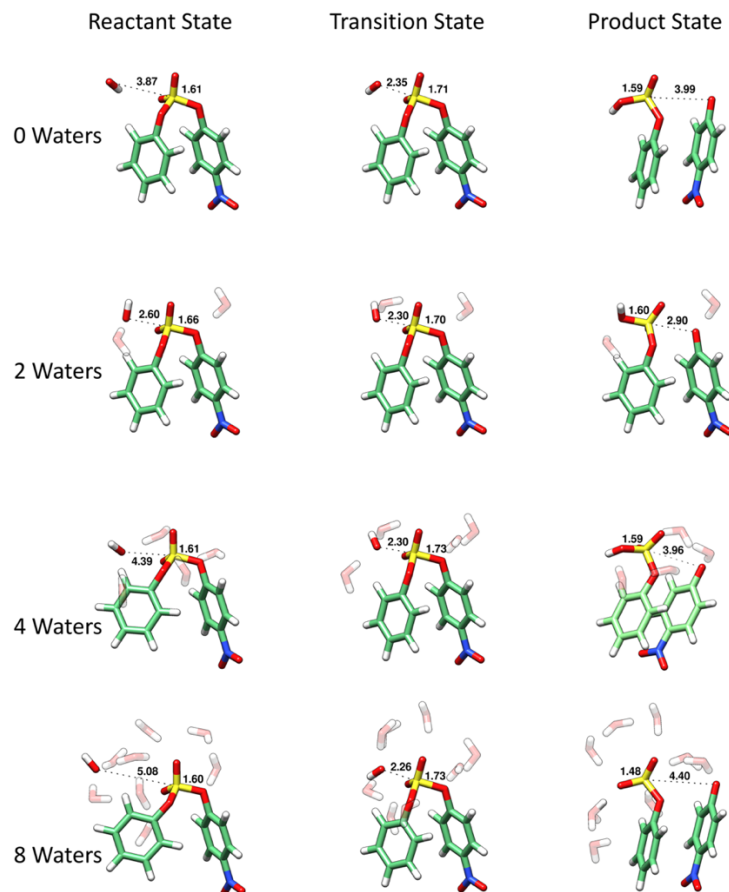


Figure 4. Representative structures of the ground, transition and product states for the alkaline hydrolysis of 4-nitrophenyl sulfate obtained using the ω B97X-D functional,⁴³ in the presence of varying numbers of explicit solvent molecules, as described in the **Methodology** section. The calculated S-O_{nuc} and S-O_{lg} distances are annotated for each optimized reacting state (in Å), and the corresponding data obtained using the M11L⁴¹ and M062X⁴² functionals is shown in **Figures S4** and **S5**, respectively. Finally, coordinates of all optimized stationary points are provided as **Supporting Information**.

Tying in with this, as there is little change in the transition state geometry upon including additional explicit water molecules into the system, unsurprisingly, the calculated ^{15}k and $^{18}k_{lg}$ KIE are very stable irrespective of density functional or number of explicit water molecules, and all systems give relatively good agreement with experiment (**Table 1**). Here, it is worth pointing out that the observed $^{18}k_{bridge}$ values are at the low end of those seen in any reaction with a nitrophenyl

leaving group, where the maximum is ~ 1.03 .⁵⁶ While it's true that some of the calculated values shown in **Table 1** are twice the experimental value, they are still all at the low end of the possible ranges of values for this effect, and in that regard are consistent with experiment. In addition, the negligible calculated ^{15}k values are consistent with the experimental value of unity.

Table 1. A comparison of experimental and calculated kinetic isotope effects for the alkaline hydrolysis of 4-nitrophenyl phenyl sulfate with varying numbers of explicit water molecules.^a

Waters	Experiment		ω B97X-D		M11L		M062X	
	$^{18}k_{\text{bridge}}$	^{15}k	$^{18}k_{\text{bridge}}$	^{15}k	$^{18}k_{\text{bridge}}$	^{15}k	$^{18}k_{\text{bridge}}$	^{15}k
	1.003 ± 0.002	1.0000 ± 0.0005						
0			1.006	1.0012	1.003	1.0006	1.005	1.0008
1			1.006	1.0014	1.004	1.0010	1.006	1.0007
2			1.007	1.0009	1.003	1.0005	1.003	1.0010
3			1.007	1.0014	1.004	1.0005	1.004	1.0010
4			1.005	1.0007	1.003	1.0007	1.005	1.0005
5			1.006	1.0010	1.003	1.0005	1.002	1.0008
6			1.006	1.0013	1.006	1.0004	1.003	1.0007
7			1.006	1.0013	1.004	1.0006	1.005	1.0007
8			1.006	1.0013	1.005	1.0006	1.003	1.0007

^a The experimental KIE were obtained from ref. ³². The computational KIE were obtained using the Bieleisen-Mayer equation⁵⁰ from vibrational frequencies calculated using the ω B97X-D,⁴³ M11L,⁴¹ and M062X⁴² functionals, as described in the **Methodology** section.

Indeed, the only significant difference to any of the physical properties of the transition state that is observed from including the explicit water molecules is on the partial charges of the nucleophile, leaving group and central sulfur atom: once at least ~ 5 water molecules have been

included into the system, the partial charge on the nucleophile oxygen becomes significantly less negative compared to that in the transition states calculated using implicit solvent alone, illustrating the stabilization of the charge on this oxygen atom by the implicit solvent molecules (**Tables S10 to S12**). This is coupled to a slight contraction on the S-O_{nuc} distance upon adding at least ~5 water molecules to the system, although the corresponding change in bond order is minimal (**Tables S16 to S18**). However, it is clear that, unlike in our previous calculations of charged systems, where there was significant benefit to including additional water molecules in the system,^{27, 36, 40} here, the water molecules appear to provide minimal additional benefit in terms of describing the transition state reliably, and add only to computational cost.

Calculated LFER for the Hydrolysis of Diaryl Sulfate Monoesters

Following from this, we have calculated an LFER for the alkaline hydrolysis of diaryl sulfate diesters, following the experimental work of ref. ³², and based on the compounds shown in **Figure 2**. We have calculated these LFER using three different density functionals as described in the **Methodology** section, and in the presence of 0, 2, 4 or 8 explicit water molecules in each case. The resulting LFER are presented in **Figure 5**, and the correlation between calculated and experimental activation free energies in **Figure S6**. The corresponding raw data is shown in **Tables S22 – S56**. Here, it can be seen that irrespective of functional and number of explicit water molecules included in the system, we frequently obtain very poor correlations between calculated and experimental data, with R^2 values as low as 0.2, and never higher than 0.9. In addition, the slopes of the calculated LFER vary widely, with β values that range from -0.16 to -1.53 (compared to an experimental value of -0.66). This discrepancy with the experimental data is again due to the fact that while the transition states tend to be very similar irrespective of how many water molecules are included in the system, the reactant states can change quite markedly, in particular

when only two or four water molecules are included in the system, in which case the water molecules sometimes do not interact with the sulfate diester, but instead with each other, pulling the nucleophile away from a position suitable for inline attack on the diester (see *e.g.* **Figure 4**, coordinates of all stationary points are provided as **Supporting Information**). Indeed, the most reliable data is obtained *without* including explicit water molecules in the system – then, the β values range from -0.62 to -0.97 with R^2 ranging from -0.58 to -0.85.

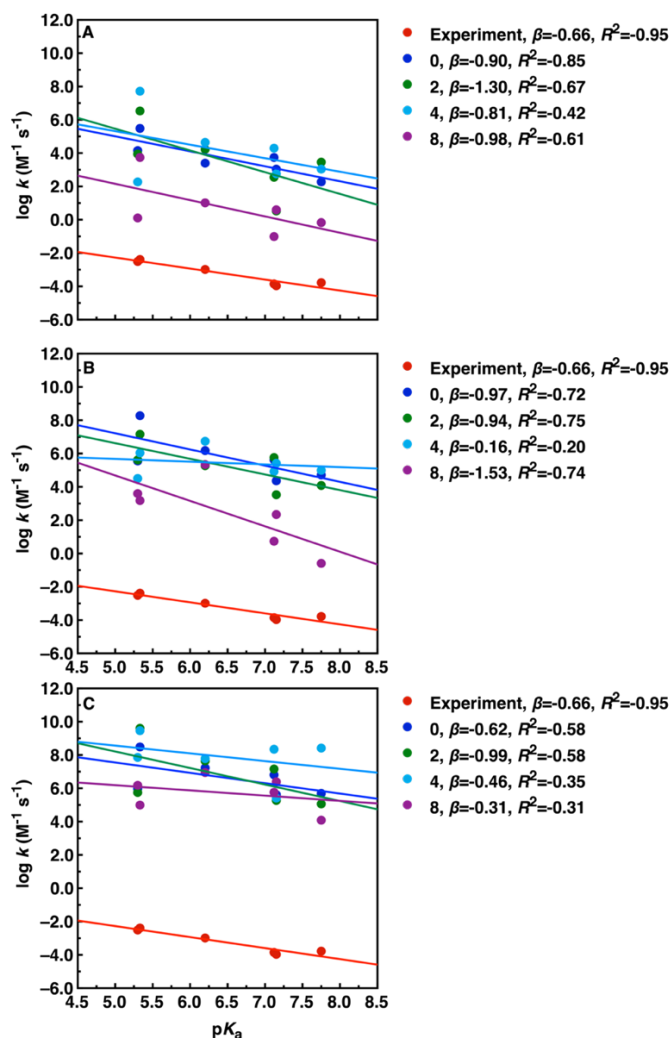


Figure 5. A comparison of calculated linear free energy relationships for the alkaline hydrolysis of the aryl sulfate diesters studied in this work (**Figure 2**), in the presence of 0 (implicit solvent), 2, 4 or 8 explicit water molecules. Data was obtained using either the (A) ω B97X-D,⁴³ (B) M11L⁴¹ or (C) M062X⁴² functionals. The corresponding raw data is presented in **Tables S22 to S33**. Experimental data was obtained from ref.³².

In terms of partial charges (**Figures 6, S7 and S8**), there are subtle overall differences in the calculated partial charges across the series, as would be expected from altering the pK_a of the leaving group, however the differences are small. It appears in addition that changing functional and/or introducing explicit water molecules in the system changes the absolute values of the calculated partial charges, but has little impact on calculated trends across the series.

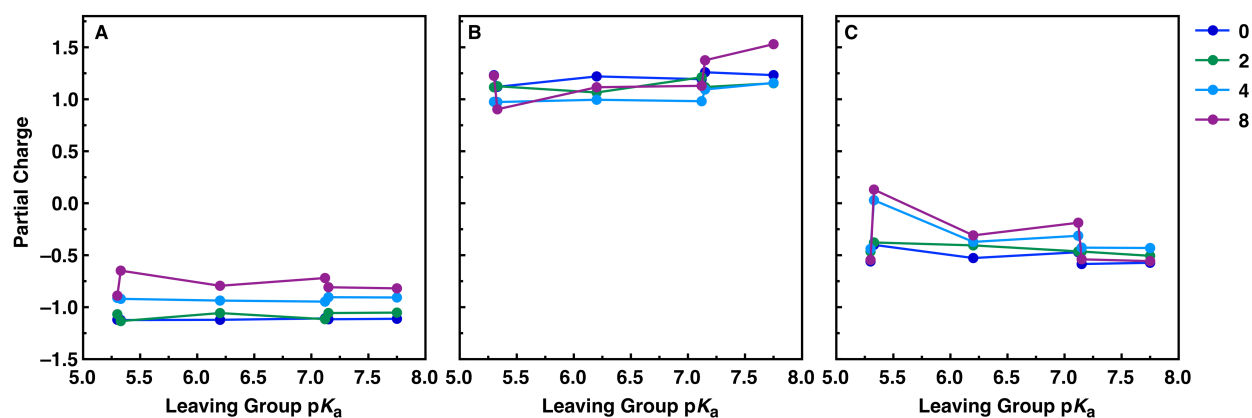


Figure 6. Partial charges on (A) the nucleophile oxygen, (B) the sulfur atom and (C) the leaving group oxygen, at the transition states for the alkaline hydrolysis of the aryl sulfate diesters studied in this work (**Figure 2**). Partial charges were calculated using the wb97xD⁴³ functional and the CHELPG charge calculation scheme⁴⁶ as described in the **Methodology** section. The corresponding charge distributions obtained using the M11L⁴¹ and M062X⁴² functionals are shown in **Figures S7 and S8**, respectively, and the corresponding raw data is shown in **Tables S57-S81**.

Finally, we have examined in detail the transition state geometries for the different systems, as the calculated KIE shown in **Table 1** suggest that despite the problems reliably modeling energetics for these compounds, the transition state geometries provided by the different functionals appear to be quite reliable. As can be seen from **Figures 7 and S9**, in all cases, we obtain dissociative but tight, concerted transition states, with partial bond cleavage to the leaving

group, and minimal bond formation to the incoming nucleophile. Geometric differences based on leaving group pK_a are minimal, and appear to primarily impact the S-O_{nuc} bond order/distance. Comparison to other previously modeled compounds^{27, 33-37} (**Figure 8**) suggest that these transition states are clearly more compact than those obtained for, for example, the spontaneous hydrolysis of phosphate monoesters,³⁶ but also those obtained for the alkaline hydrolysis of phosphate diesters.³³ In fact, the transition states are most similar to those we have previously obtained for the alkaline hydrolysis of aryl benzenesulfonates, which we have proposed are hydrolysed *via* a similar mechanistic pathway.³⁵ This provides validation to prior experimental data,³² which proposed that the hydrolysis proceeds through concerted (A_ND_N) transition states, but did not provide information into the degree of bond formation at the nucleophile.

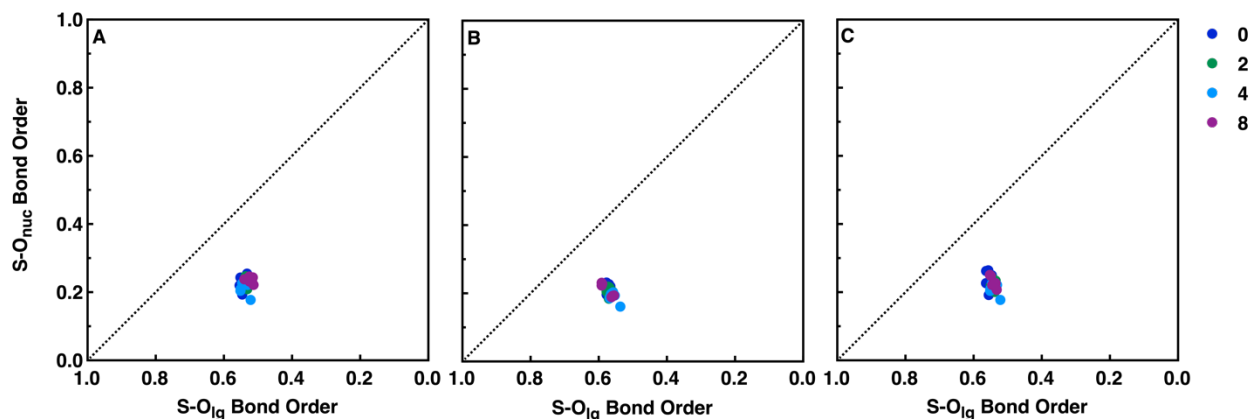


Figure 7. Calculated bond orders at the transition states for the alkaline hydrolysis of the aryl sulfate diesters studied in this work (**Figure 2**), in the presence of 0 (implicit solvent), 2, 4 or 8 explicit water molecules. Bond orders were calculated based on the Wiberg bond index⁴⁷ using natural bond orbital (NBO) analysis.⁴⁸ Data was obtained using either the (A) M11L,⁴¹ (B) M062X⁴² or (C) ωB97X-D⁴³ functionals. Note that due to data similarity between different systems it is very difficult to visualize the data with two explicit water molecules on the overlay plot; however, the corresponding raw data is presented in **Tables S82 to S105**.

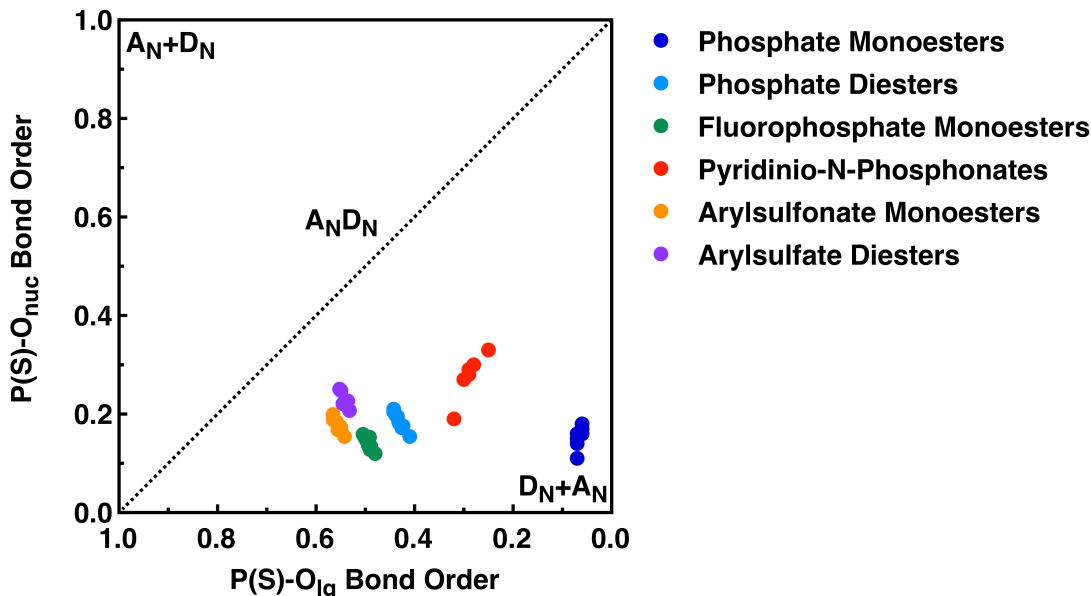


Figure 8. Comparison of the calculated bond orders at the transition states for the spontaneous hydrolysis of phosphate monoesters (dark blue), the reaction of substituted pyridinio-N-phosphonates with pyridine (red) and the alkaline hydrolysis of phosphate diesters (light blue), fluorophosphate monoesters (green), arylsulfonate monoesters (orange) and sulfate diaryl diesters (plum). In the case of the sulfate diesters, data is shown obtained in the presence of 8 explicit water molecules using the ω B97X-D⁴³ functional. All other data is from our prior work.³³⁻³⁷ Note that as the calculations were performed at differing levels of theory, this comparison is qualitative only. This figure is adapted from refs. ³⁷ and ⁵⁷.

Conclusions

The present work provides a detailed mechanistic study of the alkaline hydrolysis of diaryl sulfate diesters using different density functionals as well as both pure implicit solvation and mixed explicit/implicit solvation with different numbers of explicit water molecules. From a methodological perspective, our prior work has focused on using mixed explicit/implicit solvation to study the attack of a neutral nucleophile (H_2O) on charged electrophiles,^{27, 36, 40} whereas the current study focuses on the attack of a charged nucleophile (OH^-) on neutral sulfate diesters.

While the introduction of explicit water molecules that introduce explicit hydrogen bonding interactions was critical when modeling nucleophilic attack on charged electrophiles, it appears that in the present work, we obtain the best agreement with the experimentally measured LFER for the hydrolyses of these compounds in pure implicit solvation. In addition, unlike our prior work, the introduction of explicit water molecules does not significantly change the transition states involved compared to pure implicit solvent, with stable calculated kinetic isotope effects irrespectively of the number of explicit water molecules introduced. That is, we demonstrate that the reaction proceeds through concerted transition states for all compounds, without the involvement of an intermediate, as suggested by prior experimental data.³² However, the transition states involved are still overall slightly dissociative, with partial bond formation to the nucleophile and partial bond cleavage to the leaving group. These transition states are nevertheless more compact than any obtained from our previous studies of related compounds (**Figure 8**), and most greatly resemble those obtained for analogous aryl sulfonates. Obtaining detailed insight into the nature of the transition states involved is an important building block to understanding the chemical role of these biologically important molecules *in vivo*; however, this work also highlights the significant challenges involved in reliably modeling these compounds.

Associated Content

Absolute energies and Cartesian coordinates of all stationary points, additional details of relative energies, bond distances, and stationary points.

Acknowledgments

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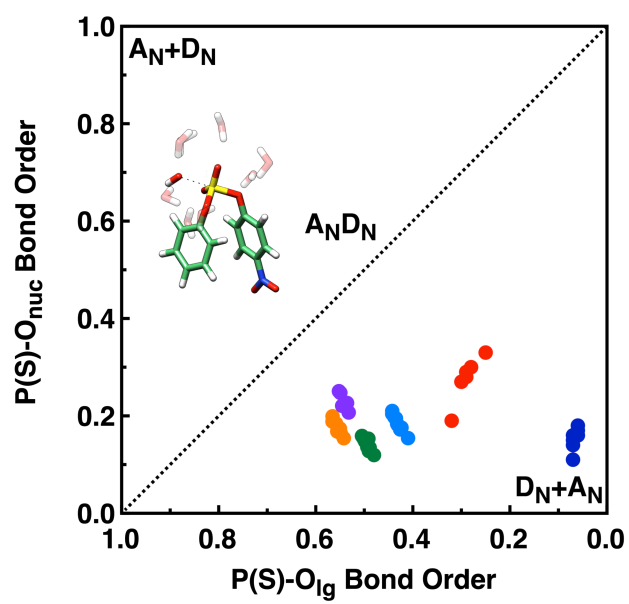
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Supporting Information for:

Modeling the Alkaline Hydrolysis of Diaryl Sulfate
Diesters: A Mechanistic Study

Klaudia Szeler,¹ Nicholas H. Williams,² Alvan C. Hengge,^{3,*} Shina C. L. Kamerlin^{1,*}

1. Department of Chemistry – BMC, Uppsala University, BMC Box 576, S-751 23 Uppsala, Sweden. 2. Department of Chemistry, University of Sheffield, Sheffield, S3 7HF, UK. 3. Department of Chemistry and Biochemistry, Utah State University, Logan, UT 84322-0300, USA.

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Supplementary Figures

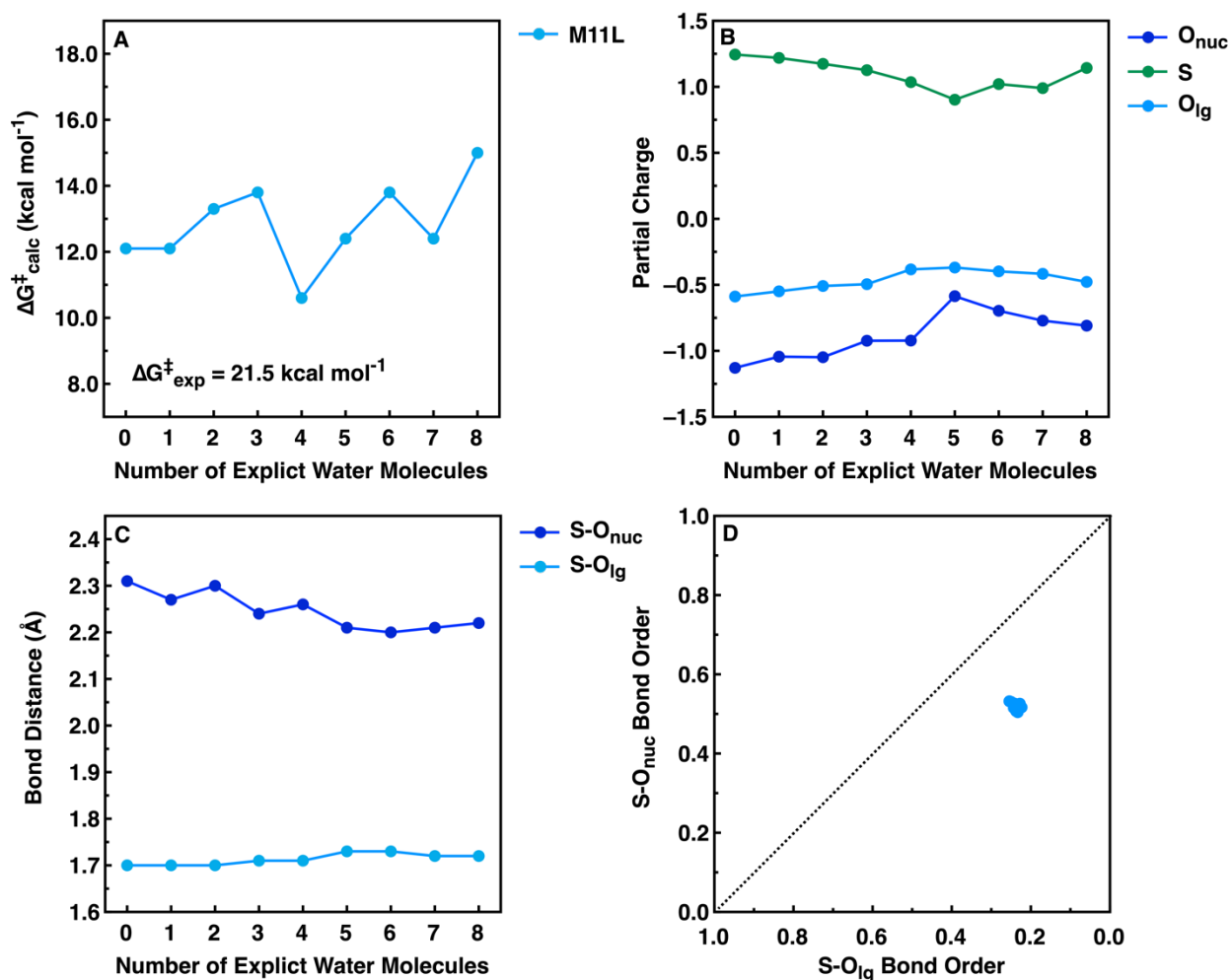


Figure S1. Overview of the (A) activation free energies, (B) partial charges at the transition state, (C) S-O_{nuc} and S-O_{lg} distances at the transition state and (D) S-O_{nuc} and S-O_{lg} bond orders at the transition state for the alkaline hydrolysis of 4-nitrophenyl sulfate with varying numbers of water molecules, obtained using the M11L¹ functional, as described in the **Methodology** section. The calculated activation free energy was obtained using transition state theory at 313.15 K, based on kinetic data provided in ref. ². For the corresponding data obtained using the ω B97X-D³ and M062X⁴ functionals, see **Figures 3** and **S2**, and for the corresponding raw data see **Tables S1** to **S21**.

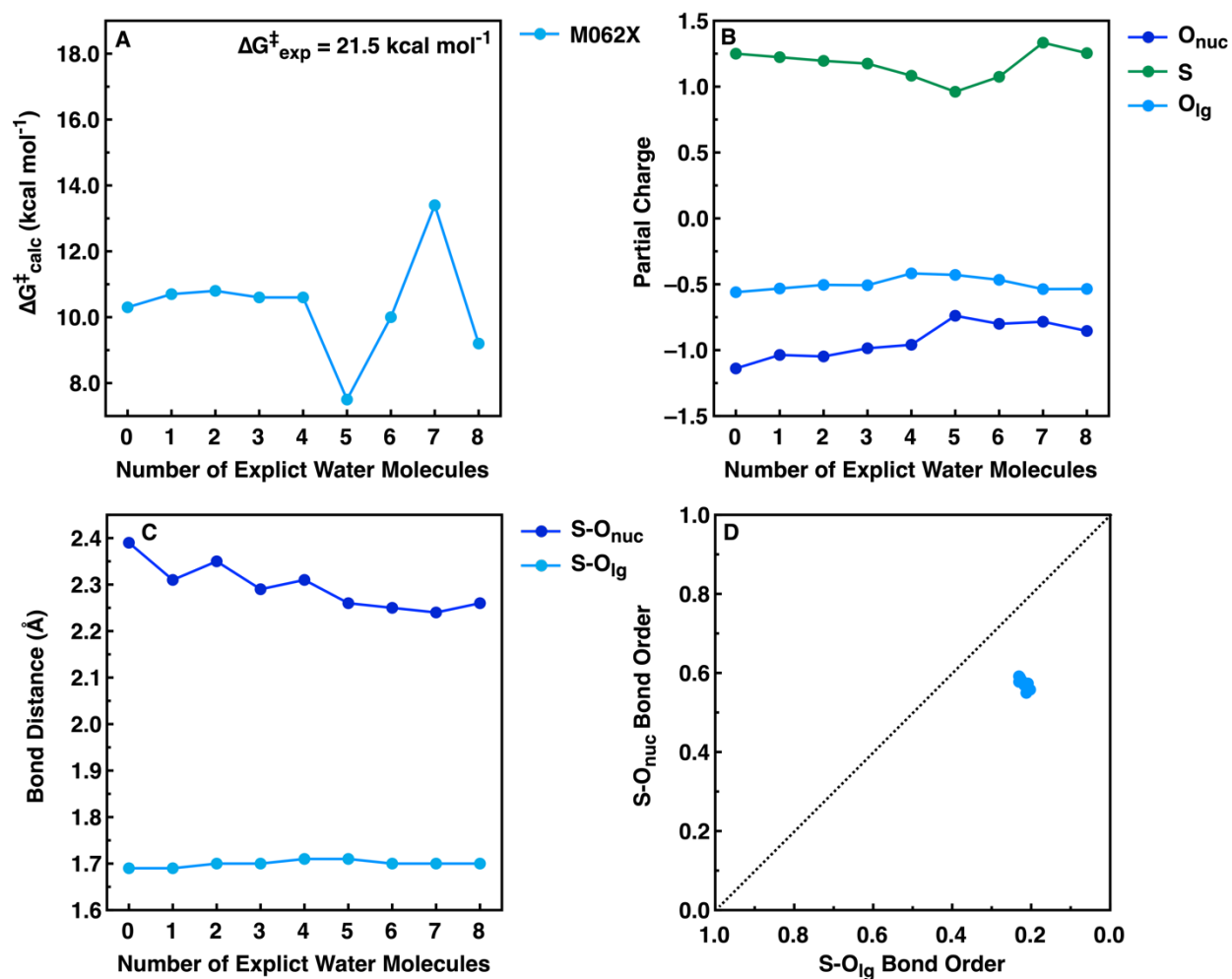


Figure S2. Overview of the (A) activation free energies, (B) partial charges at the transition state, (C) S-O_{nuc} and S-O_{lg} distances at the transition state and (D) S-O_{nuc} and S-O_{lg} bond orders at the transition state for the alkaline hydrolysis of 4-nitrophenyl sulfate with varying numbers of water molecules, obtained using the M062X⁴ functional, as described in the **Methodology** section. The calculated activation free energy was obtained using transition state theory at 313.15 K, based on kinetic data provided in ref. ². For the corresponding data obtained using the ω B97X-D³ and M11L¹ functionals, see **Figures 3** and **S1**, and for the corresponding raw data see **Tables S1** to **S21**.

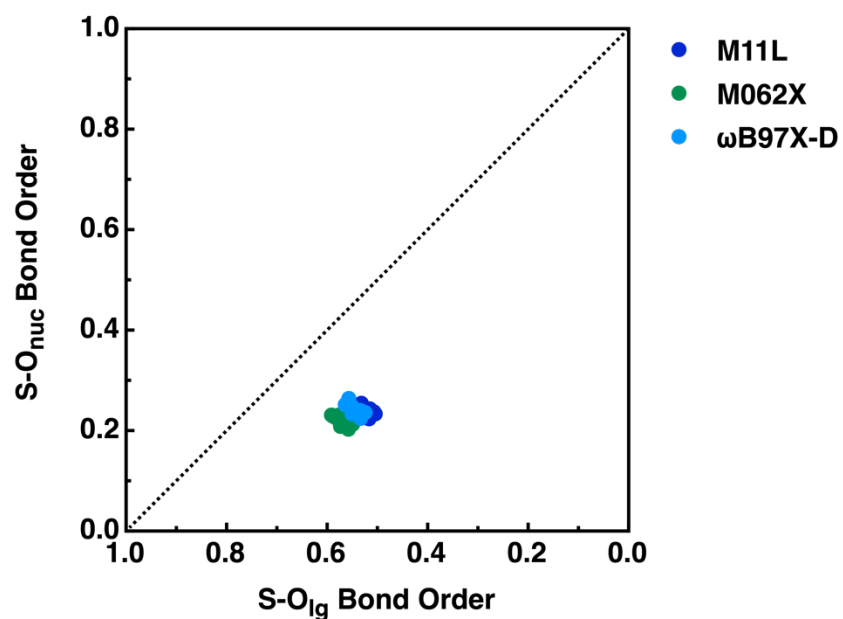


Figure S3. Overlay of the S-O_{nuc} and S-O_{lg} bond orders at the transition state for the alkaline hydrolysis of 4-nitrophenyl sulfate with varying numbers of water molecules, obtained using the ωB97X-D,³ M062X⁴ and M11L¹ functionals, as described in the **Methodology** section. For the corresponding raw data see **Tables S1** to **S21**.

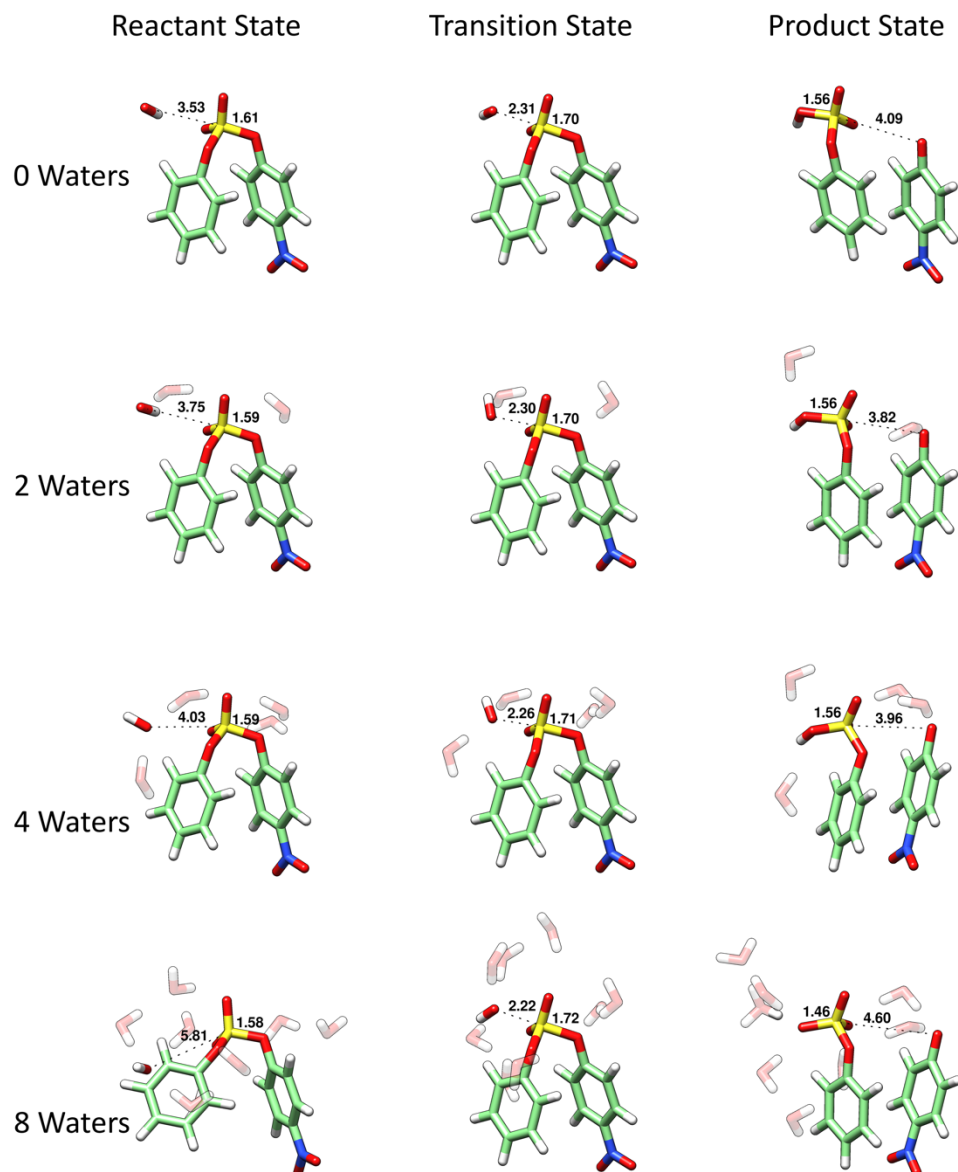


Figure S4. Representative structures of the ground, transition and product states for the alkaline hydrolysis of 4-nitrophenyl sulfate obtained using the M11L functional,¹ in the presence of varying numbers of explicit solvent molecules, as described in the **Methodology** section. The calculated S-O_{nuc} and S-O_{lg} distances are annotated for each optimized reacting state (in Å), and the corresponding data obtained using the ω B97X-D³ and M062X⁴ functionals is shown in **Figures 4** and **S5**, respectively. Finally, coordinates of all optimized stationary points are provided as **Supporting Information**.

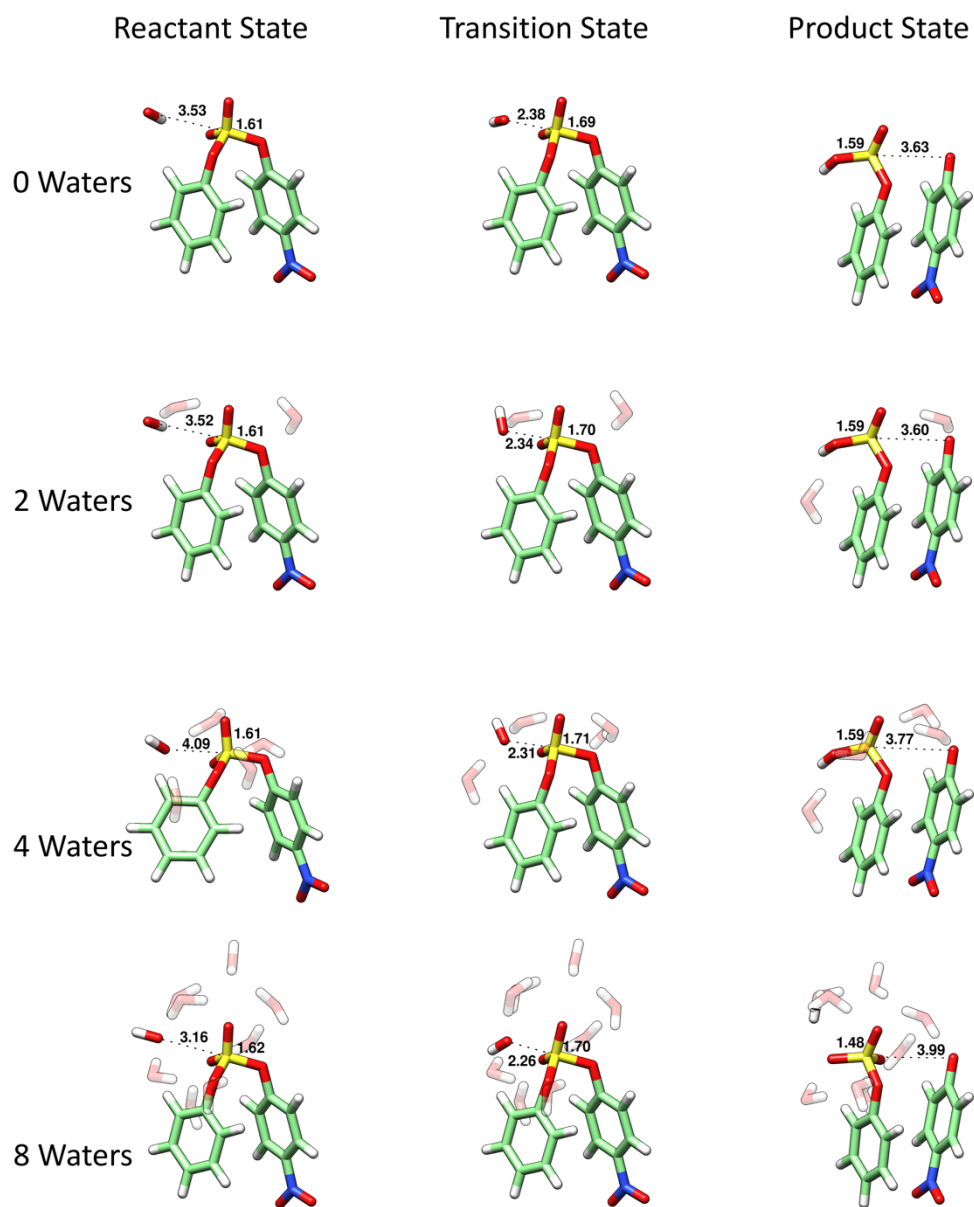


Figure S5. Representative structures of the ground, transition and product states for the alkaline hydrolysis of 4-nitrophenyl sulfate obtained using the M062X functional,⁴ in the presence of varying numbers of explicit solvent molecules, as described in the **Methodology** section. The calculated S-O_{nuc} and S-O_{lg} distances are annotated for each optimized reacting state (in Å), and the corresponding data obtained using the ω B97X-D³ and M11L¹ functionals is shown in **Figures 4** and **S4**, respectively. Finally, coordinates of all optimized stationary points are provided as **Supporting Information**.

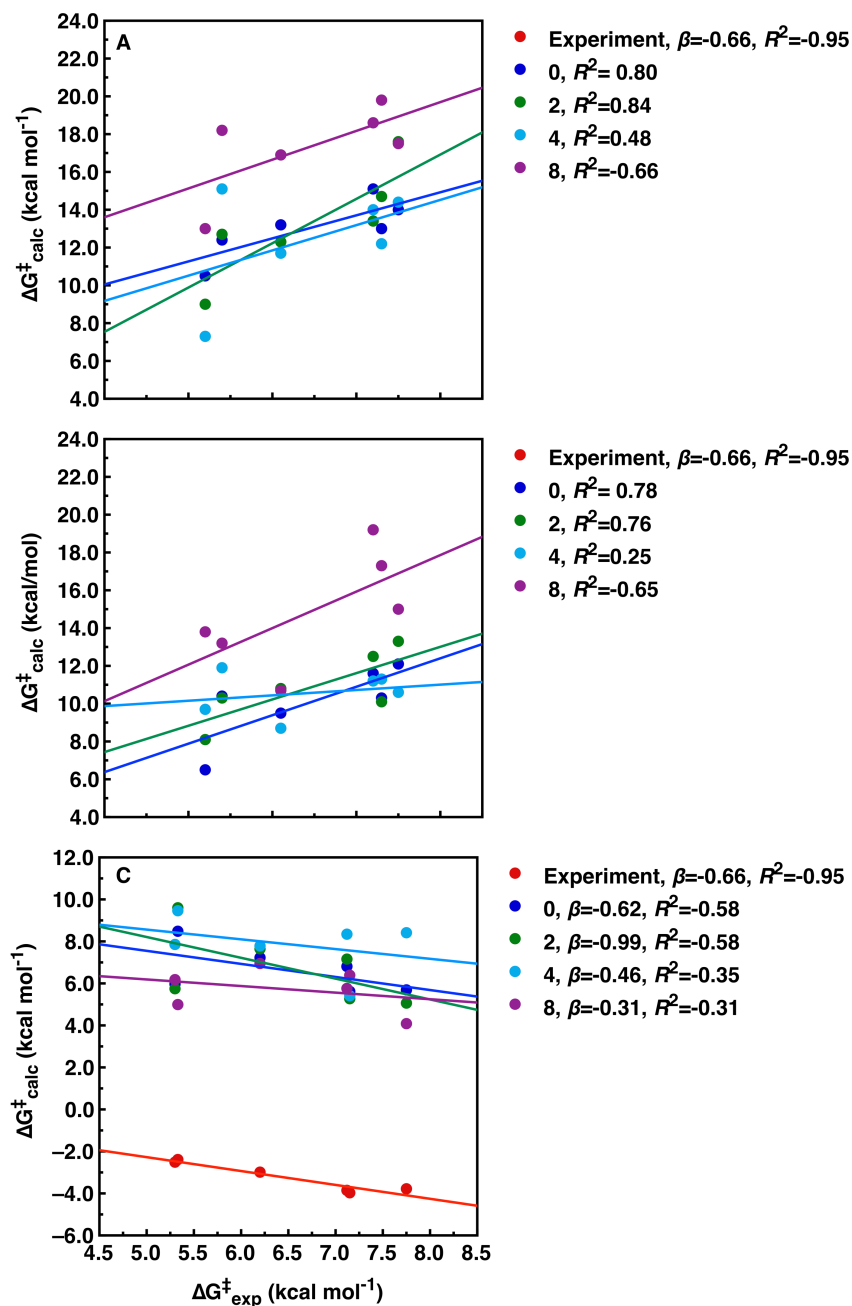


Figure S6. A comparison of experimental ($\Delta G^\ddagger_{\text{exp}}$) and calculated ($\Delta G^\ddagger_{\text{calc}}$) activation free energies for the alkaline hydrolysis of the aryl sulfate diesters studied in this work (**Figure 2**), in the presence of 0 (implicit solvent), 2, 4 or 8 explicit water molecules. Data was obtained using either the (A) ω B97X-D,³ (B) M11L¹ or (C) M062X⁴ functionals. The corresponding raw data is presented in **Tables S34 to S56**. Experimental activation free energies were obtained at 313.15 K using transition state theory based on kinetic data provided in ref.²

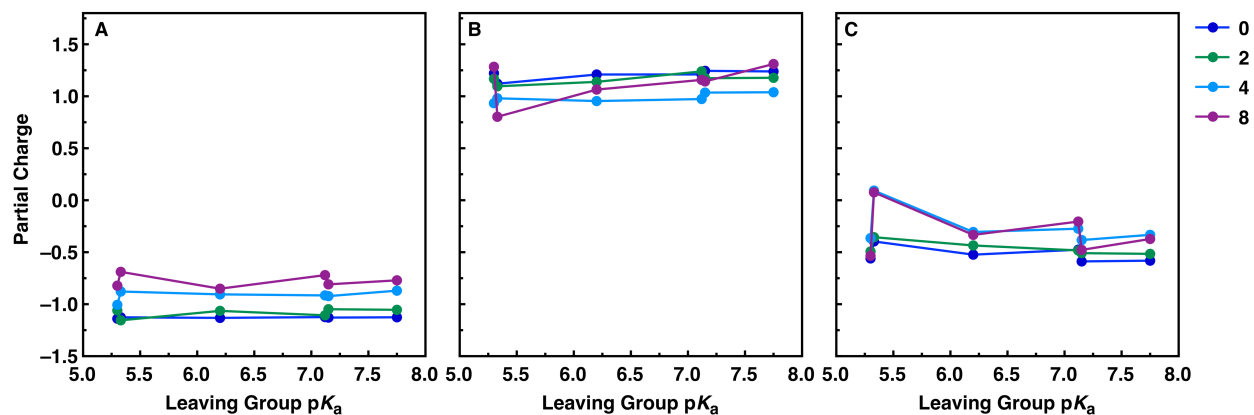


Figure S7. Partial charges on (A) the nucleophile oxygen, (B) the sulfur atom and (C) the leaving group oxygen, at the transition states for the alkaline hydrolysis of the aryl sulfate diesters studied in this work (Figure 2), in the presence of 0 (implicit solvent), 2, 4 or 8 explicit water molecules. Partial charges were calculated using the M11L¹ functional and the CHELPG charge calculation scheme⁵ as described in the **Methodology** section. The corresponding charge distributions obtained using the wB97xD³ and M062X⁴ functionals are shown in **Figures 6** and **S8**, respectively, and the corresponding raw data is shown in **Table S57 to S80**.

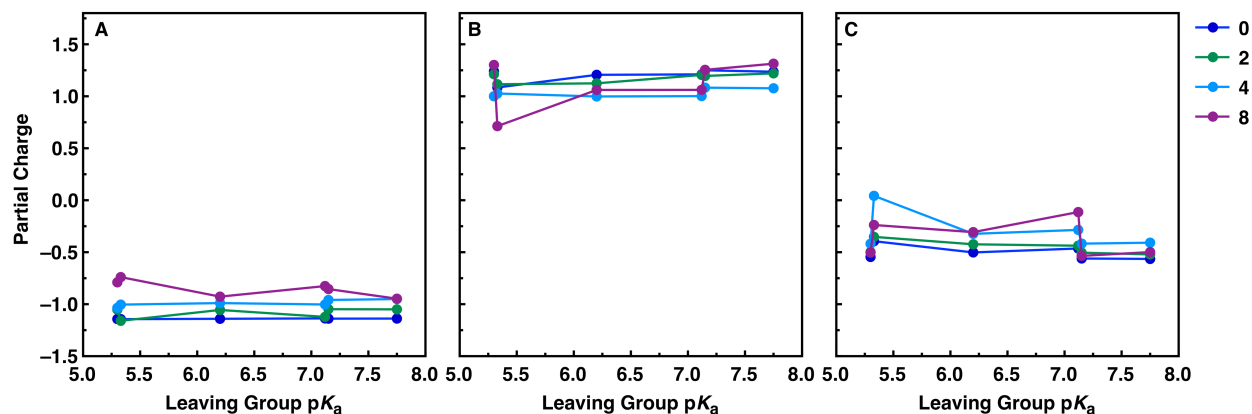


Figure S8. Partial charges on (A) the nucleophile oxygen, (B) the sulfur atom and (C) the leaving group oxygen, at the transition states for the alkaline hydrolysis of the aryl sulfate diesters studied in this work (Figure 2), in the presence of 0 (implicit solvent), 2, 4 or 8 explicit water molecules. Partial charges were calculated using the M062X⁴ functional and the CHELPG charge calculation scheme⁵ as described in the **Methodology** section. The corresponding charge distributions obtained using the wb97xD³ and M11L¹ functionals are shown in **Figures 6** and **S7**, respectively, and the corresponding raw data is shown in **Table S57 to S81**.

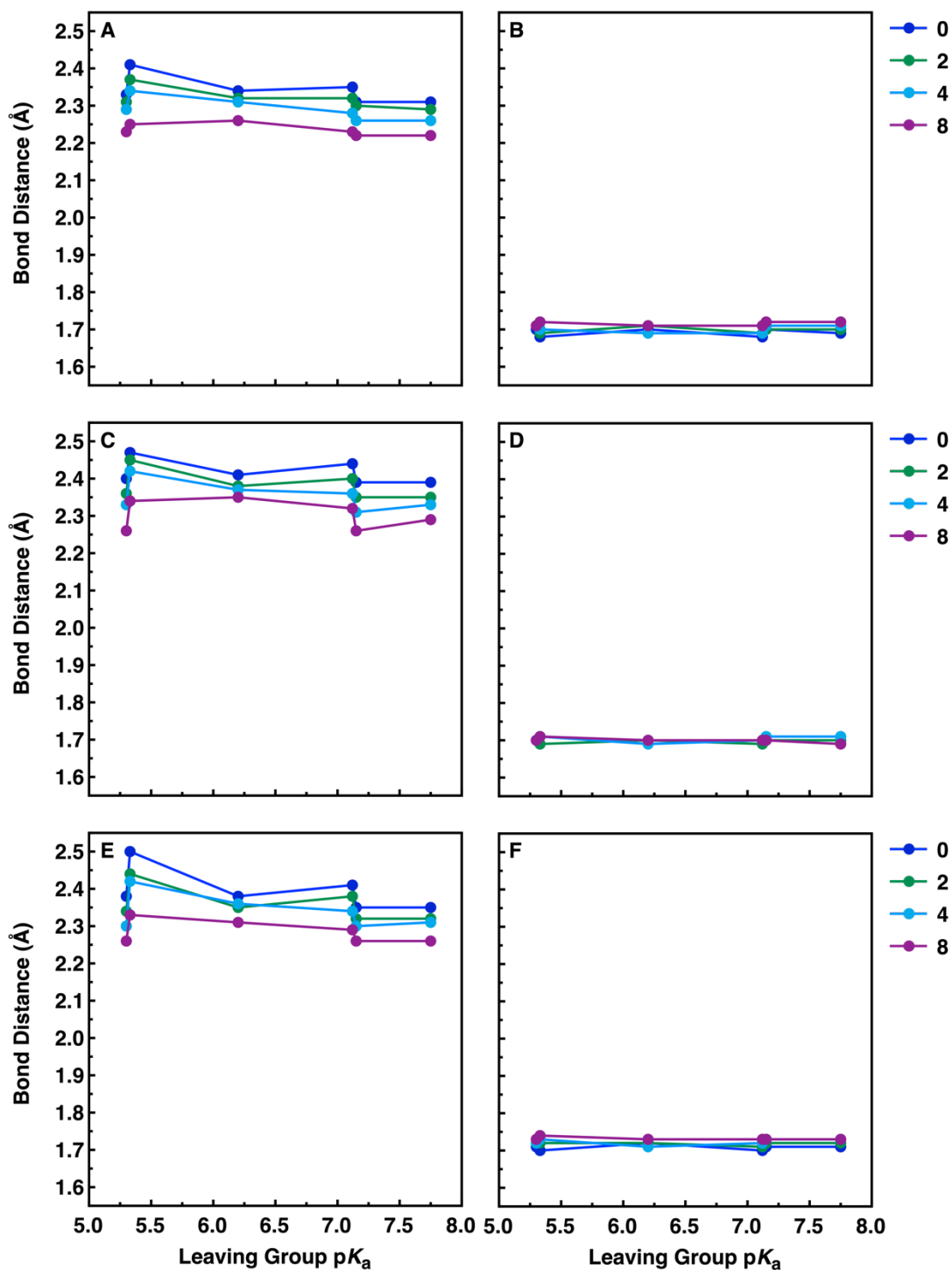


Figure S9. Calculated (A,C,E) S-O_{nuc} and (B,D,F) S-O_{lg} distances at the transition states for the alkaline hydrolysis of the aryl sulfate diesters studied in this work (**Figure 2**), in the presence of 0 (implicit solvent), 2, 4 or 8 explicit water molecules. Data was obtained using either the (A,B) M11L,¹ (C,D) M062X⁴ or (E,F) ω B97X-D³ functionals. The corresponding raw data is presented in **Table S82 to S105**.

Supplementary Tables

Table S1. Energy decomposition of the calculated activation free energies ($\Delta G^\ddagger_{\text{calc}}$) for the alkaline hydrolysis of 4-nitrophenyl sulfate in the presence of 0 to 8 additional explicit water molecules, obtained using the ω B97X-D³ functional.^a

Water Molecules	ΔE^\ddagger	$\Delta \text{ZPE}^\ddagger$	$-\text{T}\Delta S^\ddagger$	$\Delta G^\ddagger_{\text{calc}}$	$\Delta G^\ddagger_{\text{exp}}$	ν
0	10.6	0.2	3.2	14	21.5	-269.6541
1	11.8	0.4	3.2	15.4	21.5	-273.9228
2	17.4	-0.4	0.6	17.6	21.5	-289.4289
3	14.5	-0.1	1.7	16.1	21.5	-275.8035
4	13.8	-0.3	0.9	14.4	21.5	-266.4356
5	20.2	-1	-3.2	16	21.5	-282.5629
6	20.7	-0.9	-1.4	18.4	21.5	-281.2544
7	16.2	0.6	-1.4	14.2	21.5	-282.4447
8	17.3	-0.3	0.5	17.5	21.5	-281.4245

^a All energies are shown in kcal mol⁻¹, and vibrational frequencies are shown in cm⁻¹. ΔE^\ddagger , $\Delta \text{ZPE}^\ddagger$ and $-\text{T}\Delta S^\ddagger$ denote the contributions to $\Delta G^\ddagger_{\text{calc}}$ from the electronic energy, zero-point energy and activation free energy, respectively. ν denotes the first vibrational frequency. $\Delta G^\ddagger_{\text{exp}}$ denotes the experimental activation free energy at 313.15 K, obtained from the kinetic data presented in ref. ² using transition state theory.

Table S2. Energy decomposition of the calculated activation free energies ($\Delta G^\ddagger_{\text{calc}}$) for the alkaline hydrolysis of 4-nitrophenyl sulfate in the presence of 0 to 8 additional explicit water molecules, obtained using the M11L¹ functional.^a

Water Molecules	ΔE^\ddagger	$\Delta \text{ZPE}^\ddagger$	$-\text{T}\Delta S^\ddagger$	$\Delta G^\ddagger_{\text{calc}}$	$\Delta G^\ddagger_{\text{exp}}$	ν
0	9.1	-0.1	3.1	12.1	21.5	-331.4516
1	9.1	0.2	2.8	12.1	21.5	-351.8688
2	8.2	0.01	5.1	13.3	21.5	-332.1461
3	13.5	-0.4	0.7	13.8	21.5	-341.4854
4	9	-0.2	1.8	10.6	21.5	-332.1585
5	10.3	0.01	2.1	12.4	21.5	-350.3726
6	19.4	-1.5	-4.1	13.8	21.5	-349.6627
7	18.3	-1.7	-4.2	12.4	21.5	-351.3161
8	19	-1.2	-2.8	15	21.5	-349.729

^a All energies are shown in kcal mol⁻¹, and vibrational frequencies are shown in cm⁻¹. ΔE^\ddagger , $\Delta \text{ZPE}^\ddagger$ and $-\text{T}\Delta S^\ddagger$ denote the contributions to $\Delta G^\ddagger_{\text{calc}}$ from the electronic energy, zero-point energy and activation free energy, respectively. ν denotes the first vibrational frequency. $\Delta G^\ddagger_{\text{exp}}$ denotes the experimental activation free energy at 313.15 K, obtained from the kinetic data presented in ref. ² using transition state theory.

Table S3. Energy decomposition of the calculated activation free energies ($\Delta G^\ddagger_{\text{calc}}$) for the alkaline hydrolysis of 4-nitrophenyl sulfate in the presence of 0 to 8 additional explicit water molecules, obtained using the M062X⁴ functional.^a

Water Molecules	ΔE^\ddagger	$\Delta \text{ZPE}^\ddagger$	$-\text{T}\Delta S^\ddagger$	$\Delta G^\ddagger_{\text{calc}}$	$\Delta G^\ddagger_{\text{exp}}$	ν
0	7.5	0.1	2.7	10.3	21.5	-316.6842
1	8.5	0.5	2.2	10.7	21.5	-298.9999
2	6.3	0.5	4.0	10.8	21.5	-292.9074
3	9.5	0.03	1.1	10.6	21.5	-286.9348
4	11.0	-0.4	0.01	10.6	21.5	-287.6699
5	10	-0.6	-1.9	7.5	21.5	-277.9046
6	8.7	0.6	0.7	10	21.5	-278.046
7	15.1	0.01	-1.7	13.4	21.5	-279.0495
8	8.2	0.3	0.7	9.2	21.5	-283.7645

^a All energies are shown in kcal mol⁻¹, and vibrational frequencies are shown in cm⁻¹. ΔE^\ddagger , $\Delta \text{ZPE}^\ddagger$ and $-\text{T}\Delta S^\ddagger$ denote the contributions to $\Delta G^\ddagger_{\text{calc}}$ from the electronic energy, zero-point energy and activation free energy, respectively. ν denotes the first vibrational frequency. $\Delta G^\ddagger_{\text{exp}}$ denotes the experimental activation free energy at 313.15 K, obtained from the kinetic data presented in ref. ² using transition state theory.

Table S4. Experimental and calculated rate constants for the alkaline hydrolysis of 4-nitrophenyl sulfate in the presence of 0 to 8 additional explicit water molecules, obtained using the ω B97X-D³ functional.^a

Water Molecules	k_{calc}	$\log k_{\text{calc}}$	$\log k_{\text{exp}}$
0	1.090×10^3	3.0374	-3.9706
1	1.148×10^2	2.0599	-3.9706
2	3.339×10^0	0.5236	-3.9706
3	3.724×10^1	1.5710	-3.9706
4	5.728×10^2	2.7580	-3.9706
5	4.373×10^1	1.6408	-3.9706
6	9.228×10^{-1}	-0.0349	-3.9706
7	7.900×10^2	2.8976	-3.9706
8	3.922×10^0	0.5935	-3.9706

^a The calculated rate constant, k_{calc} , was derived from the calculated activation free energy, ΔG^\ddagger , at 313.15 K, using transition state theory. The corresponding experimental value was obtained from ref. ² after correcting the experimental second order rate constant by 0.017 M^{-1} to take into account the entropic cost of bringing the reacting fragments into the encounter complex, following ref. ⁶.

Table S5. Experimental and calculated rate constants for the alkaline hydrolysis of 4-nitrophenyl sulfate in the presence of 0 to 8 additional explicit water molecules, obtained using the M11L¹ functional.^a

Water Molecules	k_{calc}	$\log k_{\text{calc}}$	$\log k_{\text{exp}}$
0	2.311×10^4	4.3638	-3.9706
1	7.501×10^3	3.8751	-3.9706
2	3.356×10^3	3.5258	-3.9706
3	1.503×10^3	3.1770	-3.9706
4	2.578×10^5	5.4113	-3.9706
5	1.427×10^4	4.1544	-3.9706
6	1.503×10^3	3.1770	-3.9706
7	1.427×10^4	4.1544	-3.9706
8	2.183×10^2	2.3391	-3.9706

^a The calculated rate constant, k_{calc} , was derived from the calculated activation free energy, ΔG^\ddagger , at 313.15 K, using transition state theory. The corresponding experimental value was obtained from ref. ² after correcting the experimental second order rate constant by 0.017 M^{-1} to take into account the entropic cost of bringing the reacting fragments into the encounter complex, following ref. ⁶.

Table S6. Experimental and calculated rate constants for the alkaline hydrolysis of 4-nitrophenyl sulfate in the presence of 0 to 8 additional explicit water molecules, obtained using the M062X⁴ functional.^a

Water Molecules	k_{calc}	$\log k_{\text{calc}}$	$\log k_{\text{exp}}$
0	4.175×10^5	5.6207	-3.9706
1	2.195×10^5	5.3414	-3.9706
2	1.869×10^5	5.2716	-3.9706
3	2.578×10^5	5.4113	-3.9706
4	2.578×10^5	5.4113	-3.9706
5	3.765×10^7	7.5758	-3.9706
6	6.763×10^5	5.8301	-3.9706
7	2.073×10^3	3.3166	-3.9706
8	2.448×10^6	6.3889	-3.9706

^a The calculated rate constant, k_{calc} , was derived from the calculated activation free energy, ΔG^\ddagger , at 313.15 K, using transition state theory. The corresponding experimental value was obtained from ref. ² after correcting the experimental second order rate constant by 0.017 M^{-1} to take into account the entropic cost of bringing the reacting fragments into the encounter complex, following ref. ⁶.

Table S7. Absolute and relative energy contributions to the calculated free energies (ΔG_{calc}) for the alkaline hydrolysis of 4-nitrophenyl sulfate in the presence of 0 to 8 additional explicit water molecules, obtained using the ω B97X-D³ functional.^a

0 waters	E	ZPE	S	ΔE	ΔZPE	$-T\Delta S$	ΔG_{calc}	v
RS	-1442.7105877	135.50586	153.837	0.0	0.0	0.0	0.0	27.865
TS	-1442.6936351	135.68108	143.642	10.6	0.2	3.2	14.0	-269.6541
PS	-1442.7620338	135.88209	156.698	-32.3	0.4	-0.9	-32.8	2.5343
1 water	E	ZPE	S	ΔE	ΔZPE	$-T\Delta S$	ΔG_{calc}	v
RS	-1519.1725361	150.27362	171.609	0.0	0.0	0.0	0.0	10.226
TS	-1519.1536605	150.71761	161.301	11.8	0.4	3.2	15.4	-273.9228
PS	-1519.2144700	150.92204	170.623	-26.3	0.6	0.3	-25.4	18.9027
2 waters	E	ZPE	S	ΔE	ΔZPE	$-T\Delta S$	ΔG_{calc}	v
RS	-1595.6332193	166.11857	180.725	0.0	0.0	0.0	0.0	22.0334
TS	-1595.6054962	165.73854	178.694	17.4	-0.4	0.6	17.6	-289.4289
PS	-1595.6744573	166.80655	181.284	-25.9	0.7	-0.2	-25.4	17.7028
3 waters	E	ZPE	S	ΔE	ΔZPE	$-T\Delta S$	ΔG_{calc}	v
RS	-1672.0867685	181.02450	200.557	0.0	0.0	0.0	0.0	16.8582
TS	-1672.0636513	180.93808	195.097	14.5	-0.1	1.7	16.1	-275.8035
PS	-1672.1371688	182.14724	195.756	-31.6	1.1	1.5	-29.0	12.69610
4 waters	E	ZPE	S	ΔE	ΔZPE	$-T\Delta S$	ΔG_{calc}	v
RS	-1748.5825985	197.83378	209.165	-28.4	1.7	2.4	-24.3	20.5039
TS	-1748.5825985	197.83378	209.165	-28.4	1.7	2.4	-24.3	20.5039
PS	-1748.5825985	197.83378	209.165	-28.4	1.7	2.4	-24.3	20.5039
5 waters	E	ZPE	S	ΔE	ΔZPE	$-T\Delta S$	ΔG_{calc}	v
RS	-1825.0023189	212.77408	222.328	0.0	0.0	0.0	0.0	20.2906
TS	-1824.9701787	211.75014	232.606	20.2	-1.0	-3.2	16.0	-282.5629
PS	-1825.0481055	214.06832	220.043	-28.7	1.3	0.7	-26.7	20.0403
6 waters	E	ZPE	S	ΔE	ΔZPE	$-T\Delta S$	ΔG_{calc}	v
RS	-1901.4555423	227.69456	243.654	0.0	0.0	0.0	0.0	9.0437
TS	-1901.4226068	226.84023	248.15	20.7	-0.9	-1.4	18.4	-281.2544
PS	-1901.5139771	232.44189	221.155	-36.7	4.7	7.0	-24.9	24.6981
7 waters	E	ZPE	S	ΔE	ΔZPE	$-T\Delta S$	ΔG_{calc}	v
RS	-1977.9024920	243.68866	255.2	0.0	0.0	0.0	0.0	13.77
TS	-1977.8766201	243.11390	259.797	16.2	-0.6	-1.4	14.2	-282.4447
PS	-1977.9355331	243.31718	262.147	-20.7	-0.4	-2.2	-23.3	19.0105

8 waters	E	ZPE	S	ΔE	ΔZPE	$-T\Delta S$	ΔG_{calc}	ν
RS	-2054.3572856	259.26468	268.855	0.0	0.0	0.0	0.0	21.8354
TS	-2054.3298017	259.00254	267.27	17.2	-0.3	0.5	17.5	-281.4245
PS	-2054.4203233	262.31221	258.444	-39.6	3.0	3.3	-33.2	20.8432

^a RS, TS and PS denote the reactant, transition and product states, respectively. E, ZPE and S denote the absolute electronic energies, zero-point energies and entropies, and ΔE , ΔZPE and $-T\Delta S$ denote the corresponding values relative to the RS (all values in kcal mol⁻¹, except S which is presented in cal mol⁻¹ K⁻¹). ν denotes the first vibrational frequency (cm⁻¹).

Table S8. Absolute and relative energy contributions to the calculated free energies (ΔG_{calc}) for the alkaline hydrolysis of 4-nitrophenyl sulfate in the presence of 0 to 8 additional explicit water molecules, obtained using the M11L¹ functional.^a

0 waters	E	ZPE	S	ΔE	ΔZPE	$-T\Delta S$	ΔG_{calc}	v
RS	-1442.7758730	132.60756	153.934	0.0	0.0	0.0	0.0	26.0193
TS	-1442.7614408	132.52363	144.06	9.1	-0.1	3.1	12.1	-331.4516
PS	-1442.8369596	133.54658	154.348	-38.3	0.9	-0.1	-37.5	20.0531
1 water	E	ZPE	S	ΔE	ΔZPE	$-T\Delta S$	ΔG_{calc}	v
RS	-1519.2322701	147.70918	171.123	0.0	0.0	0.0	0.0	20.9616
TS	-1519.2178372	147.87940	162.067	9.1	0.2	2.8	12.1	-351.8688
PS	-1519.2860610	148.03910	177.37	-33.8	0.3	-2.0	-35.4	13.5424
2 waters	E	ZPE	S	ΔE	ΔZPE	$-T\Delta S$	ΔG_{calc}	v
RS	-1595.6796661	162.80622	192.494	0.0	0.0	0.0	0.0	17.8855
TS	-1595.6665795	162.81241	176.348	8.2	0.01	5.1	13.3	-332.1461
PS	-1595.7381136	163.80171	189.695	-36.7	1.0	0.9	-34.8	16.8895
3 waters	E	ZPE	S	ΔE	ΔZPE	$-T\Delta S$	ΔG_{calc}	v
RS	-1672.1435071	179.18847	197.149	0.0	0.0	0.0	0.0	14.1686
TS	-1672.1220323	178.77017	195.019	13.5	-0.4	0.7	13.8	-341.4854
PS	-1672.1899994	178.86475	206.643	-29.2	-0.3	-3.0	-32.5	19.8945
4 waters	E	ZPE	S	ΔE	ΔZPE	$-T\Delta S$	ΔG_{calc}	v
RS	-1748.5846590	193.92064	221.836	0.0	0.0	0.0	0.0	18.1209
TS	-1748.5702951	193.69953	215.956	9.0	-0.2	1.8	10.6	-332.1585
PS	-1748.6433847	194.01429	226.487	-36.9	0.1	-1.5	-38.2	13.0271
5 waters	E	ZPE	S	ΔE	ΔZPE	$-T\Delta S$	ΔG_{calc}	v
RS	-1825.0394562	209.29003	241.707	0.0	0.0	0.0	0.0	13.5004
TS	-1825.0230855	209.30180	234.984	10.3	0.01	2.1	12.4	-350.3726
PS	-1825.0927422	211.46170	234.019	-33.4	2.2	2.4	-28.9	11.3288
6 waters	E	ZPE	S	ΔE	ΔZPE	$-T\Delta S$	ΔG_{calc}	v
RS	-1901.5036073	226.17852	241.632	0.0	0.0	0.0	0.0	16.054
TS	-1901.4726305	224.63579	254.622	19.4	-1.5	-4.1	13.8	-349.6627
PS	-1901.5792210	229.84625	233.146	-47.4	3.7	2.7	-41.1	11.0626
7 waters	E	ZPE	S	ΔE	ΔZPE	$-T\Delta S$	ΔG_{calc}	v
RS	-1977.9523154	242.09906	255.206	0.0	0.0	0.0	0.0	16.2606
TS	-1977.9231450	240.41600	268.595	18.3	-1.7	-4.2	12.4	-351.3161
PS	-1978.0181196	244.63820	247.676	-41.3	2.5	2.4	-36.4	-0.8686

8 waters	E	ZPE	S	ΔE	ΔZPE	$-T\Delta S$	ΔG_{calc}	ν
RS	-2054.4041216	257.57639	270.968	0.0	0.0	0.0	0.0	16.7626
TS	-2054.3737914	256.36054	279.803	19.0	-1.2	-2.8	15.0	-349.729
PS	-2054.4710658	260.06720	267.761	-42.0	2.5	1.0	-38.5	12.8992

^a RS, TS and PS denote the reactant, transition and product states, respectively. E, ZPE and S denote the absolute electronic energies, zero-point energies and entropies, and ΔE , ΔZPE and $-T\Delta S$ denote the corresponding values relative to the RS (all values in kcal mol⁻¹, except S which is presented in cal mol⁻¹ K⁻¹). ν denotes the first vibrational frequency (cm⁻¹).

Table S9. Absolute and relative energy contributions to the calculated free energies (ΔG_{calc}) for the alkaline hydrolysis of 4-nitrophenyl sulfate in the presence of 0 to 8 additional explicit water molecules, obtained using the M062X⁴ functional.^a

0 waters	E	ZPE	S	ΔE	ΔZPE	$-T\Delta S$	ΔG_{calc}	v
RS	-1442.6434689	135.59843	151.311	0.0	0.0	0.0	0.0	29.8035
TS	-1442.6315931	135.71633	142.807	7.5	0.1	2.7	10.3	-316.6842
PS	-1442.6973623	136.14742	147.904	-33.8	0.5	1.1	-32.2	30.4802
1 water	E	ZPE	S	ΔE	ΔZPE	$-T\Delta S$	ΔG_{calc}	v
RS	-1519.0940823	149.96617	167.101	0.0	0.0	0.0	0.0	15.3596
TS	-1519.0813406	150.43057	160.043	8.0	0.5	2.2	10.7	-298.9999
PS	-1519.1352670	150.69595	171.254	-25.8	0.7	-1.3	-26.4	20.401
2 waters	E	ZPE	S	ΔE	ΔZPE	$-T\Delta S$	ΔG_{calc}	v
RS	-1595.1585719	164.92086	189.93	0.0	0.0	0.0	0.0	15.3242
TS	-1595.1485956	165.40078	177.103	6.3	0.5	4.0	10.8	-292.9074
PS	-1595.2115938	166.56085	178.44	-33.3	1.6	3.6	-28.0	21.2865
3 waters	E	ZPE	S	ΔE	ΔZPE	$-T\Delta S$	ΔG_{calc}	v
RS	-1671.9852185	180.84029	192.716	0.0	0.0	0.0	0.0	15.0767
TS	-1671.9700944	180.87399	189.063	9.5	0.03	1.1	10.6	-286.9348
PS	-1672.0265242	182.07435	191.96	-25.9	1.2	0.2	-24.4	24.4032
4 waters	E	ZPE	S	ΔE	ΔZPE	$-T\Delta S$	ΔG_{calc}	v
RS	-1748.4273098	196.06219	208.126	0.0	0.0	0.0	0.0	21.9257
TS	-1748.4097162	195.70859	208.107	11.0	-0.4	0.01	10.6	-287.6699
PS	-1748.4702918	197.12423	207.891	-27.0	1.1	0.1	-25.8	25.862
5 waters	E	ZPE	S	ΔE	ΔZPE	$-T\Delta S$	ΔG_{calc}	v
RS	-1824.8700820	211.28808	226.274	0.0	0.0	0.0	0.0	16.6705
TS	-1824.8541447	210.69593	232.445	10.0	-0.6	-1.9	7.5	-277.9046
PS	-1824.9274984	213.45421	223.182	-36.0	2.2	1.0	-32.9	11.1737
6 waters	E	ZPE	S	ΔE	ΔZPE	$-T\Delta S$	ΔG_{calc}	v
RS	-1901.3121152	226.71693	239.679	0.0	0.0	0.0	0.0	19.0124
TS	-1901.2982843	227.33679	237.594	8.7	0.6	0.7	10.0	-278.046
PS	-1901.3524776	228.28582	239.854	-25.3	1.6	-0.1	-23.8	16.8398
7 waters	E	ZPE	S	ΔE	ΔZPE	$-T\Delta S$	ΔG_{calc}	v
RS	-1977.7680384	243.84477	237.178	0.0	0.0	0.0	0.0	22.6625
TS	-1977.7439931	243.85549	242.454	15.1	0.01	-1.7	13.4	-279.0495
PS	-1977.7680384	245.60397	231.35	0.0	1.8	1.8	3.6	25.1431

8 waters	E	ZPE	S	ΔE	ΔZPE	$-T\Delta S$	ΔG_{calc}	ν
RS	-2054.1986122	258.61012	261.306	0.0	0.0	0.0	0.0	19.785
TS	-2054.1855888	258.95387	258.979	8.2	0.3	0.7	9.2	-283.7645
PS	-2054.2672984	261.38123	250.497	-43.1	2.8	3.4	-36.9	20.118

^a RS, TS and PS denote the reactant, transition and product states, respectively. E, ZPE and S denote the absolute electronic energies, zero-point energies and entropies, and ΔE , ΔZPE and $-T\Delta S$ denote the corresponding values relative to the RS (all values in kcal mol⁻¹, except S which is presented in cal mol⁻¹ K⁻¹). ν denotes the first vibrational frequency (cm⁻¹).

Table S10. Partial charges at the transition state for the alkaline hydrolysis of 4-nitrophenyl sulfate in the presence of 0 to 8 additional explicit water molecules, obtained using the ω B97X-D³ functional.^a

Water Molecules	O_{nuc}	S	O_{lg}
0	-1.116133	1.259782	-0.58486
1	-1.058482	1.183376	-0.533672
2	-1.056234	1.117773	-0.4649
3	-0.918205	1.129663	-0.504537
4	-0.903971	1.094185	-0.427313
5	-0.630151	0.977564	-0.411007
6	-0.642337	1.028546	-0.400772
7	-0.78432	1.333445	-0.536905
8	-0.808109	1.375266	-0.539817

^a Partial charges are calculated using the ChelpG⁵ charge calculation scheme, as described in the **Methodology** section.

Table S11. Partial charges at the transition state for the alkaline hydrolysis of 4-nitrophenyl sulfate in the presence of 0 to 8 additional explicit water molecules, obtained using the M11L¹ functional.^a

Water Molecules	O _{nuc}	S	O _{lg}
0	-1.128893	1.244377	-0.588531
1	-1.044112	1.218874	-0.549157
2	-1.048351	1.173881	-0.508858
3	-0.923554	1.12593	-0.495079
4	-0.922275	1.035309	-0.383091
5	-0.586031	0.902254	-0.368954
6	-0.696526	1.02064	-0.397964
7	-0.771277	0.989932	-0.41659
8	-0.809259	1.14282	-0.477867

^a Partial charges are calculated using the ChelpG⁵ charge calculation scheme, as described in the **Methodology** section.

Table S12. Partial charges at the transition state for the alkaline hydrolysis of 4-nitrophenyl sulfate in the presence of 0 to 8 additional explicit water molecules, obtained using the M062X⁴ functional.^a

Water Molecules	O _{nuc}	S	O _{lg}
0	-1.139127	1.250009	-0.560361
1	-1.03667	1.223303	-0.532325
2	-1.048017	1.195557	-0.504796
3	-0.985903	1.174767	-0.507501
4	-0.959323	1.082878	-0.417571
5	-0.739218	0.961012	-0.429012
6	-0.800466	1.074493	-0.466512
7	-0.78432	1.333445	-0.536905
8	-0.854524	1.254148	-0.535374

^a Partial charges are calculated using the ChelpG⁵ charge calculation scheme, as described in the **Methodology** section.

Table S13. Partial charges at key stationary points for the alkaline hydrolysis of 4-nitrophenyl sulfate in the presence of 0 to 8 additional explicit water molecules, obtained using the ω B97X-D³ functional.^a

0 waters	O_{nuc}	S	O_{lg}
RS	-1.296563	1.12486	-0.391163
TS	-1.116133	1.259782	-0.58486
PS	-0.537492	1.114613	-0.804766
1 water	O_{nuc}	S	O_{lg}
RS	-1.196337	1.194745	-0.425358
TS	-1.058482	1.183376	-0.533672
PS	-0.489962	1.081848	-0.804228
2 waters	O_{nuc}	S	O_{lg}
RS	-1.135373	1.179743	-0.392427
TS	-1.056234	1.117773	-0.4649
PS	-0.521243	1.113486	-0.801443
3 waters	O_{nuc}	S	O_{lg}
RS	-1.257745	1.129588	-0.403099
TS	-0.918205	1.129663	-0.504537
PS	-0.548219	1.053739	-0.803563
4 waters	O_{nuc}	S	O_{lg}
RS	-1.236077	1.037997	-0.390759
TS	-0.903971	1.094185	-0.427313
PS	-0.903971	1.094185	-0.427313
5 waters	O_{nuc}	S	O_{lg}
RS	-0.980929	1.211486	-0.373893
TS	-0.630151	0.977564	-0.411007
PS	-0.512696	0.939546	-0.604445
6 waters	O_{nuc}	S	O_{lg}
RS	-0.940799	1.179333	-0.384711
TS	-0.642337	1.028546	-0.400772
PS	-0.56652	1.087845	-0.766095
7 waters	O_{nuc}	S	O_{lg}
RS	-0.940799	1.235601	-0.396755
TS	-0.642337	1.333445	-0.536905
PS	-0.56652	1.00144	-0.749296

8 waters	O_{nuc}	S	O_{lg}
RS	-1.016168	1.025112	-0.394967
TS	-0.808109	1.375266	-0.539817
PS	-0.551013	0.968566	-0.730409

^a RS, TS and PS denote the reactant, transition and product states, respectively. Partial charges are calculated using the ChelpG⁵ charge calculation scheme, as described in the **Methodology** section.

Table S14. Partial charges at key stationary points for the alkaline hydrolysis of 4-nitrophenyl sulfate in the presence of 0 to 8 additional explicit water molecules, obtained using the M11L¹ functional.^a

0 waters	O_{nuc}	S	O_{lg}
RS	-1.284482	1.080957	-0.379139
TS	-1.128893	1.244377	-0.588531
PS	-0.585248	1.238508	-0.772942
1 water	O_{nuc}	S	O_{lg}
RS	-1.185066	1.082782	-0.379663
TS	-1.044112	1.218874	-0.549157
PS	-0.586398	1.153452	-0.782941
2 waters	O_{nuc}	S	O_{lg}
RS	-1.188192	1.032376	-0.357577
TS	-1.048351	1.173881	-0.508858
PS	-0.546385	1.050097	-0.769466
3 waters	O_{nuc}	S	O_{lg}
RS	-1.277522	1.181599	-0.402934
TS	-0.923554	1.12593	-0.495079
PS	-0.388704	0.873864	-0.789278
4 waters	O_{nuc}	S	O_{lg}
RS	-1.247046	0.996753	-0.367373
TS	-0.922275	1.035309	-0.383091
PS	-0.360786	0.822035	-0.70989
5 waters	O_{nuc}	S	O_{lg}
RS	-0.853296	1.037227	-0.416884
TS	-0.586031	0.902254	-0.368954
PS	-0.44271	1.014201	-0.788907
6 waters	O_{nuc}	S	O_{lg}
RS	-1.121692	1.198191	-0.432918
TS	-0.696526	1.02064	-0.397964
PS	-0.504618	0.985203	-0.657411
7 waters	O_{nuc}	S	O_{lg}
RS	-1.096003	0.833178	-0.308632
TS	-0.771277	0.989932	-0.41659
PS	-0.635188	1.193023	-0.654072

8 waters	O_{nuc}	S	O_{lg}
RS	-1.195468	0.879597	-0.324804
TS	-0.809259	1.14282	-0.477867
PS	-0.352874	0.977358	-0.666439

^a RS, TS and PS denote the reactant, transition and product states, respectively. Partial charges are calculated using the ChelpG⁵ charge calculation scheme, as described in the **Methodology** section.

Table S15. Partial charges at key stationary points for the alkaline hydrolysis of 4-nitrophenyl sulfate in the presence of 0 to 8 additional explicit water molecules, obtained using the M062X⁴ functional.^a

0 waters	O_{nuc}	S	O_{lg}
RS	-1.275519	1.121414	-0.387754
TS	-1.139127	1.250009	-0.560361
PS	-0.558318	1.13009	-0.804851
1 water	O_{nuc}	S	O_{lg}
RS	-1.148959	1.152355	-0.413929
TS	-1.03667	1.223303	-0.532325
PS	-0.670233	1.137449	-0.803401
2 waters	O_{nuc}	S	O_{lg}
RS	-1.174682	1.064808	-0.358528
TS	-1.048017	1.195557	-0.504796
PS	-0.454976	1.055828	-0.814666
3 waters	O_{nuc}	S	O_{lg}
RS	-1.233141	1.143523	-0.421993
TS	-0.985903	1.174767	-0.507501
PS	-0.482625	1.051778	-0.824693
4 waters	O_{nuc}	S	O_{lg}
RS	-1.238816	1.009553	-0.39931
TS	-0.959323	1.082878	-0.417571
PS	-0.455648	1.027233	-0.76437
5 waters	O_{nuc}	S	O_{lg}
RS	-1.058445	0.812448	-0.20884
TS	-0.739218	0.961012	-0.429012
PS	-0.409062	0.919341	-0.726438
6 waters	O_{nuc}	S	O_{lg}
RS	-1.053489	0.999697	-0.303922
TS	-0.800466	1.074493	-0.466512
PS	-0.571694	1.024421	-0.758974
7 waters	O_{nuc}	S	O_{lg}
RS	-0.815996	1.331497	-0.466748
TS	-0.846032	1.137617	-0.497321
PS	-0.568987	1.062263	-0.79949

8 waters	O_{nuc}	S	O_{lg}
RS	-0.964724	1.12928	-0.397992
TS	-0.854524	1.254148	-0.535374
PS	-0.621103	1.146464	-0.805452

^a RS, TS and PS denote the reactant, transition and product states, respectively. Partial charges are calculated using the ChelpG⁵ charge calculation scheme, as described in the **Methodology** section.

Table S16. Geometries at the transition state for the alkaline hydrolysis of 4-nitrophenyl sulfate in the presence of 0 to 8 additional explicit water molecules, obtained using the ω B97X-D³ functional.^a

Water Molecules	S-O_{nuc} Distance	S-O_{lg} Distance	S-O_{nuc} BO	S-O_{lg} BO
0	2.35	1.71	0.2639	0.5569
1	2.30	1.71	0.2515	0.5641
2	2.32	1.72	0.2456	0.5485
3	2.27	1.73	0.2333	0.5505
4	2.30	1.73	0.2242	0.5336
5	2.23	1.74	0.2359	0.5244
6	2.24	1.74	0.2399	0.5334
7	2.24	1.73	0.2458	0.5488
8	2.26	1.73	0.2506	0.5523

^a Bond distances are shown in Å. Bond orders (BO) were calculated based on the Wiberg bond index⁷ using natural bond orbital (NBO) analysis.⁸

Table S17. Geometries at the transition state for the alkaline hydrolysis of 4-nitrophenyl sulfate in the presence of 0 to 8 additional explicit water molecules, obtained using the M11L¹ functional.^a

Water Molecules	S-O _{nuc} Distance	S-O _{lg} Distance	S-O _{nuc} BO	S-O _{lg} BO
0	2.31	1.70	0.2543	0.532
1	2.27	1.70	0.2498	0.5303
2	2.30	1.70	0.2412	0.5261
3	2.24	1.71	0.2279	0.5258
4	2.26	1.71	0.2234	0.5166
5	2.21	1.73	0.2332	0.5043
6	2.20	1.73	0.2373	0.5072
7	2.21	1.72	0.2368	0.5154
8	2.22	1.72	0.2432	0.5151

^a Bond distances are shown in Å. Bond orders (BO) were calculated based on the Wiberg bond index⁷ using natural bond orbital (NBO) analysis.⁸

Table S18. Geometries at the transition state for the alkaline hydrolysis of 4-nitrophenyl sulfate in the presence of 0 to 8 additional explicit water molecules, obtained using the M062X⁴ functional.^a

Water Molecules	S-O _{nuc} Distance	S-O _{lg} Distance	S-O _{nuc} BO	S-O _{lg} BO
0	2.39	1.69	0.2306	0.5775
1	2.31	1.69	0.225	0.582
2	2.35	1.70	0.2173	0.5692
3	2.29	1.70	0.2082	0.5734
4	2.31	1.71	0.2027	0.5577
5	2.26	1.71	0.2122	0.5495
6	2.25	1.70	0.2242	0.5785
7	2.24	1.70	0.2285	0.5885
8	2.26	1.7	0.2308	0.5915

^a Bond distances are shown in Å. Bond orders (BO) were calculated based on the Wiberg bond index⁷ using natural bond orbital (NBO) analysis.⁸

Table S19. Geometries at key stationary points for the alkaline hydrolysis of 4-nitrophenyl sulfate in the presence of 0 to 8 additional explicit water molecules, obtained using the ω B97X-D³ functional.^a

0 waters	S-O_{nuc} Distance	S-O_{lg} Distance	S-O_{nuc} BO	S-O_{lg} BO
RS	3.87	1.61	0.0059	0.6746
TS	2.35	1.71	0.2639	0.5569
PS	1.59	3.99	0.7569	0.0007
1 water	S-O_{nuc} Distance	S-O_{lg} Distance	S-O_{nuc} BO	S-O_{lg} BO
RS	4.58	1.61	0.0017	0.6882
TS	2.30	1.71	0.2515	0.5641
PS	1.59	3.98	0.742	0.0007
2 waters	S-O_{nuc} Distance	S-O_{lg} Distance	S-O_{nuc} BO	S-O_{lg} BO
RS	4.62	1.61	0.0013	0.7122
TS	2.32	1.72	0.2456	0.5485
PS	1.59	4.72	0.7438	0.0002
3 waters	S-O_{nuc} Distance	S-O_{lg} Distance	S-O_{nuc} BO	S-O_{lg} BO
RS	4.49	1.61	0.0003	0.7117
TS	2.27	1.73	0.2333	0.5505
PS	1.56	4.72	0.8144	0.0001
4 waters	S-O_{nuc} Distance	S-O_{lg} Distance	S-O_{nuc} BO	S-O_{lg} BO
RS	4.39	1.61	0.0003	0.6907
TS	2.30	1.73	0.2242	0.5336
PS	1.45	1.59	0.7446	0.0008
5 waters	S-O_{nuc} Distance	S-O_{lg} Distance	S-O_{nuc} BO	S-O_{lg} BO
RS	4.35	1.61	0.0002	0.7031
TS	2.23	1.74	0.2359	0.5244
PS	1.48	4.57	1.1637	0.0001
6 waters	S-O_{nuc} Distance	S-O_{lg} Distance	S-O_{nuc} BO	S-O_{lg} BO
RS	4.30	1.61	0.0002	0.7175
TS	2.24	1.74	0.2399	0.5334
PS	1.49	4.76	1.0107	0.0002
7 waters	S-O_{nuc} Distance	S-O_{lg} Distance	S-O_{nuc} BO	S-O_{lg} BO
RS	3.95	1.61	0.001	0.6984
TS	2.24	1.73	0.2458	0.5488
PS	1.59	3.92	0.7508	0.0017

8 waters	S-O_{nuc} Distance	S-O_{lg} Distance	S-O_{nuc} BO	S-O_{lg} BO
RS	5.08	1.60	0.0004	0.719
TS	2.26	1.73	0.2506	0.5523
PS	1.48	4.40	1.0432	0.0006

^a RS, TS and PS denote the reactant, transition and product states, respectively. Bond distances are shown in Å. Bond orders (BO) were calculated based on the Wiberg bond index⁷ using natural bond orbital (NBO) analysis.⁸

Table S20. Geometries at key stationary points for the alkaline hydrolysis of 4-nitrophenyl sulfate in the presence of 0 to 8 additional explicit water molecules, obtained using the M11L¹ functional.^a

0 waters	S-O_{nuc} Distance	S-O_{lg} Distance	S-O_{nuc} BO	S-O_{lg} BO
RS	3.79	1.59	0.0027	0.6817
TS	2.31	1.70	0.2543	0.532
PS	1.56	4.09	0.7523	0.0012
1 water	S-O_{nuc} Distance	S-O_{lg} Distance	S-O_{nuc} BO	S-O_{lg} BO
RS	3.78	1.59	0.0008	0.6748
TS	2.27	1.70	0.2498	0.5303
PS	1.56	3.84	0.7336	0.0012
2 waters	S-O_{nuc} Distance	S-O_{lg} Distance	S-O_{nuc} BO	S-O_{lg} BO
RS	3.75	1.59	0.0047	0.6768
TS	2.30	1.70	0.2412	0.5261
PS	1.56	3.82	0.737	0.0016
3 waters	S-O_{nuc} Distance	S-O_{lg} Distance	S-O_{nuc} BO	S-O_{lg} BO
RS	4.16	1.59	0.0005	0.6929
TS	2.24	1.71	0.2279	0.5258
PS	1.56	3.83	0.738	0.0013
4 waters	S-O_{nuc} Distance	S-O_{lg} Distance	S-O_{nuc} BO	S-O_{lg} BO
RS	4.03	1.59	0.0005	0.676
TS	2.26	1.71	0.2234	0.5166
PS	1.56	3.96	0.7451	0.0012
5 waters	S-O_{nuc} Distance	S-O_{lg} Distance	S-O_{nuc} BO	S-O_{lg} BO
RS	4.31	1.58	0.0009	0.6844
TS	2.21	1.73	0.2332	0.5043
PS	1.55	3.94	0.7662	0.0011
6 waters	S-O_{nuc} Distance	S-O_{lg} Distance	S-O_{nuc} BO	S-O_{lg} BO
RS	4.29	1.58	0.0006	0.6909
TS	2.20	1.73	0.2373	0.5072
PS	1.45	4.54	1.069	0.0002
7 waters	S-O_{nuc} Distance	S-O_{lg} Distance	S-O_{nuc} BO	S-O_{lg} BO
RS	4.53	1.58	0.0006	0.6857
TS	2.21	1.72	0.2368	0.5154
PS	1.46	4.29	1.0261	0.0011

8 waters	S-O_{nuc} Distance	S-O_{lg} Distance	S-O_{nuc} BO	S-O_{lg} BO
RS	5.81	1.58	0.0001	0.6991
TS	2.22	1.72	0.2432	0.5151
PS	1.46	4.6	0.9886	0.0004

^a RS, TS and PS denote the reactant, transition and product states, respectively. Bond distances are shown in Å. Bond orders (BO) were calculated based on the Wiberg bond index⁷ using natural bond orbital (NBO) analysis.⁸

Table S21. Geometries at key stationary points for the alkaline hydrolysis of 4-nitrophenyl sulfate in the presence of 0 to 8 additional explicit water molecules, obtained using the M062X⁴ functional.^a

0 waters	S-O_{nuc} Distance	S-O_{lg} Distance	S-O_{nuc} BO	S-O_{lg} BO
RS	3.53	1.61	0.0112	0.6722
TS	2.39	1.69	0.2306	0.5775
PS	1.59	3.63	0.7535	0.0014
1 water	S-O_{nuc} Distance	S-O_{lg} Distance	S-O_{nuc} BO	S-O_{lg} BO
RS	3.47	1.61	0.0103	0.6764
TS	2.31	1.69	0.225	0.582
PS	1.59	3.73	0.7316	0.0013
2 waters	S-O_{nuc} Distance	S-O_{lg} Distance	S-O_{nuc} BO	S-O_{lg} BO
RS	3.52	1.61	0.0085	0.6682
TS	2.35	1.70	0.2173	0.5692
PS	1.59	3.60	0.7435	0.0018
3 waters	S-O_{nuc} Distance	S-O_{lg} Distance	S-O_{nuc} BO	S-O_{lg} BO
RS	4.34	1.61	0.0009	0.682
TS	2.29	1.70	0.2082	0.5734
PS	1.59	3.60	0.7371	0.0018
4 waters	S-O_{nuc} Distance	S-O_{lg} Distance	S-O_{nuc} BO	S-O_{lg} BO
RS	4.09	1.61	0.0005	0.696
TS	2.31	1.71	0.2027	0.5577
PS	1.59	3.77	0.7513	0.0013
5 waters	S-O_{nuc} Distance	S-O_{lg} Distance	S-O_{nuc} BO	S-O_{lg} BO
RS	3.50	1.61	0.0014	0.6616
TS	2.26	1.71	0.2122	0.5495
PS	1.50	4.57	0.9411	0.0002
6 waters	S-O_{nuc} Distance	S-O_{lg} Distance	S-O_{nuc} BO	S-O_{lg} BO
RS	3.40	1.61	0.0019	0.6893
TS	2.25	1.70	0.2242	0.5785
PS	1.58	3.71	0.7623	0.0013
7 waters	S-O_{nuc} Distance	S-O_{lg} Distance	S-O_{nuc} BO	S-O_{lg} BO
RS	3.40	1.61	0.0016	0.681
TS	2.24	1.70	0.2285	0.5885
PS	1.48	3.97	1.1253	0.0012

8 waters	S-O _{nuc} Distance	S-O _{lg} Distance	S-O _{nuc} BO	S-O _{lg} BO
RS	3.16	1.62	0.004	0.6855
TS	2.26	1.7	0.2308	0.5915
PS	1.48	3.99	1.1272	0.0013

^a RS, TS and PS denote the reactant, transition and product states, respectively. Bond distances are shown in Å. Bond orders (BO) were calculated based on the Wiberg bond index⁷ using natural bond orbital (NBO) analysis.⁸

Table S22. Experimental and calculated rate constants for the alkaline hydrolysis of substituted sulfate diesters in the presence of 0 explicit water molecules (pure implicit solvation), obtained using the ω B97X-D³ functional.^a

Substituent	k_{calc}	$\log k_{\text{calc}}$	$\log k_{\text{exp}}$
4-chloro-3-nitro	1.859×10^2	2.2693	-3.7799
4-nitro	1.090×10^3	3.0374	-3.9706
2,6-difluoro	5.439×10^3	3.7355	-3.8539
2-fluoro-4-nitro	3.943×10^3	3.3958	-2.9872
2,3,4,5,6-pentafluoro	3.027×10^5	5.4810	-2.3872
3-fluoro-4-nitro	1.427×10^4	4.1544	-2.5114

^a The calculated rate constant, k_{calc} , was derived from the calculated activation free energy, ΔG^\ddagger , at 313.15 K, using transition state theory. The corresponding experimental value was obtained from ref. ² after correcting the experimental second order rate constant by 0.017 M^{-1} to take into account the entropic cost of bringing the reacting fragments into the encounter complex, following ref. ⁶.

Table S23. Experimental and calculated rate constants for the alkaline hydrolysis of substituted sulfate diesters in the presence of 2 explicit water molecules, obtained using the ω B97X-D³ functional.^a

Substituent	k_{calc}	$\log k_{\text{calc}}$	$\log k_{\text{exp}}$
4-chloro-3-nitro	2.859×10^3	3.4562	-3.7799
4-nitro	3.339×10^0	0.5236	-3.9706
2,6-difluoro	3.536×10^2	2.5485	-3.8539
2-fluoro-4-nitro	1.676×10^4	4.2243	-2.9872
2,3,4,5,6-pentafluoro	3.376×10^6	6.5284	-2.3872
3-fluoro-4-nitro	8.810×10^3	3.9450	-2.5114

^a The calculated rate constant, k_{calc} , was derived from the calculated activation free energy, ΔG^\ddagger , at 313.15 K, using transition state theory. The corresponding experimental value was obtained from ref. ² after correcting the experimental second order rate constant by 0.017 M^{-1} to take into account the entropic cost of bringing the reacting fragments into the encounter complex, following ref. ⁶.

Table S24. Experimental and calculated rate constants for the alkaline hydrolysis of substituted sulfate diesters in the presence of 4 explicit water molecules, obtained using the ω B97X-D³ functional.^a

Substituent	k_{calc}	$\log k_{\text{calc}}$	$\log k_{\text{exp}}$
4-chloro-3-nitro	1.090×10^3	3.0374	-3.7799
4-nitro	5.728×10^2	2.7580	-3.9706
2,6-difluoro	1.968×10^4	4.2940	-3.8539
2-fluoro-4-nitro	4.397×10^4	4.6432	-2.9872
2,3,4,5,6-pentafluoro	5.192×10^7	7.7153	-2.3872
3-fluoro-4-nitro	1.858×10^2	2.2690	-2.5114

^a The calculated rate constant, k_{calc} , was derived from the calculated activation free energy, ΔG^\ddagger , at 313.15 K, using transition state theory. The corresponding experimental value was obtained from ref. ² after correcting the experimental second order rate constant by 0.017 M^{-1} to take into account the entropic cost of bringing the reacting fragments into the encounter complex, following ref. ⁶.

Table S25. Experimental and calculated rate constants for the alkaline hydrolysis of substituted sulfate diesters in the presence of 8 explicit water molecules, obtained using the ω B97X-D³ functional.^a

Substituent	k_{calc}	$\log k_{\text{calc}}$	$\log k_{\text{exp}}$
4-chloro-3-nitro	6.690×10^{-1}	-0.1746	-3.7799
4-nitro	3.922×10^0	0.5935	-3.9706
2,6-difluoro	9.718×10^{-2}	-1.0124	-3.8539
2-fluoro-4-nitro	1.029×10^1	1.0124	-2.9872
2,3,4,5,6-pentafluoro	5.439×10^3	3.7355	-2.3872
3-fluoro-4-nitro	1.273×10^0	0.1048	-2.5114

^a The calculated rate constant, k_{calc} , was derived from the calculated activation free energy, ΔG^\ddagger , at 313.15 K, using transition state theory. The corresponding experimental value was obtained from ref. ² after correcting the experimental second order rate constant by 0.017 M^{-1} to take into account the entropic cost of bringing the reacting fragments into the encounter complex, following ref. ⁶.

Table S26. Experimental and calculated rate constants for the alkaline hydrolysis of substituted sulfate diesters in the presence of 0 explicit water molecules (pure implicit solvation), obtained using the M11L¹ functional.^a

Substituent	k_{calc}	$\log k_{\text{calc}}$	$\log k_{\text{exp}}$
4-chloro-3-nitro	5.164×10^4	4.7130	-3.7799
4-nitro	2.311×10^4	4.3638	-3.9706
2,6-difluoro	4.175×10^5	5.6207	-3.8539
2-fluoro-4-nitro	1.511×10^6	6.1793	-2.9872
2,3,4,5,6-pentafluoro	1.879×10^8	8.2739	-2.3872
3-fluoro-4-nitro	3.555×10^5	5.5508	-2.5114

^a The calculated rate constant, k_{calc} , was derived from the calculated activation free energy, ΔG^\ddagger , at 313.15 K, using transition state theory. The corresponding experimental value was obtained from ref. ² after correcting the experimental second order rate constant by 0.017 M^{-1} to take into account the entropic cost of bringing the reacting fragments into the encounter complex, following ref. ⁶.

Table S27. Experimental and calculated rate constants for the alkaline hydrolysis of substituted sulfate diesters in the presence of 2 explicit water molecules, obtained using the M11L¹ functional.^a

Substituent	k_{calc}	$\log k_{\text{calc}}$	$\log k_{\text{exp}}$
4-chloro-3-nitro	1.215×10^4	4.0846	-3.7799
4-nitro	3.356×10^3	3.5258	-3.9706
2,6-difluoro	5.759×10^5	5.7603	-3.8539
2-fluoro-4-nitro	1.869×10^5	5.2716	-2.9872
2,3,4,5,6-pentafluoro	1.435×10^7	7.1569	-2.3872
3-fluoro-4-nitro	4.175×10^5	5.6207	-2.5114

^a The calculated rate constant, k_{calc} , was derived from the calculated activation free energy, ΔG^\ddagger , at 313.15 K, using transition state theory. The corresponding experimental value was obtained from ref. ² after correcting the experimental second order rate constant by 0.017 M^{-1} to take into account the entropic cost of bringing the reacting fragments into the encounter complex, following ref. ⁶.

Table S28. Experimental and calculated rate constants for the alkaline hydrolysis of substituted sulfate diesters in the presence of 4 explicit water molecules, obtained using the M11L¹ functional.^a

Substituent	k_{calc}	$\log k_{\text{calc}}$	$\log k_{\text{exp}}$
4-chloro-3-nitro	9.824×10^4	4.9923	-3.7799
4-nitro	2.578×10^5	5.4113	-3.9706
2,6-difluoro	8.365×10^4	4.9225	-3.8539
2-fluoro-4-nitro	5.468×10^6	6.7378	-2.9872
2,3,4,5,6-pentafluoro	1.096×10^6	6.0399	-2.3872
3-fluoro-4-nitro	3.188×10^4	4.5035	-2.5114

^a The calculated rate constant, k_{calc} , was derived from the calculated activation free energy, ΔG^\ddagger , at 313.15 K, using transition state theory. The corresponding experimental value was obtained from ref. ² after correcting the experimental second order rate constant by 0.017 M^{-1} to take into account the entropic cost of bringing the reacting fragments into the encounter complex, following ref. ⁶.

Table S29. Experimental and calculated rate constants for the alkaline hydrolysis of substituted sulfate diesters in the presence of 8 explicit water molecules, obtained using the M11L¹ functional.^a

Substituent	k_{calc}	$\log k_{\text{calc}}$	$\log k_{\text{exp}}$
4-chloro-3-nitro	2.550×10^{-1}	-0.5935	-3.7799
4-nitro	2.183×10^2	2.3391	-3.9706
2,6-difluoro	5.409×10^0	0.7331	-3.8539
2-fluoro-4-nitro	2.195×10^5	5.3414	-2.9872
2,3,4,5,6-pentafluoro	1.503×10^3	3.1770	-2.3872
3-fluoro-4-nitro	3.943×10^3	3.5958	-2.5114

^a The calculated rate constant, k_{calc} , was derived from the calculated activation free energy, ΔG^\ddagger , at 313.15 K, using transition state theory. The corresponding experimental value was obtained from ref. ² after correcting the experimental second order rate constant by 0.017 M^{-1} to take into account the entropic cost of bringing the reacting fragments into the encounter complex, following ref. ⁶.

Table S30. Experimental and calculated rate constants for the alkaline hydrolysis of substituted sulfate diesters in the presence of 0 explicit water molecules (pure implicit solvent), obtained using the M062X⁴ functional.^a

Substituent	k_{calc}	$\log k_{\text{calc}}$	$\log k_{\text{exp}}$
4-chloro-3-nitro	4.904×10^5	5.6906	-3.7799
4-nitro	4.175×10^5	5.6207	-3.9706
2,6-difluoro	6.422×10^6	6.8078	-3.8539
2-fluoro-4-nitro	1.685×10^7	7.2266	-2.9872
2,3,4,5,6-pentafluoro	3.044×10^8	8.4834	-2.3872
3-fluoro-4-nitro	9.328×10^5	5.9698	-2.5114

^a The calculated rate constant, k_{calc} , was derived from the calculated activation free energy, ΔG^\ddagger , at 313.15 K, using transition state theory. The corresponding experimental value was obtained from ref. ² after correcting the experimental second order rate constant by 0.017 M^{-1} to take into account the entropic cost of bringing the reacting fragments into the encounter complex, following ref. ⁶.

Table S31. Experimental and calculated rate constants for the alkaline hydrolysis of substituted sulfate diesters in the presence of 2 explicit water molecules, obtained using the M062X⁴ functional.^a

Substituent	k_{calc}	$\log k_{\text{calc}}$	$\log k_{\text{exp}}$
4-chloro-3-nitro	1.154×10^5	5.0622	-3.7799
4-nitro	1.869×10^5	5.2716	-3.9706
2,6-difluoro	1.435×10^7	7.1569	-3.8539
2-fluoro-4-nitro	4.421×10^7	7.6455	-2.9872
2,3,4,5,6-pentafluoro	3.986×10^9	9.6005	-2.3872
3-fluoro-4-nitro	5.579×10^5	5.7466	-2.5114

^a The calculated rate constant, k_{calc} , was derived from the calculated activation free energy, ΔG^\ddagger , at 313.15 K, using transition state theory. The corresponding experimental value was obtained from ref. ² after correcting the experimental second order rate constant by 0.017 M^{-1} to take into account the entropic cost of bringing the reacting fragments into the encounter complex, following ref. ⁶.

Table S32. Experimental and calculated rate constants for the alkaline hydrolysis of substituted sulfate diesters in the presence of 4 explicit water molecules, obtained using the M062X⁴ functional.^a

Substituent	k_{calc}	$\log k_{\text{calc}}$	$\log k_{\text{exp}}$
4-chloro-3-nitro	2.592×10^8	8.4136	-3.7799
4-nitro	2.578×10^5	5.4112	-3.9706
2,6-difluoro	2.207×10^8	8.3438	-3.8539
2-fluoro-4-nitro	6.098×10^7	7.7852	-2.9872
2,3,4,5,6-pentafluoro	2.890×10^9	9.4609	-2.3872
3-fluoro-4-nitro	7.162×10^7	7.8550	-2.5114

^a The calculated rate constant, k_{calc} , was derived from the calculated activation free energy, ΔG^\ddagger , at 313.15 K, using transition state theory. The corresponding experimental value was obtained from ref. ² after correcting the experimental second order rate constant by 0.017 M^{-1} to take into account the entropic cost of bringing the reacting fragments into the encounter complex, following ref. ⁶.

Table S33. Experimental and calculated rate constants for the alkaline hydrolysis of substituted sulfate diesters in the presence of 8 explicit water molecules, obtained using the M062X⁴ functional.^a

Substituent	k_{calc}	$\log k_{\text{calc}}$	$\log k_{\text{exp}}$
4-chloro-3-nitro	1.215×10^4	4.0846	-3.7799
4-nitro	2.448×10^6	6.3889	-3.9706
2,6-difluoro	5.759×10^5	5.7603	-3.8539
2-fluoro-4-nitro	8.858×10^6	6.9473	-2.9872
2,3,4,5,6-pentafluoro	9.824×10^4	4.9923	-2.3872
3-fluoro-4-nitro	1.511×10^6	6.1793	-2.5114

^a The calculated rate constant, k_{calc} , was derived from the calculated activation free energy, ΔG^\ddagger , at 313.15 K, using transition state theory. The corresponding experimental value was obtained from ref. ² after correcting the experimental second order rate constant by 0.017 M^{-1} to take into account the entropic cost of bringing the reacting fragments into the encounter complex, following ref. ⁶.

Table S34. Energy decomposition of the calculated activation free energies ($\Delta G^\ddagger_{\text{calc}}$) for the alkaline hydrolysis of substituted sulfate diesters in the presence of 0 explicit water molecules (pure implicit solvation), obtained using the ω B97X-D³ functional.^a

Substituent	ΔE^\ddagger	$\Delta \text{ZPE}^\ddagger$	$-\text{T}\Delta S^\ddagger$	$\Delta G^\ddagger_{\text{calc}}$	$\Delta G^\ddagger_{\text{exp}}$	ν
4-chloro-3-nitro	10.5	0.5	4.1	15.1	21.2	-285.8424
4-nitro	10.6	0.2	3.2	14	21.5	-269.6541
2,6-difluoro	8.2	0.6	4.2	13	21.3	-255.3195
2-fluoro-4-nitro	9.2	0.3	3.7	13.2	20.1	-269.6949
2,3,4,5,6-pentafluoro	6	0.4	4.3	10.5	19.2	-191.8671
3-fluoro-4-nitro	10	-0.04	2.4	12.4	19.4	-269.1173

^a All energies are shown in kcal mol^{-1} , and vibrational frequencies are shown in cm^{-1} . ΔE^\ddagger , $\Delta \text{ZPE}^\ddagger$ and $-\text{T}\Delta S^\ddagger$ denote the contributions to $\Delta G^\ddagger_{\text{calc}}$ from the electronic energy, zero-point energy and activation free energy, respectively. ν denotes the first vibrational frequency. $\Delta G^\ddagger_{\text{exp}}$ denotes the experimental activation free energy at 313.15 K, obtained from the kinetic data presented in ref. ² using transition state theory.

Table S35. Energy decomposition of the calculated activation free energies ($\Delta G^\ddagger_{\text{calc}}$) for the alkaline hydrolysis of substituted sulfate diesters in the presence of 2 explicit water molecules, obtained using the ω B97X-D³ functional.^a

Substituent	ΔE^\ddagger	ΔZPE^\ddagger	$-T\Delta S^\ddagger$	$\Delta G^\ddagger_{\text{calc}}$	$\Delta G^\ddagger_{\text{exp}}$	ν
4-chloro-3-nitro	10.4	0.2	2.8	13.4	21.2	-275.4637
4-nitro	17.4	-0.4	0.6	17.6	21.5	-289.4289
2,6-difluoro	7.8	1.4	5.5	14.7	21.3	-241.8208
2-fluoro-4-nitro	9.2	0.4	2.7	12.3	20.1	-280.3696
2,3,4,5,6-pentafluoro	5	0.7	3.3	9	19.2	-208.8696
3-fluoro-4-nitro	9.9	0.2	2.6	12.7	19.4	-283.2926

^a All energies are shown in kcal mol⁻¹, and vibrational frequencies are shown in cm⁻¹. ΔE^\ddagger , ΔZPE^\ddagger and $-T\Delta S^\ddagger$ denote the contributions to $\Delta G^\ddagger_{\text{calc}}$ from the electronic energy, zero-point energy and activation free energy, respectively. ν denotes the first vibrational frequency. $\Delta G^\ddagger_{\text{exp}}$ denotes the experimental activation free energy at 313.15 K, obtained from the kinetic data presented in ref. ² using transition state theory.

Table S36. Energy decomposition of the calculated activation free energies ($\Delta G^\ddagger_{\text{calc}}$) for the alkaline hydrolysis of substituted sulfate diesters in the presence of 4 explicit water molecules, obtained using the ω B97X-D³ functional.^a

Substituent	ΔE^\ddagger	ΔZPE^\ddagger	$-T\Delta S^\ddagger$	$\Delta G^\ddagger_{\text{calc}}$	$\Delta G^\ddagger_{\text{exp}}$	ν
4-chloro-3-nitro	11.8	0.03	2.2	14	21.2	-256.1365
4-nitro	13.8	-0.3	0.9	14.4	21.5	-266.4356
2,6-difluoro	6.1	1.2	4.9	12.2	21.3	-228.9236
2-fluoro-4-nitro	5.7	1	5	11.7	20.1	-225.2576
2,3,4,5,6-pentafluoro	4.3	0.4	2.6	7.3	19.2	-196.2121
3-fluoro-4-nitro	9.9	1.1	4.1	15.1	19.4	-271.425

^a All energies are shown in kcal mol⁻¹, and vibrational frequencies are shown in cm⁻¹. ΔE^\ddagger , ΔZPE^\ddagger and $-T\Delta S^\ddagger$ denote the contributions to $\Delta G^\ddagger_{\text{calc}}$ from the electronic energy, zero-point energy and activation free energy, respectively. ν denotes the first vibrational frequency. $\Delta G^\ddagger_{\text{exp}}$ denotes the experimental activation free energy at 313.15 K, obtained from the kinetic data presented in ref. ² using transition state theory.

Table S37. Energy decomposition of the calculated activation free energies ($\Delta G^\ddagger_{\text{calc}}$) for the alkaline hydrolysis of substituted sulfate diesters in the presence of 8 explicit water molecules, obtained using the ω B97X-D³ functional.^a

Substituent	ΔE^\ddagger	ΔZPE^\ddagger	$-T\Delta S^\ddagger$	$\Delta G^\ddagger_{\text{calc}}$	$\Delta G^\ddagger_{\text{exp}}$	ν
4-chloro-3-nitro	24.7	-1.9	-4.2	18.6	21.2	-274.1009
4-nitro	17.3	-0.3	0.5	17.5	21.5	-281.4245
2,6-difluoro	18.2	0.6	1	19.8	21.3	-244.4031
2-fluoro-4-nitro	16.9	-1.1	0.1	16.9	20.1	-253.072
2,3,4,5,6-pentafluoro	11.4	0.5	1.1	13	19.2	-242.0959
3-fluoro-4-nitro	24.7	-1.9	-4.2	18.2	19.4	-274.1009

^a All energies are shown in kcal mol⁻¹, and vibrational frequencies are shown in cm⁻¹. ΔE^\ddagger , ΔZPE^\ddagger and $-T\Delta S^\ddagger$ denote the contributions to $\Delta G^\ddagger_{\text{calc}}$ from the electronic energy, zero-point energy and activation free energy, respectively. ν denotes the first vibrational frequency. $\Delta G^\ddagger_{\text{exp}}$ denotes the experimental activation free energy at 313.15 K, obtained from the kinetic data presented in ref. ² using transition state theory.

Table S38. Energy decomposition of the calculated activation free energies ($\Delta G^\ddagger_{\text{calc}}$) for the alkaline hydrolysis of substituted sulfate diesters in the presence of 0 explicit water molecules (pure implicit solvation), obtained using the M11L¹ functional.^a

Substituent	ΔE^\ddagger	ΔZPE^\ddagger	$-T\Delta S^\ddagger$	$\Delta G^\ddagger_{\text{calc}}$	$\Delta G^\ddagger_{\text{exp}}$	ν
4-chloro-3-nitro	9.1	-0.1	2.6	11.6	21.2	-342.7198
4-nitro	9.1	-0.1	3.1	12.1	21.5	-331.4516
2,6-difluoro	6.6	0.2	3.5	10.3	21.3	-268.0216
2-fluoro-4-nitro	7.8	-0.3	2	9.5	20.1	-324.8034
2,3,4,5,6-pentafluoro	3.6	0.1	2.8	6.5	19.2	-189.2089
3-fluoro-4-nitro	8.4	-0.3	2.3	10.4	19.4	-319.3068

^a All energies are shown in kcal mol⁻¹, and vibrational frequencies are shown in cm⁻¹. ΔE^\ddagger , ΔZPE^\ddagger and $-T\Delta S^\ddagger$ denote the contributions to $\Delta G^\ddagger_{\text{calc}}$ from the electronic energy, zero-point energy and activation free energy, respectively. ν denotes the first vibrational frequency. $\Delta G^\ddagger_{\text{exp}}$ denotes the experimental activation free energy at 313.15 K, obtained from the kinetic data presented in ref. ² using transition state theory.

Table S39. Energy decomposition of the calculated activation free energies ($\Delta G^\ddagger_{\text{calc}}$) for the alkaline hydrolysis of substituted sulfate diesters in the presence of 2 explicit water molecules, obtained using the M11L¹ functional.^a

Substituent	ΔE^\ddagger	ΔZPE^\ddagger	$-T\Delta S^\ddagger$	$\Delta G^\ddagger_{\text{calc}}$	$\Delta G^\ddagger_{\text{exp}}$	ν
4-chloro-3-nitro	8.5	0.5	3.5	12.5	21.2	-323.5784
4-nitro	8.2	0.01	5.1	13.3	21.5	-332.1461
2,6-difluoro	6.6	0.4	3.1	10.1	21.3	-274.2715
2-fluoro-4-nitro	7.2	0.2	3.4	10.8	20.1	-310.5195
2,3,4,5,6-pentafluoro	3.9	0.3	3.9	8.1	19.2	-226.258
3-fluoro-4-nitro	7.9	0.3	2.1	10.3	19.4	-319.1242

^a All energies are shown in kcal mol⁻¹, and vibrational frequencies are shown in cm⁻¹. ΔE^\ddagger , ΔZPE^\ddagger and $-T\Delta S^\ddagger$ denote the contributions to $\Delta G^\ddagger_{\text{calc}}$ from the electronic energy, zero-point energy and activation free energy, respectively. ν denotes the first vibrational frequency. $\Delta G^\ddagger_{\text{exp}}$ denotes the experimental activation free energy at 313.15 K, obtained from the kinetic data presented in ref. ² using transition state theory.

Table S40. Energy decomposition of the calculated activation free energies ($\Delta G^\ddagger_{\text{calc}}$) for the alkaline hydrolysis of substituted sulfate diesters in the presence of 4 explicit water molecules, obtained using the M11L¹ functional.^a

Substituent	ΔE^\ddagger	ΔZPE^\ddagger	$-T\Delta S^\ddagger$	$\Delta G^\ddagger_{\text{calc}}$	$\Delta G^\ddagger_{\text{exp}}$	ν
4-chloro-3-nitro	12.2	-0.9	-0.1	11.2	21.2	-318.2203
4-nitro	9	-0.2	1.8	10.6	21.5	-332.1585
2,6-difluoro	9.4	0.3	1.6	11.3	21.3	-286.8493
2-fluoro-4-nitro	4.8	0.6	3.3	8.7	20.1	-270.3738
2,3,4,5,6-pentafluoro	7.7	-0.05	2.1	9.7	19.2	-241.5549
3-fluoro-4-nitro	7.3	0.8	3.8	11.9	19.4	-321.7632

^a All energies are shown in kcal mol⁻¹, and vibrational frequencies are shown in cm⁻¹. ΔE^\ddagger , ΔZPE^\ddagger and $-T\Delta S^\ddagger$ denote the contributions to $\Delta G^\ddagger_{\text{calc}}$ from the electronic energy, zero-point energy and activation free energy, respectively. ν denotes the first vibrational frequency. $\Delta G^\ddagger_{\text{exp}}$ denotes the experimental activation free energy at 313.15 K, obtained from the kinetic data presented in ref. ² using transition state theory.

Table S41. Energy decomposition of the calculated activation free energies ($\Delta G^\ddagger_{\text{calc}}$) for the alkaline hydrolysis of substituted sulfate diesters in the presence of 8 explicit water molecules, obtained using the M11L¹ functional.^a

Substituent	ΔE^\ddagger	ΔZPE^\ddagger	$-T\Delta S^\ddagger$	$\Delta G^\ddagger_{\text{calc}}$	$\Delta G^\ddagger_{\text{exp}}$	ν
4-chloro-3-nitro	18.8	-0.2	0.6	19.2	21.2	-342.5189
4-nitro	19	-1.2	-2.8	15	21.5	-349.729
2,6-difluoro	18.2	0.2	-1.1	17.3	21.3	-325.0493
2-fluoro-4-nitro	7.7	0.8	2.2	10.7	20.1	-322.0363
2,3,4,5,6-pentafluoro	19.4	-2.3	-3.3	13.8	19.2	-317.5782
3-fluoro-4-nitro	14.8	-1.1	-0.5	13.2	19.4	-348.1176

^a All energies are shown in kcal mol⁻¹, and vibrational frequencies are shown in cm⁻¹. ΔE^\ddagger , ΔZPE^\ddagger and $-T\Delta S^\ddagger$ denote the contributions to $\Delta G^\ddagger_{\text{calc}}$ from the electronic energy, zero-point energy and activation free energy, respectively. ν denotes the first vibrational frequency. $\Delta G^\ddagger_{\text{exp}}$ denotes the experimental activation free energy at 313.15 K, obtained from the kinetic data presented in ref. ² using transition state theory.

Table S42. Energy decomposition of the calculated activation free energies ($\Delta G^\ddagger_{\text{calc}}$) for the alkaline hydrolysis of substituted sulfate diesters in the presence of 0 explicit water molecules (pure implicit solvation), obtained using the M062X⁴ functional.^a

Substituent	ΔE^\ddagger	ΔZPE^\ddagger	$-T\Delta S^\ddagger$	$\Delta G^\ddagger_{\text{calc}}$	$\Delta G^\ddagger_{\text{exp}}$	ν
4-chloro-3-nitro	7	0.2	3	10.2	21.2	-302.0405
4-nitro	7.5	0.1	2.7	10.3	21.5	-316.6842
2,6-difluoro	4.3	0.4	3.9	8.6	21.3	-263.5941
2-fluoro-4-nitro	6.2	-0.2	2	8	20.1	-303.4558
2,3,4,5,6-pentafluoro	5	-0.1	1.3	6.2	19.2	-259.2123
3-fluoro-4-nitro	6.9	0.04	2.9	9.8	19.4	-311.5082

^a All energies are shown in kcal mol⁻¹, and vibrational frequencies are shown in cm⁻¹. ΔE^\ddagger , ΔZPE^\ddagger and $-T\Delta S^\ddagger$ denote the contributions to $\Delta G^\ddagger_{\text{calc}}$ from the electronic energy, zero-point energy and activation free energy, respectively. ν denotes the first vibrational frequency. $\Delta G^\ddagger_{\text{exp}}$ denotes the experimental activation free energy at 313.15 K, obtained from the kinetic data presented in ref. ² using transition state theory.

Table S43. Energy decomposition of the calculated activation free energies ($\Delta G^\ddagger_{\text{calc}}$) for the alkaline hydrolysis of substituted sulfate diesters in the presence of 2 explicit water molecules, obtained using the M062X⁴ functional.^a

Substituent	ΔE^\ddagger	$\Delta \text{ZPE}^\ddagger$	$-\text{T}\Delta S^\ddagger$	$\Delta G^\ddagger_{\text{calc}}$	$\Delta G^\ddagger_{\text{exp}}$	ν
4-chloro-3-nitro	6.8	1.0	3.3	11.1	21.2	-286.8049
4-nitro	6.3	0.5	4.0	10.8	21.5	-292.9074
2,6-difluoro	3.5	0.8	3.8	8.1	21.3	-263.6809
2-fluoro-4-nitro	6.4	0.1	0.9	7.4	20.1	-287.2524
2,3,4,5,6-pentafluoro	7.4	0.8	2.1	4.6	19.2	-242.4723
3-fluoro-4-nitro	6.6	0.6	2.9	10.1	19.4	-285.2326

^a All energies are shown in kcal mol⁻¹, and vibrational frequencies are shown in cm⁻¹. ΔE^\ddagger , $\Delta \text{ZPE}^\ddagger$ and $-\text{T}\Delta S^\ddagger$ denote the contributions to $\Delta G^\ddagger_{\text{calc}}$ from the electronic energy, zero-point energy and activation free energy, respectively. ν denotes the first vibrational frequency. $\Delta G^\ddagger_{\text{exp}}$ denotes the experimental activation free energy at 313.15 K, obtained from the kinetic data presented in ref. ² using transition state theory.

Table S44. Energy decomposition of the calculated activation free energies ($\Delta G^\ddagger_{\text{calc}}$) for the alkaline hydrolysis of substituted sulfate in the presence of 4 explicit water molecules, obtained using the M062X⁴ functional.^a

Substituent	ΔE^\ddagger	$\Delta \text{ZPE}^\ddagger$	$-\text{T}\Delta S^\ddagger$	$\Delta G^\ddagger_{\text{calc}}$	$\Delta G^\ddagger_{\text{exp}}$	ν
4-chloro-3-nitro	9.0	-1.2	-1.5	6.3	21.2	-285.5131
4-nitro	11.0	-0.4	0.01	10.6	21.5	-287.6699
2,6-difluoro	3.5	0.7	2.2	6.4	21.3	-254.0158
2-fluoro-4-nitro	3.3	1.3	2.7	7.2	20.1	-250.3784
2,3,4,5,6-pentafluoro	1.8	0.9	2.1	4.8	19.2	-229.391
3-fluoro-4-nitro	6.4	0.1	0.6	7.1	19.4	-292.3245

^a All energies are shown in kcal mol⁻¹, and vibrational frequencies are shown in cm⁻¹. ΔE^\ddagger , $\Delta \text{ZPE}^\ddagger$ and $-\text{T}\Delta S^\ddagger$ denote the contributions to $\Delta G^\ddagger_{\text{calc}}$ from the electronic energy, zero-point energy and activation free energy, respectively. ν denotes the first vibrational frequency. $\Delta G^\ddagger_{\text{exp}}$ denotes the experimental activation free energy at 313.15 K, obtained from the kinetic data presented in ref. ² using transition state theory.

Table S45. Energy decomposition of the calculated activation free energies ($\Delta G^\ddagger_{\text{calc}}$) for the alkaline hydrolysis of substituted sulfate diesters in the presence of 8 explicit water molecules, obtained using the M062X⁴ functional.^a

Substituent	ΔE^\ddagger	ΔZPE^\ddagger	$-T\Delta S^\ddagger$	$\Delta G^\ddagger_{\text{calc}}$	$\Delta G^\ddagger_{\text{exp}}$	ν
4-chloro-3-nitro	10.8	0.04	1.7	12.5	21.2	-279.4276
4-nitro	8.2	0.3	0.7	9.2	21.5	-283.7645
2,6-difluoro	12.1	0.1	-2.5	10.1	21.3	-266.2105
2-fluoro-4-nitro	6.3	0.8	1.3	8.4	21.3	-275.8933
2,3,4,5,6-pentafluoro	5.6	2.6	3	11.2	19.2	-265.0677
3-fluoro-4-nitro	7.5	0.5	1.7	9.5	19.4	-275.3139

^a All energies are shown in kcal mol⁻¹, and vibrational frequencies are shown in cm⁻¹. ΔE^\ddagger , ΔZPE^\ddagger and $-T\Delta S^\ddagger$ denote the contributions to $\Delta G^\ddagger_{\text{calc}}$ from the electronic energy, zero-point energy and activation free energy, respectively. ν denotes the first vibrational frequency. $\Delta G^\ddagger_{\text{exp}}$ denotes the experimental activation free energy at 313.15 K, obtained from the kinetic data presented in ref. ² using transition state theory.

Table S46. Absolute and relative energy contributions to the calculated free energies (ΔG_{calc}) for the alkaline hydrolysis of substituted sulfate diesters in the presence of 0 additional explicit water molecules (pure implicit solvation), obtained using the ω B97X-D³ functional.^a

4-chloro-3-nitro	E	ZPE	S	ΔE	ΔZPE	$-T\Delta S$	ΔG_{calc}	ν
RS	-1902.3042145	129.07579	163.163	0.0	0.0	0.0	0.0	17.0736
TS	-1902.2875000	129.59369	150.068	10.5	0.5	4.1	15.1	-285.8424
PS	-1902.3512863	129.96548	153.386	-29.5	0.9	3.1	-25.6	-1.6775 ^b
4-nitro	E	ZPE	S	ΔE	ΔZPE	$-T\Delta S$	ΔG_{calc}	ν
RS	-1442.7105877	135.50586	153.837	0.0	0.0	0.0	0.0	27.865
TS	-1442.6936351	135.68108	143.642	10.6	0.2	3.2	14.0	-269.6541
PS	-1442.7620338	135.88209	156.698	-32.3	0.4	-0.9	-32.8	2.5343
2,6-difluoro	E	ZPE	S	ΔE	ΔZPE	$-T\Delta S$	ΔG_{calc}	ν
RS	-1436.6836856	123.07560	152.237	0.0	0.0	0.0	0.0	17.421
TS	-1436.6706435	123.64884	138.719	8.2	0.6	4.2	13.0	-255.3195
PS	-1436.7285555	124.22134	147.713	-28.2	1.1	1.4	-25.6	20.3575
2-fluoro-4-nitro	E	ZPE	S	ΔE	ΔZPE	$-T\Delta S$	ΔG_{calc}	ν
RS	-1541.9430306	130.18239	159.802	0.0	0.0	0.0	0.0	26.2503
TS	-1541.9283346	130.46140	147.827	9.2	0.3	3.7	1.3	-269.6949
PS	-1541.9997668	130.96907	159.984	-35.6	0.8	0.0	-34.8	11.2244
2,3,4,5,6-pentafluoro	E	ZPE	S	ΔE	ΔZPE	$-T\Delta S$	ΔG_{calc}	ν
RS	-1734.3655992	107.69555	166.047	0.0	0.0	0.0	0.0	14.5274
TS	-1734.3560598	107.98307	152.786	6.0	0.3	4.2	10.5	-191.8671
PS	-1734.4264982	108.46310	157.865	-38.2	0.8	2.6	-34.9	-7.6942 ^b
3-fluoro-4-nitro	E	ZPE	S	ΔE	ΔZPE	$-T\Delta S$	ΔG_{calc}	ν
RS	-1541.9399398	130.17666	158.212	0.0	0.0	0.0	0.0	26.73270
TS	-1541.9240006	130.13265	150.672	10.0	-0.04	2.4	12.4	-269.1173
PS	-1541.9948830	131.21003	157.313	-34.5	1.0	0.3	-33.2	19.4349

^a RS, TS and PS denote the reactant, transition and product states, respectively. E, ZPE and S denote the absolute electronic energies, zero-point energies and entropies, and ΔE , ΔZPE and $-T\Delta S$ denote the corresponding values relative to the RS (all values in kcal mol⁻¹, except S which is presented in cal mol⁻¹ K⁻¹). ν denotes the first vibrational frequency (cm⁻¹). ^b As this imaginary frequency is so small and it's in the product state (thus not affecting the calculated activation free energy for the hydrolysis of this compound), we have ignored it. We note that these structures were obtained using a super fine optimization grid.

Table S47. Absolute and relative energy contributions to the calculated free energies (ΔG_{calc}) for the alkaline hydrolysis of substituted sulfate diesters in the presence of 2 additional explicit water molecules, obtained using the ω B97X-D³ functional.^a

4-chloro-3-nitro	E	ZPE	S	ΔE	ΔZPE	$-T\Delta S$	ΔG_{calc}	ν
RS	-2055.2159043	159.50741	194.514	0.0	0.0	0.0	0.0	14.4781
TS	-2055.1992769	159.68388	185.652	10.4	0.2	2.8	13.4	-275.4637
PS	-2055.2621140	160.73052	189.1	-29.0	1.2	1.7	-26.1	16.1674
4-nitro	E	ZPE	S	ΔE	ΔZPE	$-T\Delta S$	ΔG_{calc}	ν
RS	-1595.6332193	166.11857	180.725	0.0	0.0	0.0	0.0	22.0334
TS	-1595.6054962	165.73854	178.694	17.4	-0.4	0.6	17.6	-289.4289
PS	-1595.6744573	166.80655	181.284	-25.9	0.7	-0.2	-25.4	17.7028
2,6-difluoro	E	ZPE	S	ΔE	ΔZPE	$-T\Delta S$	ΔG_{calc}	ν
RS	-1589.5941658	152.82038	186.29	0.0	0.0	0.0	0.0	17.7358
TS	-1589.5818073	154.26010	168.853	7.8	1.4	5.5	14.7	-241.8208
PS	-1589.6434680	155.32919	174.728	-30.9	2.5	3.6	-24.8	13.9686
2-fluoro-4-nitro	E	ZPE	S	ΔE	ΔZPE	$-T\Delta S$	ΔG_{calc}	ν
RS	-1694.8547048	159.94999	193.151	0.0	0.0	0.0	0.0	19.3376
TS	-1694.8400412	160.39707	184.485	9.2	0.4	2.7	12.3	-280.3696
PS	-1694.9138037	161.26591	188.452	-37.1	1.3	1.5	-34.3	13.2216
2,3,4,5,6-pentafluoro	E	ZPE	S	ΔE	ΔZPE	$-T\Delta S$	ΔG_{calc}	ν
RS	-1887.2747775	137.54657	197.269	0.0	0.0	0.0	0.0	19.1679
TS	-1887.2668689	138.25343	186.78	5.0	0.7	3.3	9.0	-208.8696
PS	-1887.3365707	139.75578	189.2	-38.8	2.2	2.5	-34.0	12.0491
3-fluoro-4-nitro	E	ZPE	S	ΔE	ΔZPE	$-T\Delta S$	ΔG_{calc}	ν
RS	-1694.8517863	159.98096	193.219	0.0	0.0	0.0	0.0	16.7567
TS	-1694.8359636	160.17970	184.801	9.9	0.2	2.6	12.7	-283.2926
PS	-1694.9069808	161.36655	186.269	-34.6	1.4	2.2	-31.1	18.7284

^a RS, TS and PS denote the reactant, transition and product states, respectively. E, ZPE and S denote the absolute electronic energies, zero-point energies and entropies, and ΔE , ΔZPE and $-T\Delta S$ denote the corresponding values relative to the RS (all values in kcal mol⁻¹, except S which is presented in cal mol⁻¹ K⁻¹). ν denotes the first vibrational frequency (cm⁻¹).

Table S48. Absolute and relative energy contributions to the calculated free energies (ΔG_{calc}) for the alkaline hydrolysis of substituted sulfate diesters in the presence of 4 additional explicit water molecules, obtained using the ω B97X-D³ functional.^a

4-chloro-3-nitro	E	ZPE	S	ΔE	ΔZPE	$-T\Delta S$	ΔG_{calc}	ν
RS	-2208.1289185	189.89797	225.274	0.0	0.0	0.0	0.0	11.3064
TS	-2208.1100991	189.93258	218.261	11.8	0.03	2.2	14.0	-256.1365
PS	-2208.1842302	191.43654	213.383	-34.7	1.5	3.7	-29.4	15.1949
4-nitro	E	ZPE	S	ΔE	ΔZPE	$-T\Delta S$	ΔG_{calc}	ν
RS	-1748.5825985	197.83378	209.165	-28.4	1.7	2.4	-24.3	20.5039
TS	-1748.5825985	197.83378	209.165	-28.4	1.7	2.4	-24.3	20.5039
PS	-1748.5825985	197.83378	209.165	-28.4	1.7	2.4	-24.3	20.5039
2,6-difluoro	E	ZPE	S	ΔE	ΔZPE	$-T\Delta S$	ΔG_{calc}	ν
RS	-1742.5069474	184.45982	209.868	0.0	0.0	0.0	0.0	18.3166
TS	-1742.4971831	185.65766	194.29	6.1	1.2	4.9	12.2	-228.9236
PS	-1742.5663798	186.22158	196.878	-37.3	1.8	4.1	-31.5	23.2154
2-fluoro-4-nitro	E	ZPE	S	ΔE	ΔZPE	$-T\Delta S$	ΔG_{calc}	ν
RS	-1847.7652977	191.03741	223.554	0.0	0.0	0.0	0.0	8.2604
TS	-1847.7561367	192.00850	207.574	5.7	1.0	5.0	11.7	-225.2576
PS	-1847.8319125	192.73182	210.003	-41.8	1.7	4.2	-35.9	24.0498
2,3,4,5,6-pentafluoro	E	ZPE	S	ΔE	ΔZPE	$-T\Delta S$	ΔG_{calc}	ν
RS	-2040.1873760	168.63691	226.542	0.0	0.0	0.0	0.0	15.6112
TS	-2040.1804955	169.01223	218.176	4.3	0.4	2.6	7.3	-196.2121
PS	-2040.2527854	169.89541	226.09	-41.0	1.3	0.1	-39.6	13.8064
3-fluoro-4-nitro	E	ZPE	S	ΔE	ΔZPE	$-T\Delta S$	ΔG_{calc}	ν
RS	-1847.7643492	190.76985	223.165	0.0	0.0	0.0	0.0	14.25260
TS	-1847.7485130	191.90362	210.141	9.9	1.1	4.1	15.1	-271.425
PS	-1847.8427036	194.82563	201.175	-49.2	4.1	6.9	-38.2	19.6845

^a RS, TS and PS denote the reactant, transition and product states, respectively. E, ZPE and S denote the absolute electronic energies, zero-point energies and entropies, and ΔE , ΔZPE and $-T\Delta S$ denote the corresponding values relative to the RS (all values in kcal mol⁻¹, except S which is presented in cal mol⁻¹ K⁻¹). ν denotes the first vibrational frequency (cm⁻¹).

Table S49. Absolute and relative energy contributions to the calculated free energies (ΔG_{calc}) for the alkaline hydrolysis of substituted sulfate diesters in the presence of 8 additional explicit water molecules, obtained using the ω B97X-D³ functional.^a

4-chloro-3-nitro	E	ZPE	S	ΔE	ΔZPE	$-T\Delta S$	ΔG_{calc}	ν
RS	-2513.9649011	255.10002	257.71	0.0	0.0	0.0	0.0	16.4417
TS	-2513.9254724	253.17055	271.131	24.7	-1.9	-4.2	18.6	-274.1009
PS	-2513.9892573	256.05744	268.033	-15.3	1.0	-3.2	-17.6	9.5019
4-nitro	E	ZPE	S	ΔE	ΔZPE	$-T\Delta S$	ΔG_{calc}	ν
RS	-2054.3572856	259.26468	268.855	0.0	0.0	0.0	0.0	21.8354
TS	-2054.3298017	259.00254	267.27	17.2	-0.3	0.5	17.5	-281.4245
PS	-2054.4203233	262.31221	258.444	-39.6	3.0	3.3	-33.2	20.8432
2,6-difluoro	E	ZPE	S	ΔE	ΔZPE	$-T\Delta S$	ΔG_{calc}	ν
RS	-2048.3334825	247.61469	258.819	0.0	0.0	0.0	0.0	10.0192
TS	-2048.3044759	248.23546	255.612	18.2	0.6	1.0	19.8	-244.4031
PS	-2048.3669334	250.31496	252.422	-21.0	2.7	2.0	-16.3	19.5536
2-fluoro-4-nitro	E	ZPE	S	ΔE	ΔZPE	$-T\Delta S$	ΔG_{calc}	ν
RS	-2153.5990449	256.42344	260.295	0.0	0.0	0.0	0.0	15.4432
TS	-2153.5721200	255.36330	259.948	16.9	-1.1	0.1	15.9	-253.072
PS	-2153.6296227	254.21948	281.277	-19.2	-2.2	-6.6	-28.0	16.2566
2,3,4,5,6-pentafluoro	E	ZPE	S	ΔE	ΔZPE	$-T\Delta S$	ΔG_{calc}	ν
RS	-2346.0082839	231.51664	278.407	0.0	0.0	0.0	0.0	16.7679
TS	-2345.9901827	232.00887	274.755	11.4	0.5	1.1	13.0	-242.0959
PS	-2346.1026374	235.97442	256.471	-59.2	4.5	6.9	-47.9	13.8433
3-fluoro-4-nitro	E	ZPE	S	ΔE	ΔZPE	$-T\Delta S$	ΔG_{calc}	ν
RS	-2513.9649011	255.10002	257.71	0.0	0.0	0.0	0.0	16.4417
TS	-2513.9254724	253.17055	271.131	24.7	-1.9	-4.2	18.6	-274.1009
PS	-2513.9892573	256.05744	268.033	-15.3	1.0	-3.2	-17.6	9.5019

^a RS, TS and PS denote the reactant, transition and product states, respectively. E, ZPE and S denote the absolute electronic energies, zero-point energies and entropies, and ΔE , ΔZPE and $-T\Delta S$ denote the corresponding values relative to the RS (all values in kcal mol⁻¹, except S which is presented in cal mol⁻¹ K⁻¹). ν denotes the first vibrational frequency (cm⁻¹).

Table S50. Absolute and relative energy contributions to the calculated free energies (ΔG_{calc}) for the alkaline hydrolysis of substituted sulfate diesters in the presence of 0 additional explicit water molecules (pure implicit solvation), obtained using the M11L¹ functional.^a

4-chloro-3-nitro	E	ZPE	S	ΔE	ΔZPE	$-T\Delta S$	ΔG_{calc}	ν
RS	-1902.3578193	126.83627	158.971	0.0	0.0	0.0	0.0	27.8721
TS	-1902.3433531	126.70291	150.819	9.1	-0.1	2.6	11.6	-342.7198
PS	-1902.4121718	127.26183	160.952	-34.1	0.4	-0.6	-34.3	15.1231
4-nitro	E	ZPE	S	ΔE	ΔZPE	$-T\Delta S$	ΔG_{calc}	ν
RS	-1442.7758730	132.60756	153.934	0.0	0.0	0.0	0.0	26.0193
TS	-1442.7614408	132.52363	144.06	9.1	-0.1	3.1	12.1	-331.4516
PS	-1442.8369596	133.54658	154.348	-38.3	0.9	-0.1	-37.5	20.0531
2,6-difluoro	E	ZPE	S	ΔE	ΔZPE	$-T\Delta S$	ΔG_{calc}	ν
RS	-1436.7306633	120.90060	149.583	0.0	0.0	0.0	0.0	21.9297
TS	-1436.7201611	121.10522	138.459	6.6	0.2	3.5	10.3	-268.0216
PS	-1436.7804009	121.64097	148.945	-31.2	0.7	0.2	-30.3	22.6591
2-fluoro-4-nitro	E	ZPE	S	ΔE	ΔZPE	$-T\Delta S$	ΔG_{calc}	ν
RS	-1542.0000347	127.89485	156.893	0.0	0.0	0.0	0.0	27.3537
TS	-1541.9875827	127.56909	150.364	7.8	-0.3	2.0	9.5	-324.8034
PS	-1542.0698566	128.61707	156.149	-43.8	0.7	0.2	-42.9	25.387
2,3,4,5,6-pentafluoro	E	ZPE	S	ΔE	ΔZPE	$-T\Delta S$	ΔG_{calc}	ν
RS	-1734.3856029	106.40281	160.883	0.0	0.0	0.0	0.0	20.0889
TS	-1734.3798443	106.49258	152.094	3.6	0.1	2.8	6.5	-189.2089
PS	-1734.4467195	107.06774	164.707	-38.4	0.7	-1.2	-38.9	5.4584
3-fluoro-4-nitro	E	ZPE	S	ΔE	ΔZPE	$-T\Delta S$	ΔG_{calc}	ν
RS	-1541.9975490	127.66277	159.563	0.0	0.0	0.0	0.0	21.6879
TS	-1541.9842218	127.31597	152.27	8.4	-0.3	2.3	10.4	-319.3068
PS	-1542.0661308	128.68973	155.292	-43.0	1.0	1.3	-40.7	20.5933

^a RS, TS and PS denote the reactant, transition and product states, respectively. E, ZPE and S denote the absolute electronic energies, zero-point energies and entropies, and ΔE , ΔZPE and $-T\Delta S$ denote the corresponding values relative to the RS (all values in kcal mol⁻¹, except S which is presented in cal mol⁻¹ K⁻¹). ν denotes the first vibrational frequency (cm⁻¹).

Table S51. Absolute and relative energy contributions to the calculated free energies (ΔG_{calc}) for the alkaline hydrolysis of substituted sulfate diesters in the presence of 2 additional explicit water molecules, obtained using the M11L¹ functional.^a

4-chloro-3-nitro	E	ZPE	S	ΔE	ΔZPE	$-T\Delta S$	ΔG_{calc}	ν
RS	-2055.2620499	156.67046	197.705	0.0	0.0	0.0	0.0	22.4306
TS	-2055.2484667	157.17314	186.581	8.5	0.5	3.5	12.5	-323.5784
PS	-2055.3134990	157.84919	198	-32.3	1.2	-0.1	-31.2	13.3636
4-nitro	E	ZPE	S	ΔE	ΔZPE	$-T\Delta S$	ΔG_{calc}	ν
RS	-1595.6796661	162.80622	192.494	0.0	0.0	0.0	0.0	17.8855
TS	-1595.6665795	162.81241	176.348	8.2	0.01	5.1	13.3	-332.1461
PS	-1595.7381136	163.80171	189.695	-36.7	1.0	0.9	-34.8	16.8895
2,6-difluoro	E	ZPE	S	ΔE	ΔZPE	$-T\Delta S$	ΔG_{calc}	ν
RS	-1589.6353623	151.08293	184.634	0.0	0.0	0.0	0.0	19.8214
TS	-1589.6248656	151.50084	174.591	6.6	0.4	3.1	10.1	-274.2715
PS	-1589.6818927	152.30770	183.626	-29.2	1.2	0.3	-27.7	21.3463
2-fluoro-4-nitro	E	ZPE	S	ΔE	ΔZPE	$-T\Delta S$	ΔG_{calc}	ν
RS	-1694.9037957	157.64879	197.713	0.0	0.0	0.0	0.0	16.6447
TS	-1694.8923934	157.89537	186.996	7.2	0.2	3.4	10.8	-310.5195
PS	-1694.9696190	158.80770	194.94	-41.3	1.2	0.9	-39.3	13.9617
2,3,4,5,6-pentafluoro	E	ZPE	S	ΔE	ΔZPE	$-T\Delta S$	ΔG_{calc}	ν
RS	-1887.2905617	136.20351	202.435	0.0	0.0	0.0	0.0	20.6642
TS	-1887.2843890	136.52097	190.066	3.9	0.3	3.9	8.1	-226.258
PS	-1887.3557432	138.58635	190.688	-40.9	2.4	3.7	-34.8	15.1247
3-fluoro-4-nitro	E	ZPE	S	ΔE	ΔZPE	$-T\Delta S$	ΔG_{calc}	ν
RS	-1694.9020537	157.81168	193.711	0.0	0.0	0.0	0.0	22.6421
TS	-1694.8893891	158.09203	186.94	7.9	0.3	2.1	10.3	-319.1242
PS	-1694.9639396	158.83893	193.659	-38.8	1.0	0.0	-37.8	18.7402

^a RS, TS and PS denote the reactant, transition and product states, respectively. E, ZPE and S denote the absolute electronic energies, zero-point energies and entropies, and ΔE , ΔZPE and $-T\Delta S$ denote the corresponding values relative to the RS (all values in kcal mol⁻¹, except S which is presented in cal mol⁻¹ K⁻¹). ν denotes the first vibrational frequency (cm⁻¹).

Table S52. Absolute and relative energy contributions to the calculated free energies (ΔG_{calc}) for the alkaline hydrolysis of substituted sulfate diesters in the presence of 4 additional explicit water molecules, obtained using the M11L¹ functional.^a

4-chloro-3-nitro	E	ZPE	S	ΔE	ΔZPE	$-T\Delta S$	ΔG_{calc}	ν
RS	-2208.1731695	188.51369	220.321	0.0	0.0	0.0	0.0	19.1392
TS	-2208.1537816	187.62340	220.625	12.2	-0.9	-0.1	11.2	-318.2203
PS	-2208.2230609	189.34747	222.784	-31.3	0.8	-0.8	-31.2	15.7009
4-nitro	E	ZPE	S	ΔE	ΔZPE	$-T\Delta S$	ΔG_{calc}	ν
RS	-1748.5846590	193.92064	221.836	0.0	0.0	0.0	0.0	18.1209
TS	-1748.5702951	193.69953	215.956	9.0	-0.2	1.8	10.6	-332.1585
PS	-1748.6433847	194.01429	226.487	-36.9	0.1	-1.5	-38.2	13.0271
2,6-difluoro	E	ZPE	S	ΔE	ΔZPE	$-T\Delta S$	ΔG_{calc}	ν
RS	-1742.4098809	184.17449	201.372	0.0	0.0	0.0	0.0	23.1067
TS	-1742.4002826	184.73336	195.444	6.0	0.6	1.9	8.5	-254.0158
PS	-1742.4378561	184.81254	208.664	-17.6	0.6	-2.3	-19.2	14.5464
2-fluoro-4-nitro	E	ZPE	S	ΔE	ΔZPE	$-T\Delta S$	ΔG_{calc}	ν
RS	-1847.8123900	189.36537	220.815	0.0	0.0	0.0	0.0	18.7224
TS	-1847.8046853	190.00686	210.408	4.8	0.6	3.3	8.7	-270.3738
PS	-1847.8813220	190.75027	218.078	-43.3	1.4	0.9	-41.0	18.0807
2,3,4,5,6-pentafluoro	E	ZPE	S	ΔE	ΔZPE	$-T\Delta S$	ΔG_{calc}	ν
RS	-2040.2035249	168.10969	225.341	0.0	0.0	0.0	0.0	11.7815
TS	-2040.1912314	168.05982	218.789	7.7	-0.05	2.1	9.7	-241.5549
PS	-2040.2709492	169.72211	215.335	-42.3	1.6	3.1	-37.6	14.9447
3-fluoro-4-nitro	E	ZPE	S	ΔE	ΔZPE	$-T\Delta S$	ΔG_{calc}	ν
RS	-1847.808703	188.71113	227.776	0.0	0.0	0.0	0.0	11.5219
TS	-1847.7970222	189.54466	215.567	7.3	0.8	3.8	11.9	-321.7632
PS	-1847.8733499	190.83091	215.823	-40.6	2.1	3.7	-34.7	24.913

^a RS, TS and PS denote the reactant, transition and product states, respectively. E, ZPE and S denote the absolute electronic energies, zero-point energies and entropies, and ΔE , ΔZPE and $-T\Delta S$ denote the corresponding values relative to the RS (all values in kcal mol⁻¹, except S which is presented in cal mol⁻¹ K⁻¹). ν denotes the first vibrational frequency (cm⁻¹).

Table S53. Absolute and relative energy contributions to the calculated free energies (ΔG_{calc}) for the alkaline hydrolysis of substituted sulfate diesters in the presence of 8 additional explicit water molecules, obtained using the M11L¹ functional.^a

4-chloro-3-nitro	E	ZPE	S	ΔE	ΔZPE	$-T\Delta S$	ΔG_{calc}	ν
RS	-2513.9880841	253.18732	263.722	0.0	0.0	0.0	0.0	21.2262
TS	-2513.9582942	252.10255	272.726	18.7	-1.1	-2.8	19.2	-342.5189
PS	-2514.0591272	256.97688	258.78	-44.6	-1.6	1.5	-44.7	13.7788
4-nitro	E	ZPE	S	ΔE	ΔZPE	$-T\Delta S$	ΔG_{calc}	ν
RS	-2054.4041216	257.57639	270.968	0.0	0.0	0.0	0.0	16.7626
TS	-2054.3737914	256.36054	279.803	19.0	-1.2	-2.8	15.0	-349.729
PS	-2054.4710658	260.06720	267.761	-42.0	2.5	1.0	-38.5	12.8992
2,6-difluoro	E	ZPE	S	ΔE	ΔZPE	$-T\Delta S$	ΔG_{calc}	ν
RS	-2048.3575885	246.02196	264.398	0.0	0.0	0.0	0.0	17.7056
TS	-2048.3289186	245.82629	268.283	18.0	-0.2	-1.2	17.3	-325.0493
PS	-2048.3935449	247.00953	269.499	-22.6	1.0	-1.6	-23.2	12.141
2-fluoro-4-nitro	E	ZPE	S	ΔE	ΔZPE	$-T\Delta S$	ΔG_{calc}	ν
RS	-2153.6223468	252.61400	273.807	0.0	0.0	0.0	0.0	20.7761
TS	-2153.6100237	253.37812	266.733	7.7	0.8	2.2	10.7	-322.0363
PS	-2153.6845054	255.03453	271.99	-39.0	2.4	0.6	-36.0	6.3165
2,3,4,5,6-pentafluoro	E	ZPE	S	ΔE	ΔZPE	$-T\Delta S$	ΔG_{calc}	ν
RS	-2346.0206453	233.05359	270.252	0.0	0.0	0.0	0.0	12.3535
TS	-2345.9896939	230.71353	280.841	19.4	-2.3	-3.3	13.8	-317.5782
PS	-2346.0625396	232.67986	281.569	-26.3	-0.4	-3.5	-30.2	15.7874
3-fluoro-4-nitro	E	ZPE	S	ΔE	ΔZPE	$-T\Delta S$	ΔG_{calc}	ν
RS	-2153.6300518	253.95391	271.178	0.0	0.0	0.0	0.0	14.0848
TS	-2153.6064029	252.85472	272.923	14.8	-1.1	-0.5	13.2	-348.1176
PS	-2153.6926118	255.45433	269.709	-39.3	1.5	0.5	-37.3	14.0572

^a RS, TS and PS denote the reactant, transition and product states, respectively. E, ZPE and S denote the absolute electronic energies, zero-point energies and entropies, and ΔE , ΔZPE and $-T\Delta S$ denote the corresponding values relative to the RS (all values in kcal mol⁻¹, except S which is presented in cal mol⁻¹ K⁻¹). ν denotes the first vibrational frequency (cm⁻¹).

Table S54. Absolute and relative energy contributions to the calculated free energies (ΔG_{calc}) for the alkaline hydrolysis of substituted sulfate diesters in the presence of 0 additional explicit water molecules (pure implicit solvation), obtained using the M062X⁴ functional.^a

4-chloro-3-nitro	E	ZPE	S	ΔE	ΔZPE	$-T\Delta S$	ΔG_{calc}	ν
RS	-1902.2303188	129.47170	158.174	0.0	0.0	0.0	0.0	24.8632
TS	-1902.2191858	129.66221	148.557	7.0	0.2	3.0	10.2	-302.0405
PS	-1902.2763628	129.97825	158.163	-28.9	0.5	0.0	-28.4	21.8115
4-nitro	E	ZPE	S	ΔE	ΔZPE	$-T\Delta S$	ΔG_{calc}	ν
RS	-1442.6434689	135.59843	151.311	0.0	0.0	0.0	0.0	29.8035
TS	-1442.6315931	135.71633	142.807	7.5	0.1	2.7	10.3	-316.6842
PS	-1442.6973623	136.14742	147.904	-33.8	0.5	1.1	-32.2	30.4802
2,6-difluoro	E	ZPE	S	ΔE	ΔZPE	$-T\Delta S$	ΔG_{calc}	ν
RS	-1436.6228870	123.25751	150.624	0.0	0.0	0.0	0.0	16.7084
TS	-1436.6159961	123.66497	138.298	4.3	0.4	3.9	8.6	-263.5941
PS	-1436.6695536	124.32118	143.773	-29.3	1.1	2.1	-26.1	29.8583
2-fluoro-4-nitro	E	ZPE	S	ΔE	ΔZPE	$-T\Delta S$	ΔG_{calc}	ν
RS	-1541.8755269	130.54571	154.853	0.0	0.0	0.0	0.0	26.5774
TS	-1541.8657148	130.37507	148.341	6.2	-0.2	2.0	8.0	-303.4558
PS	-1541.9376867	130.77852	155.359	-39.0	0.2	-0.2	-38.9	15.2376
2,3,4,5,6-pentafluoro	E	ZPE	S	ΔE	ΔZPE	$-T\Delta S$	ΔG_{calc}	ν
RS	-1734.3035296	108.33934	158.701	0.0	0.0	0.0	0.0	25.7602
TS	-1734.2955291	108.21717	154.41	5.0	-0.1	1.3	6.2	-259.2123
PS	-1734.3648894	109.06680	158.021	-38.5	0.7	0.2	-37.6	19.671
3-fluoro-4-nitro	E	ZPE	S	ΔE	ΔZPE	$-T\Delta S$	ΔG_{calc}	ν
RS	-1541.8724892	130.38582	156.102	0.0	0.0	0.0	0.0	24.0205
TS	-1541.8615694	130.42208	146.815	6.9	0.04	2.9	9.8	-311.5082
PS	-1541.9334583	130.96407	152.615	-38.3	0.6	1.1	-36.6	26.5388

^a RS, TS and PS denote the reactant, transition and product states, respectively. E, ZPE and S denote the absolute electronic energies, zero-point energies and entropies, and ΔE , ΔZPE and $-T\Delta S$ denote the corresponding values relative to the RS (all values in kcal mol⁻¹, except S which is presented in cal mol⁻¹ K⁻¹). ν denotes the first vibrational frequency (cm⁻¹).

Table S55. Absolute and relative energy contributions to the calculated free energies (ΔG_{calc}) for the alkaline hydrolysis of substituted sulfate diesters in the presence of 2 additional explicit water molecules, obtained using the M062X⁴ functional.^a

4-chloro-3-nitro	E	ZPE	S	ΔE	ΔZPE	$-T\Delta S$	ΔG_{calc}	ν
RS	-2055.1207362	158.94941	189.054	0.0	0.0	0.0	0.0	25.6321
TS	-2055.1098227	159.91714	178.383	6.8	1.0	3.3	11.1	-286.8049
PS	-2055.1628737	159.91984	190.532	-26.4	1.0	-0.5	-25.9	18.4388
4-nitro	E	ZPE	S	ΔE	ΔZPE	$-T\Delta S$	ΔG_{calc}	ν
RS	-1595.1585719	164.92086	189.93	0.0	0.0	0.0	0.0	15.3242
TS	-1595.1485956	165.40078	177.103	6.3	0.5	4.0	10.8	-292.9074
PS	-1595.2115938	166.56085	178.44	-33.3	1.6	3.6	-28.0	21.2865
2,6-difluoro	E	ZPE	S	ΔE	ΔZPE	$-T\Delta S$	ΔG_{calc}	ν
RS	-1589.5139781	153.55655	176.472	0.0	0.0	0.0	0.0	12.6314
TS	-1589.5084384	154.32346	164.288	3.5	0.8	3.8	8.1	-263.6809
PS	-1589.5608268	154.86447	172.585	-29.4	1.3	1.2	-26.9	13.7385
2-fluoro-4-nitro	E	ZPE	S	ΔE	ΔZPE	$-T\Delta S$	ΔG_{calc}	ν
RS	-1694.7662152	159.96108	186.04	0.0	0.0	0.0	0.0	16.8048
TS	-1694.7559900	160.02391	183.316	6.4	0.1	0.9	7.4	-287.2524
PS	-1694.8218693	160.97527	188.798	-34.9	1.0	-0.9	-34.8	8.7122
2,3,4,5,6-pentafluoro	E	ZPE	S	ΔE	ΔZPE	$-T\Delta S$	ΔG_{calc}	ν
RS	-1887.1950942	138.44987	186.076	0.0	0.0	0.0	0.0	20.7785
TS	-1887.1918690	138.86566	178.975	2.0	0.4	2.2	4.6	-242.4723
PS	-1887.2553077	139.56447	185.411	-37.8	1.1	0.2	-36.5	16.0994
3-fluoro-4-nitro	E	ZPE	S	ΔE	ΔZPE	$-T\Delta S$	ΔG_{calc}	ν
RS	-1694.7628895	160.01382	186.428	0.0	0.0	0.0	0.0	28.4589
TS	-1694.7524415	160.56909	177.313	6.6	0.6	2.9	10.1	-285.2326
PS	-1694.8179632	161.09238	185.261	-34.6	1.1	0.4	-33.1	25.7666

^a RS, TS and PS denote the reactant, transition and product states, respectively. E, ZPE and S denote the absolute electronic energies, zero-point energies and entropies, and ΔE , ΔZPE and $-T\Delta S$ denote the corresponding values relative to the RS (all values in kcal mol⁻¹, except S which is presented in cal mol⁻¹ K⁻¹). ν denotes the first vibrational frequency (cm⁻¹).

Table S56. Absolute and relative energy contributions to the calculated free energies (ΔG_{calc}) for the alkaline hydrolysis of substituted sulfate diesters in the presence of 4 additional explicit water molecules, obtained using the M062X⁴ functional.^a

4-chloro-3-nitro	E	ZPE	S	ΔE	ΔZPE	$-T\Delta S$	ΔG_{calc}	ν
RS	-2208.0122575	189.95869	215.269	0.0	0.0	0.0	0.0	19.9339
TS	-2207.9979597	188.73019	220.196	9.0	-1.2	-1.5	6.3	-285.5131
PS	-2208.0758671	192.54810	203.591	-39.9	2.6	3.7	-33.7	24.2042
4-nitro	E	ZPE	S	ΔE	ΔZPE	$-T\Delta S$	ΔG_{calc}	ν
RS	-1748.4273098	196.06219	208.126	0.0	0.0	0.0	0.0	21.9257
TS	-1748.4097162	195.70859	208.107	11.0	-0.4	0.01	10.6	-287.6699
PS	-1748.4702918	197.12423	207.891	-27.0	1.1	0.1	-25.8	25.862
2,6-difluoro	E	ZPE	S	ΔE	ΔZPE	$-T\Delta S$	ΔG_{calc}	ν
RS	-1742.4059059	183.99968	202.582	0.0	0.0	0.0	0.0	19.9971
TS	-1742.4002826	184.73336	195.444	3.5	0.7	2.2	6.4	-254.0158
PS	-1742.4378561	184.81254	208.664	-20.0	0.8	-1.9	-21.1	14.5464
2-fluoro-4-nitro	E	ZPE	S	ΔE	ΔZPE	$-T\Delta S$	ΔG_{calc}	ν
RS	-1847.6577928	190.12158	215.848	0.0	0.0	0.0	0.0	22.5405
TS	-1847.6525576	191.31248	207.305	3.3	1.2	2.7	7.2	-250.3784
PS	-1847.7387341	194.05504	201.412	-50.8	3.9	4.5	-42.3	12.2827
2,3,4,5,6-pentafluoro	E	ZPE	S	ΔE	ΔZPE	$-T\Delta S$	ΔG_{calc}	ν
RS	-2040.0836239	167.75719	222.958	0.0	0.0	0.0	0.0	22.5661
TS	-2040.0807041	168.61569	216.178	1.8	0.9	2.1	4.8	-229.391
PS	-2040.1413948	169.68559	219.142	-36.3	1.9	1.2	-33.1	13.3498
3-fluoro-4-nitro	E	ZPE	S	ΔE	ΔZPE	$-T\Delta S$	ΔG_{calc}	ν
RS	-1847.6523257	190.45813	214.769	0.0	0.0	0.0	0.0	18.2816
TS	-1847.6420810	190.53481	212.837	6.4	0.1	0.6	7.1	-292.3245
PS	-1847.7025905	192.16771	214.846	-31.5	1.7	0.0	-29.9	23.3278

^a RS, TS and PS denote the reactant, transition and product states, respectively. E, ZPE and S denote the absolute electronic energies, zero-point energies and entropies, and ΔE , ΔZPE and $-T\Delta S$ denote the corresponding values relative to the RS (all values in kcal mol⁻¹, except S which is presented in cal mol⁻¹ K⁻¹). ν denotes the first vibrational frequency (cm⁻¹).

Table S57. Absolute and relative energy contributions to the calculated free energies (ΔG_{calc}) for the alkaline hydrolysis of substituted sulfate diesters in the presence of 8 additional explicit water molecules, obtained using the M062X⁴ functional.^a

4-chloro-3-nitro	E	ZPE	S	ΔE	ΔZPE	$-T\Delta S$	ΔG_{calc}	ν
RS	-2513.7909346	253.34747	260.123	0.0	0.0	0.0	0.0	21.437
TS	-2513.7737635	253.38714	254.641	10.8	0.04	1.7	12.5	-279.4276
PS	-2513.8669030	256.52395	246.337	-47.7	3.2	4.3	-40.2	17.5961
4-nitro	E	ZPE	S	ΔE	ΔZPE	$-T\Delta S$	ΔG_{calc}	ν
RS	-2054.1986122	258.61012	261.306	0.0	0.0	0.0	0.0	19.785
TS	-2054.1855888	258.95387	258.979	8.2	0.3	0.7	9.2	-283.7645
PS	-2054.2672984	261.38123	250.497	-43.1	2.8	3.4	-36.9	20.118
2,6-difluoro	E	ZPE	S	ΔE	ΔZPE	$-T\Delta S$	ΔG_{calc}	ν
RS	-2048.1832695	246.33395	252.61	0.0	0.0	0.0	0.0	22.5942
TS	-2048.1633144	246.38654	260.715	12.5	0.1	-2.5	10.1	-266.2105
PS	-2048.2254820	248.24379	249.356	-26.5	1.9	1.0	-23.6	19.2489
2-fluoro-4-nitro	E	ZPE	S	ΔE	ΔZPE	$-T\Delta S$	ΔG_{calc}	ν
RS	-2153.4343846	253.86993	261.213	0.0	0.0	0.0	0.0	26.7784
TS	-2153.4243330	254.63689	257.159	6.3	0.8	1.3	8.4	-275.8933
PS	-2153.5234315	257.25805	241.666	-55.9	3.4	6.1	-46.4	19.9415
2,3,4,5,6-pentafluoro	E	ZPE	S	ΔE	ΔZPE	$-T\Delta S$	ΔG_{calc}	ν
RS	-2345.8626304	230.60870	268.447	0.0	0.0	0.0	0.0	25.7861
TS	-2345.8536709	233.20247	258.991	5.6	2.6	3.0	11.2	-265.0677
PS	-2345.9524015	233.84567	253.307	-56.3	3.2	4.7	-48.4	21.7803
3-fluoro-4-nitro	E	ZPE	S	ΔE	ΔZPE	$-T\Delta S$	ΔG_{calc}	ν
RS	-2153.4318381	253.79773	262.279	0.0	0.0	0.0	0.0	24.0739
TS	-2153.4202168	254.34733	256.71	7.3	0.5	1.7	9.5	-275.3139
PS	-2153.4952908	256.84594	252.461	-39.8	3.0	3.1	-33.7	23.4957

^a RS, TS and PS denote the reactant, transition and product states, respectively. E, ZPE and S denote the absolute electronic energies, zero-point energies and entropies, and ΔE , ΔZPE and $-T\Delta S$ denote the corresponding values relative to the RS (all values in kcal mol⁻¹, except S which is presented in cal mol⁻¹ K⁻¹). ν denotes the first vibrational frequency (cm⁻¹).

Table S58. Partial charges at the transition state for the alkaline hydrolysis of substituted sulfate diesters in the presence of 0 additional explicit water molecules (pure implicit solvation), obtained using the ω B97X-D³ functional.^a

Water Molecules	O _{nuc}	S	O _{lg}
4-chloro-3-nitro	-1.111641	1.232147	-0.572697
4-nitro	-1.116133	1.259782	-0.58486
2,6-difluoro	-1.10774	1.19289	-0.471096
2-fluoro-4-nitro	-1.121515	1.219911	-0.527337
2,3,4,5,6-pentafluoro	-1.123791	1.119482	-0.400261
3-fluoro-4-nitro	-1.120591	1.231624	-0.559804

^a Partial charges are calculated using the ChelpG⁵ charge calculation scheme, as described in the **Methodology** section.

Table S59. Partial charges at the transition state for the alkaline hydrolysis of substituted sulfate diesters in the presence of 2 additional explicit water molecules, obtained using the ω B97X-D³ functional.^a

Water Molecules	O _{nuc}	S	O _{lg}
4-chloro-3-nitro	-1.052228	1.154162	-0.505857
4-nitro	-1.056234	1.117773	-0.4649
2,6-difluoro	-1.115392	1.211859	-0.463366
2-fluoro-4-nitro	-1.056456	1.065096	-0.405403
2,3,4,5,6-pentafluoro	-1.133838	1.125565	-0.377429
3-fluoro-4-nitro	-1.068044	1.115811	-0.464594

^a Partial charges are calculated using the ChelpG⁵ charge calculation scheme, as described in the **Methodology** section.

Table S60. Partial charges at the transition state for the alkaline hydrolysis of substituted sulfate diesters in the presence of 4 additional explicit water molecules, obtained using the ω B97X-D³ functional.^a

Water Molecules	O _{nuc}	S	O _{lg}
4-chloro-3-nitro	-0.906699	1.15772	-0.430702
4-nitro	-0.903971	1.094185	-0.427313
2,6-difluoro	-0.946515	0.981219	-0.312967
2-fluoro-4-nitro	-0.936568	0.995378	-0.372016
2,3,4,5,6-pentafluoro	-0.919628	0.973341	0.029137
3-fluoro-4-nitro	-0.911288	0.975482	-0.438907

^a Partial charges are calculated using the ChelpG⁵ charge calculation scheme, as described in the **Methodology** section.

Table S61. Partial charges at the transition state for the alkaline hydrolysis of substituted sulfate diesters in the presence of 8 additional explicit water molecules, obtained using the ω B97X-D³ functional.^a

Water Molecules	O _{nuc}	S	O _{lg}
4-chloro-3-nitro	-0.818968	1.53004	-0.557081
4-nitro	-0.808109	1.375266	-0.539817
2,6-difluoro	-0.719478	1.129583	-0.187656
2-fluoro-4-nitro	-0.794135	1.115757	-0.309453
2,3,4,5,6-pentafluoro	-0.648572	0.903609	0.131355
3-fluoro-4-nitro	-0.889096	1.226026	-0.545571

^a Partial charges are calculated using the ChelpG⁵ charge calculation scheme, as described in the **Methodology** section.

Table S62. Partial charges at the transition state for the alkaline hydrolysis of substituted sulfate diesters in the presence of 0 additional explicit water molecules (pure implicit solvation), obtained using the M11L¹ functional.^a

Water Molecules	O _{nuc}	S	O _{lg}
4-chloro-3-nitro	-1.126065	1.238842	-0.581367
4-nitro	-1.128893	1.244377	-0.588531
2,6-difluoro	-1.123921	1.210062	-0.475852
2-fluoro-4-nitro	-1.131816	1.20932	-0.523576
2,3,4,5,6-pentafluoro	-1.126397	1.120806	-0.396262
3-fluoro-4-nitro	-1.139186	1.221296	-0.559813

^a Partial charges are calculated using the ChelpG⁵ charge calculation scheme, as described in the **Methodology** section.

Table S63. Partial charges at the transition state for the alkaline hydrolysis of substituted sulfate diesters in the presence of 2 additional explicit water molecules, obtained using the M11L¹ functional.^a

Water Molecules	O _{nuc}	S	O _{lg}
4-chloro-3-nitro	-1.054268	1.177652	-0.516051
4-nitro	-1.048351	1.173881	-0.508858
2,6-difluoro	-1.107014	1.239456	-0.483114
2-fluoro-4-nitro	-1.064281	1.138652	-0.434989
2,3,4,5,6-pentafluoro	-1.155153	1.095868	-0.355669
3-fluoro-4-nitro	-1.060325	1.167686	-0.493242

^a Partial charges are calculated using the ChelpG⁵ charge calculation scheme, as described in the **Methodology** section.

Table S64. Partial charges at the transition state for the alkaline hydrolysis of substituted sulfate diesters in the presence of 4 additional explicit water molecules, obtained using the M11L¹ functional.^a

Water Molecules	O _{nuc}	S	O _{lg}
4-chloro-3-nitro	-0.869986	1.038718	-0.332873
4-nitro	-0.922275	1.035309	-0.383091
2,6-difluoro	-0.915672	0.973609	-0.273618
2-fluoro-4-nitro	-0.905535	0.953933	-0.305688
2,3,4,5,6-pentafluoro	-0.878166	0.980448	0.092381
3-fluoro-4-nitro	-1.006325	0.933329	-0.364949

^a Partial charges are calculated using the ChelpG⁵ charge calculation scheme, as described in the **Methodology** section.

Table S65. Partial charges at the transition state for the alkaline hydrolysis of substituted sulfate diesters in the presence of 8 additional explicit water molecules, obtained using the M11L¹ functional.^a

Water Molecules	O _{nuc}	S	O _{lg}
4-chloro-3-nitro	-0.770574	1.310195	-0.37252
4-nitro	-0.809259	1.14282	-0.477867
2,6-difluoro	-0.720382	1.157698	-0.205206
2-fluoro-4-nitro	-0.850967	1.064396	-0.333301
2,3,4,5,6-pentafluoro	-0.688973	0.802573	0.075625
3-fluoro-4-nitro	-0.822024	1.283624	-0.535008

^a Partial charges are calculated using the ChelpG⁵ charge calculation scheme, as described in the **Methodology** section.

Table S66. Partial charges at the transition state for the alkaline hydrolysis of substituted sulfate diesters in the presence of 0 additional explicit water molecules (pure implicit solvation), obtained using the M062X⁴ functional.^a

Water Molecules	O _{nuc}	S	O _{lg}
4-chloro-3-nitro	-1.138291	1.236014	-0.564708
4-nitro	-1.139127	1.250009	-0.560361
2,6-difluoro	-1.136644	1.210623	-0.464085
2-fluoro-4-nitro	-1.140526	1.206306	-0.502166
2,3,4,5,6-pentafluoro	-1.144043	1.084718	-0.393913
3-fluoro-4-nitro	-1.142764	1.240041	-0.545671

^a Partial charges are calculated using the ChelpG⁵ charge calculation scheme, as described in the **Methodology** section.

Table S67. Partial charges at the transition state for the alkaline hydrolysis of substituted sulfate diesters in the presence of 2 additional explicit water molecules, obtained using the M062X⁴ functional.^a

Water Molecules	O _{nuc}	S	O _{lg}
4-chloro-3-nitro	-1.049775	1.22034	-0.521161
4-nitro	-1.048017	1.195557	-0.504796
2,6-difluoro	-1.12217	1.205036	-0.437561
2-fluoro-4-nitro	-1.055519	1.124415	-0.423785
2,3,4,5,6-pentafluoro	-1.159782	1.115634	-0.352506
3-fluoro-4-nitro	-1.052143	1.212126	-0.498027

^a Partial charges are calculated using the ChelpG⁵ charge calculation scheme, as described in the **Methodology** section.

Table S68. Partial charges at the transition state for the alkaline hydrolysis of substituted sulfate diesters in the presence of 4 additional explicit water molecules, obtained using the M062X⁴ functional.^a

Water Molecules	O _{nuc}	S	O _{lg}
4-chloro-3-nitro	-0.950593	1.076789	-0.408504
4-nitro	-0.959323	1.082878	-0.417571
2,6-difluoro	-1.002794	1.001605	-0.285461
2-fluoro-4-nitro	-0.989268	0.998185	-0.323282
2,3,4,5,6-pentafluoro	-1.004115	1.026607	0.042262
3-fluoro-4-nitro	-1.035300	1.000186	-0.418766

^a Partial charges are calculated using the ChelpG⁵ charge calculation scheme, as described in the **Methodology** section.

Table S69. Partial charges at the transition state for the alkaline hydrolysis of substituted sulfate diesters in the presence of 8 additional explicit water molecules, obtained using the M062X⁴ functional.^a

Water Molecules	O _{nuc}	S	O _{lg}
4-chloro-3-nitro	-0.94733	1.313362	-0.498923
4-nitro	-0.854524	1.254148	-0.535374
2,6-difluoro	-0.825784	1.061389	-0.11393
2-fluoro-4-nitro	-0.927407	1.060805	-0.306961
2,3,4,5,6-pentafluoro	-0.739404	0.712602	-0.238053
3-fluoro-4-nitro	-0.789773	1.301197	-0.50345

^a Partial charges are calculated using the ChelpG⁵ charge calculation scheme, as described in the **Methodology** section.

Table S70. Partial charges at key stationary points for the alkaline hydrolysis of substituted sulfate diesters in the presence of 0 additional explicit water molecules (pure implicit solvation), obtained using the ω B97X-D³ functional.^a

4-chloro-3-nitro	O_{nuc}	S	O_{lg}
RS	-1.291921	1.096961	-0.387663
TS	-1.111641	1.232147	-0.572697
PS	-0.509717	1.072833	-0.855893
4-nitro	O_{nuc}	S	O_{lg}
RS	-1.296563	1.12486	-0.391163
TS	-1.116133	1.259782	-0.58486
PS	-0.537492	1.114613	-0.804766
2,6-difluoro	O_{nuc}	S	O_{lg}
RS	-1.323328	1.183321	-0.347723
TS	-1.10774	1.19289	-0.471096
PS	-0.605661	1.191238	-0.802531
2-fluoro-4-nitro	O_{nuc}	S	O_{lg}
RS	-1.296515	1.091244	-0.338531
TS	-1.121515	1.219911	-0.527337
PS	-0.582166	1.231353	-0.770628
2,3,4,5,6-pentafluoro	O_{nuc}	S	O_{lg}
RS	-1.307134	1.160055	-0.296363
TS	-1.123791	1.119482	-0.400261
PS	-0.509743	1.102915	-0.782979
3-fluoro-4-nitro	O_{nuc}	S	O_{lg}
RS	-1.296716	1.091253	-0.374008
TS	-1.120591	1.231624	-0.559804
PS	-0.578857	1.21737	-0.798075

^a RS, TS and PS denote the reactant, transition and product states, respectively. Partial charges are calculated using the ChelpG⁵ charge calculation scheme, as described in the **Methodology** section.

Table S71. Partial charges at key stationary points for the alkaline hydrolysis of substituted sulfate diesters in the presence of 2 additional explicit water molecules, obtained using the ω B97X-D³ functional.^a

4-chloro-3-nitro	O_{nuc}	S	O_{lg}
RS	-1.205177	1.139172	-0.406195
TS	-1.052228	1.154162	-0.505857
PS	-0.50458	1.091234	-0.85603
4-nitro	O_{nuc}	S	O_{lg}
RS	-1.135373	1.179743	-0.392427
TS	-1.056234	1.117773	-0.4649
PS	-0.521243	1.113486	-0.801443
2,6-difluoro	O_{nuc}	S	O_{lg}
RS	-1.193485	1.176152	-0.351537
TS	-1.115392	1.211859	-0.463366
PS	-0.529381	1.099076	-0.811984
2-fluoro-4-nitro	O_{nuc}	S	O_{lg}
RS	-1.201943	1.11984	-0.377146
TS	-1.056456	1.065096	-0.405403
PS	-0.501699	1.100824	-0.750857
2,3,4,5,6-pentafluoro	O_{nuc}	S	O_{lg}
RS	-1.219956	1.041389	-0.237303
TS	-1.133838	1.125565	-0.377429
PS	-0.477058	1.01544	-0.741634
3-fluoro-4-nitro	O_{nuc}	S	O_{lg}
RS	-1.200008	1.125621	-0.377
TS	-1.068044	1.115811	-0.464594
PS	-0.515291	1.049907	-0.812597

^a RS, TS and PS denote the reactant, transition and product states, respectively. Partial charges are calculated using the ChelpG⁵ charge calculation scheme, as described in the **Methodology** section.

Table S72. Partial charges at key stationary points for the alkaline hydrolysis of substituted sulfate diesters in the presence of 4 additional explicit water molecules, obtained using the ω B97X-D³ functional.^a

4-chloro-3-nitro	O_{nuc}	S	O_{lg}
RS	-1.229317	1.041916	-0.341015
TS	-0.906699	1.15772	-0.430702
PS	-0.479935	0.96767	-0.755464
4-nitro	O_{nuc}	S	O_{lg}
RS	-1.236077	1.037997	-0.390759
TS	-0.903971	1.094185	-0.427313
PS	-0.903971	1.094185	-0.427313
2,6-difluoro	O_{nuc}	S	O_{lg}
RS	-1.088478	0.971709	-0.220458
TS	-0.946515	0.981219	-0.312967
PS	-0.515885	0.992838	-0.707345
2-fluoro-4-nitro	O_{nuc}	S	O_{lg}
RS	-1.085704	0.989754	-0.264487
TS	-0.936568	0.995378	-0.372016
PS	-0.500829	1.017799	-0.776886
2,3,4,5,6-pentafluoro	O_{nuc}	S	O_{lg}
RS	-1.092728	0.966197	-0.002528
TS	-0.919628	0.973341	0.029137
PS	-0.512507	1.054881	-0.696406
3-fluoro-4-nitro	O_{nuc}	S	O_{lg}
RS	-1.246425	0.990739	-0.357892
TS	-0.911288	0.975482	-0.438907
PS	-0.602037	1.111286	-0.819751

^a RS, TS and PS denote the reactant, transition and product states, respectively. Partial charges are calculated using the ChelpG⁵ charge calculation scheme, as described in the **Methodology** section.

Table S73. Partial charges at key stationary points for the alkaline hydrolysis of substituted sulfate diesters in the presence of 8 additional explicit water molecules, obtained using the ω B97X-D³ functional.^a

4-chloro-3-nitro	O_{nuc}	S	O_{lg}
RS	-0.718829	1.146725	-0.413029
TS	-0.818968	1.53004	-0.557081
PS	-0.419947	0.891689	-0.805632
4-nitro	O_{nuc}	S	O_{lg}
RS	-1.016168	1.025112	-0.394967
TS	-0.808109	1.375266	-0.539817
PS	-0.551013	0.968566	-0.730409
2,6-difluoro	O_{nuc}	S	O_{lg}
RS	-0.962349	1.128122	-0.29799
TS	-0.719478	1.129583	-0.187656
PS	-0.49093	1.060843	-0.673744
2-fluoro-4-nitro	O_{nuc}	S	O_{lg}
RS	-1.027716	1.108502	-0.489306
TS	-0.794135	1.115757	-0.309453
PS	-0.433804	0.912395	-0.505965
2,3,4,5,6-pentafluoro	O_{nuc}	S	O_{lg}
RS	-1.058844	0.899329	-0.193228
TS	-0.648572	0.903609	0.131355
PS	-0.58977	1.110336	-0.706082
3-fluoro-4-nitro	O_{nuc}	S	O_{lg}
RS	-0.976802	1.184277	-0.393949
TS	-0.889096	1.226026	-0.545571
PS	-0.617534	1.044413	-0.770858

^a RS, TS and PS denote the reactant, transition and product states, respectively. Partial charges are calculated using the ChelpG⁵ charge calculation scheme, as described in the **Methodology** section.

Table S74. Partial charges at key stationary points for the alkaline hydrolysis of substituted sulfate diesters in the presence of 0 additional explicit water molecules (pure implicit solvation), obtained using the M11L¹ functional.^a

4-chloro-3-nitro	O_{nuc}	S	O_{lg}
RS	-1.283734	1.078308	-0.382041
TS	-1.126065	1.238842	-0.581367
PS	-0.556229	1.119408	-0.845815
4-nitro	O_{nuc}	S	O_{lg}
RS	-1.284482	1.080957	-0.379139
TS	-1.128893	1.244377	-0.588531
PS	-0.585248	1.238508	-0.772942
2,6-difluoro	O_{nuc}	S	O_{lg}
RS	-1.325572	1.136336	-0.317996
TS	-1.123921	1.210062	-0.475852
PS	-0.528407	1.121804	-0.783681
2-fluoro-4-nitro	O_{nuc}	S	O_{lg}
RS	-1.277816	1.019658	-0.314991
TS	-1.131816	1.20932	-0.523576
PS	-0.549292	1.10734	-0.737144
2,3,4,5,6-pentafluoro	O_{nuc}	S	O_{lg}
RS	-1.288597	0.996416	-0.243606
TS	-1.126397	1.120806	-0.396262
PS	-0.541094	1.095936	-0.769538
3-fluoro-4-nitro	O_{nuc}	S	O_{lg}
RS	-1.285697	1.028887	-0.352591
TS	-1.139186	1.221296	-0.559813
PS	-0.554839	1.120693	-0.780017

^a RS, TS and PS denote the reactant, transition and product states, respectively. Partial charges are calculated using the ChelpG⁵ charge calculation scheme, as described in the **Methodology** section.

Table S75. Partial charges at key stationary points for the alkaline hydrolysis of substituted sulfate diesters in the presence of 2 additional explicit water molecules, obtained using the M11L¹ functional.^a

4-chloro-3-nitro	O_{nuc}	S	O_{lg}
RS	-1.193072	1.083588	-0.38828
TS	-1.054268	1.177652	-0.516051
PS	-0.592371	1.058217	-0.851023
4-nitro	O_{nuc}	S	O_{lg}
RS	-1.188192	1.032376	-0.357577
TS	-1.048351	1.173881	-0.508858
PS	-0.546385	1.050097	-0.769466
2,6-difluoro	O_{nuc}	S	O_{lg}
RS	-1.227928	1.033377	-0.336466
TS	-1.107014	1.239456	-0.483114
PS	-0.499219	1.156265	-0.795488
2-fluoro-4-nitro	O_{nuc}	S	O_{lg}
RS	-1.183884	0.997508	-0.345811
TS	-1.064281	1.138652	-0.434989
PS	-0.604822	1.038779	-0.733007
2,3,4,5,6-pentafluoro	O_{nuc}	S	O_{lg}
RS	-1.224148	0.98398	-0.234458
TS	-1.155153	1.095868	-0.355669
PS	-0.520891	1.03032	-0.724211
3-fluoro-4-nitro	O_{nuc}	S	O_{lg}
RS	-1.196171	1.072024	-0.374475
TS	-1.060325	1.167686	-0.493242
PS	-0.574846	1.083251	-0.767394

^a RS, TS and PS denote the reactant, transition and product states, respectively. Partial charges are calculated using the ChelpG⁵ charge calculation scheme, as described in the **Methodology** section.

Table S76. Partial charges at key stationary points for the alkaline hydrolysis of substituted sulfate diesters in the presence of 4 additional explicit water molecules, obtained using the M11L¹ functional.^a

4-chloro-3-nitro	O_{nuc}	S	O_{lg}
RS	-1.293306	0.996599	-0.396281
TS	-0.869986	1.038718	-0.332873
PS	-0.48212	1.019022	-0.745712
4-nitro	O_{nuc}	S	O_{lg}
RS	-1.247046	0.996753	-0.367373
TS	-0.922275	1.035309	-0.383091
PS	-0.360786	0.822035	-0.70989
2,6-difluoro	O_{nuc}	S	O_{lg}
RS	-1.101469	0.929305	-0.220078
TS	-0.915672	0.973609	-0.273618
PS	-0.625749	1.041767	-0.770563
2-fluoro-4-nitro	O_{nuc}	S	O_{lg}
RS	-1.100258	0.907941	-0.222727
TS	-0.905535	0.953933	-0.305688
PS	-0.520253	0.94726	-0.723689
2,3,4,5,6-pentafluoro	O_{nuc}	S	O_{lg}
RS	-1.082253	0.980383	-0.17232
TS	-0.878166	0.980448	0.092381
PS	-0.50781	0.949684	-0.621905
3-fluoro-4-nitro	O_{nuc}	S	O_{lg}
RS	-1.247119	0.994394	-0.298148
TS	-1.006325	0.933329	-0.364949
PS	-0.610627	1.19919	-0.758327

^a RS, TS and PS denote the reactant, transition and product states, respectively. Partial charges are calculated using the ChelpG⁵ charge calculation scheme, as described in the **Methodology** section.

Table S77. Partial charges at key stationary points for the alkaline hydrolysis of substituted sulfate diesters in the presence of 8 additional explicit water molecules, obtained using the M11L¹ functional.^a

4-chloro-3-nitro	O_{nuc}	S	O_{lg}
RS	-1.217712	1.25397	-0.383196
TS	-0.770574	1.310195	-0.37252
PS	-0.563039	1.160276	-0.788853
4-nitro	O_{nuc}	S	O_{lg}
RS	-1.195468	0.879597	-0.324804
TS	-0.809259	1.14282	-0.477867
PS	-0.352874	0.977358	-0.666439
2,6-difluoro	O_{nuc}	S	O_{lg}
RS	-1.120235	0.957035	-0.214598
TS	-0.720382	1.157698	-0.205206
PS	-0.550149	0.895955	-0.64519
2-fluoro-4-nitro	O_{nuc}	S	O_{lg}
RS	-1.121165	1.002055	-0.311068
TS	-0.850967	1.064396	-0.333301
PS	-0.563774	1.009113	-0.528711
2,3,4,5,6-pentafluoro	O_{nuc}	S	O_{lg}
RS	-1.038878	0.917971	-0.202779
TS	-0.688973	0.802573	0.075625
PS	-0.467841	0.81433	-0.580926
3-fluoro-4-nitro	O_{nuc}	S	O_{lg}
RS	-1.120558	1.31893	-0.445532
TS	-0.822024	1.283624	-0.535008
PS	-0.519243	1.116256	-0.766397

^a RS, TS and PS denote the reactant, transition and product states, respectively. Partial charges are calculated using the ChelpG⁵ charge calculation scheme, as described in the **Methodology** section.

Table S78. Partial charges at key stationary points for the alkaline hydrolysis of substituted sulfate diesters in the presence of 0 additional explicit water molecules (pure implicit solvation), obtained using the M062X⁴ functional.^a

4-chloro-3-nitro	O_{nuc}	S	O_{lg}
RS	-1.278676	1.10438	-0.386967
TS	-1.138291	1.236014	-0.564708
PS	-0.55209	1.113685	-0.868249
4-nitro	O_{nuc}	S	O_{lg}
RS	-1.275519	1.121414	-0.387754
TS	-1.139127	1.250009	-0.560361
PS	-0.558318	1.13009	-0.804851
2,6-difluoro	O_{nuc}	S	O_{lg}
RS	-1.333103	1.171004	-0.332848
TS	-1.136644	1.210623	-0.464085
PS	-0.535889	1.121027	-0.799473
2-fluoro-4-nitro	O_{nuc}	S	O_{lg}
RS	-1.277332	1.055781	-0.330178
TS	-1.140526	1.206306	-0.502166
PS	-0.541	1.090886	-0.761832
2,3,4,5,6-pentafluoro	O_{nuc}	S	O_{lg}
RS	-1.302291	1.047271	-0.27546
TS	-1.144043	1.084718	-0.393913
PS	-0.542495	1.094986	-0.779909
3-fluoro-4-nitro	O_{nuc}	S	O_{lg}
RS	-1.281241	1.083053	-0.368749
TS	-1.142764	1.240041	-0.545671
PS	-0.550723	1.110838	-0.79328

^a RS, TS and PS denote the reactant, transition and product states, respectively. Partial charges are calculated using the ChelpG⁵ charge calculation scheme, as described in the **Methodology** section.

Table S79. Partial charges at key stationary points for the alkaline hydrolysis of substituted sulfate diesters in the presence of 2 additional explicit water molecules, obtained using the M062X⁴ functional.^a

4-chloro-3-nitro	O_{nuc}	S	O_{lg}
RS	-1.183837	1.149404	-0.419296
TS	-1.049775	1.22034	-0.521161
PS	-0.548575	1.033961	-0.855738
4-nitro	O_{nuc}	S	O_{lg}
RS	-1.174682	1.064808	-0.358528
TS	-1.048017	1.195557	-0.504796
PS	-0.454976	1.055828	-0.814666
2,6-difluoro	O_{nuc}	S	O_{lg}
RS	-1.235459	1.131061	-0.32058
TS	-1.12217	1.205036	-0.437561
PS	-0.5427	1.143453	-0.770924
2-fluoro-4-nitro	O_{nuc}	S	O_{lg}
RS	-1.177047	1.123947	-0.371349
TS	-1.055519	1.124415	-0.423785
PS	-0.525182	1.072611	-0.783297
2,3,4,5,6-pentafluoro	O_{nuc}	S	O_{lg}
RS	-1.230799	1.026602	-0.260471
TS	-1.159782	1.115634	-0.352506
PS	-0.538141	1.114017	-0.737218
3-fluoro-4-nitro	O_{nuc}	S	O_{lg}
RS	-1.185341	1.13244	-0.384258
TS	-1.052143	1.212126	-0.498027
PS	-0.545217	1.096529	-0.817359

^a RS, TS and PS denote the reactant, transition and product states, respectively. Partial charges are calculated using the ChelpG⁵ charge calculation scheme, as described in the **Methodology** section.

Table S80. Partial charges at key stationary points for the alkaline hydrolysis of substituted sulfate diesters in the presence of 4 additional explicit water molecules, obtained using the M062X⁴ functional.^a

4-chloro-3-nitro	O_{nuc}	S	O_{lg}
RS	-1.225708	1.027141	-0.429412
TS	-0.950593	1.076789	-0.408504
PS	-0.596497	1.090874	-0.847179
4-nitro	O_{nuc}	S	O_{lg}
RS	-1.238816	1.009553	-0.39931
TS	-0.959323	1.082878	-0.417571
PS	-0.455648	1.027233	-0.76437
2,6-difluoro	O_{nuc}	S	O_{lg}
RS	-1.114188	0.938976	-0.195632
TS	-1.002794	1.001605	-0.285461
PS	-0.599429	1.001954	-0.704403
2-fluoro-4-nitro	O_{nuc}	S	O_{lg}
RS	-1.110392	0.977804	-0.252159
TS	-0.989268	0.998185	-0.323282
PS	-0.616365	1.168065	-0.781993
2,3,4,5,6-pentafluoro	O_{nuc}	S	O_{lg}
RS	-1.134079	1.010442	0.018025
TS	-1.004115	1.026607	0.042262
PS	-0.511334	1.016364	-0.580361
3-fluoro-4-nitro	O_{nuc}	S	O_{lg}
RS	-1.189591	0.934662	-0.309007
TS	-1.0353	1.000186	-0.418766
PS	-0.483169	1.016664	-0.752615

^a RS, TS and PS denote the reactant, transition and product states, respectively. Partial charges are calculated using the ChelpG⁵ charge calculation scheme, as described in the **Methodology** section.

Table S81. Partial charges at key stationary points for the alkaline hydrolysis of substituted sulfate diesters in the presence of 8 additional explicit water molecules, obtained using the M062X⁴ functional.^a

4-chloro-3-nitro	O_{nuc}	S	O_{lg}
RS	-1.026154	1.294638	-0.404148
TS	-0.94733	1.313362	-0.498923
PS	-0.604425	0.917057	-0.82233
4-nitro	O_{nuc}	S	O_{lg}
RS	-0.964724	1.12928	-0.397992
TS	-0.854524	1.254148	-0.535374
PS	-0.621103	1.146464	-0.805452
2,6-difluoro	O_{nuc}	S	O_{lg}
RS	-0.881376	0.889385	-0.252883
TS	-0.825784	1.061389	-0.11393
PS	-0.556304	1.08863	-0.587597
2-fluoro-4-nitro	O_{nuc}	S	O_{lg}
RS	-1.078287	1.068172	-0.322814
TS	-0.927407	1.060805	-0.306961
PS	-0.607599	1.087578	-0.7628
2,3,4,5,6-pentafluoro	O_{nuc}	S	O_{lg}
RS	-0.724007	0.746927	-0.156613
TS	-0.739404	0.712602	-0.238053
PS	-0.627537	0.998366	-0.667454
3-fluoro-4-nitro	O_{nuc}	S	O_{lg}
RS	-1.061803	1.267365	-0.408913
TS	-0.789773	1.301197	-0.50345
PS	-0.467775	0.952009	-0.77534

^a RS, TS and PS denote the reactant, transition and product states, respectively. Partial charges are calculated using the ChelpG⁵ charge calculation scheme, as described in the **Methodology** section.

Table S82. Geometries at the transition state for the alkaline hydrolysis of substituted sulfate diesters in the presence of 0 additional explicit water molecules (pure implicit solvation), obtained using the ω B97X-D³ functional.^a

Water Molecules	S-O _{nuc} Distance	S-O _{lg} Distance	S-O _{nuc} BO	S-O _{lg} BO
4-chloro-3-nitro	2.35	1.71	0.2621	0.5633
4-nitro	2.35	1.71	0.2639	0.5569
2,6-difluoro	2.41	1.70	0.2263	0.5636
2-fluoro-4-nitro	2.38	1.72	0.2496	0.5467
2,3,4,5,6-pentafluoro	2.50	1.70	0.1916	0.5556
3-fluoro-4-nitro	2.38	1.71	0.2529	0.552

^a Bond distances are shown in Å. Bond orders (BO) were calculated based on the Wiberg bond index⁷ using natural bond orbital (NBO) analysis.⁸

Table S83. Geometries at the transition state for the alkaline hydrolysis of substituted sulfate diesters in the presence of 2 additional explicit water molecules, obtained using the ω B97X-D³ functional.^a

Water Molecules	S-O _{nuc} Distance	S-O _{lg} Distance	S-O _{nuc} BO	S-O _{lg} BO
4-chloro-3-nitro	2.32	1.72	0.2476	0.549
4-nitro	2.32	1.72	0.2456	0.5485
2,6-difluoro	2.38	1.71	0.2188	0.5496
2-fluoro-4-nitro	2.35	1.72	0.2335	0.5353
2,3,4,5,6-pentafluoro	2.44	1.72	0.2005	0.5381
3-fluoro-4-nitro	2.34	1.72	0.2381	0.5415

^a Bond distances are shown in Å. Bond orders (BO) were calculated based on the Wiberg bond index⁷ using natural bond orbital (NBO) analysis.⁸

Table S84. Geometries at the transition state for the alkaline hydrolysis of substituted sulfate diesters in the presence of 4 additional explicit water molecules, obtained using the ω B97X-D³ functional.^a

Water Molecules	S-O _{nuc} Distance	S-O _{lg} Distance	S-O _{nuc} BO	S-O _{lg} BO
4-chloro-3-nitro	2.31	1.73	0.2211	0.5312
4-nitro	2.30	1.73	0.2242	0.5336
2,6-difluoro	2.34	1.72	0.2088	0.551
2-fluoro-4-nitro	2.36	1.71	0.2039	0.5515
2,3,4,5,6-pentafluoro	2.42	1.73	0.1772	0.5216
3-fluoro-4-nitro	2.30	1.72	0.226	0.5462

^a Bond distances are shown in Å. Bond orders (BO) were calculated based on the Wiberg bond index⁷ using natural bond orbital (NBO) analysis.⁸

Table S85. Geometries at the transition state for the alkaline hydrolysis of substituted sulfate diesters in the presence of 8 additional explicit water molecules, obtained using the ω B97X-D³ functional.^a

Water Molecules	S-O _{nuc} Distance	S-O _{lg} Distance	S-O _{nuc} BO	S-O _{lg} BO
4-chloro-3-nitro	2.26	1.73	0.2475	0.5495
4-nitro	2.26	1.73	0.2506	0.5523
2,6-difluoro	2.29	1.73	0.2207	0.5456
2-fluoro-4-nitro	2.31	1.73	0.2264	0.5356
2,3,4,5,6-pentafluoro	2.33	1.74	0.207	0.5322
3-fluoro-4-nitro	2.26	1.73	0.2475	0.5495

^a Bond distances are shown in Å. Bond orders (BO) were calculated based on the Wiberg bond index⁷ using natural bond orbital (NBO) analysis.⁸

Table S86. Geometries at the transition state for the alkaline hydrolysis of substituted sulfate diesters in the presence of 0 additional explicit water molecules (pure implicit solvation), obtained using the M11L¹ functional.^a

Water Molecules	S-O _{nuc} Distance	S-O _{lg} Distance	S-O _{nuc} BO	S-O _{lg} BO
4-chloro-3-nitro	2.31	1.69	0.2428	0.5515
4-nitro	2.31	1.70	0.2543	0.532
2,6-difluoro	2.35	1.68	0.2196	0.554
2-fluoro-4-nitro	2.34	1.70	0.2327	0.5274
2,3,4,5,6-pentafluoro	2.41	1.68	0.193	0.5462
3-fluoro-4-nitro	2.33	1.70	0.2408	0.5268

^a Bond distances are shown in Å. Bond orders (BO) were calculated based on the Wiberg bond index⁷ using natural bond orbital (NBO) analysis.⁸

Table S87. Geometries at the transition state for the alkaline hydrolysis of substituted sulfate diesters in the presence of 2 additional explicit water molecules, obtained using the M11L¹ functional.^a

Water Molecules	S-O _{nuc} Distance	S-O _{lg} Distance	S-O _{nuc} BO	S-O _{lg} BO
4-chloro-3-nitro	2.29	1.70	0.2466	0.536
4-nitro	2.30	1.70	0.2412	0.5261
2,6-difluoro	2.32	1.69	0.2294	0.5407
2-fluoro-4-nitro	2.32	1.71	0.231	0.5176
2,3,4,5,6-pentafluoro	2.37	1.69	0.2087	0.5316
3-fluoro-4-nitro	2.31	1.71	0.2377	0.5171

^a Bond distances are shown in Å. Bond orders (BO) were calculated based on the Wiberg bond index⁷ using natural bond orbital (NBO) analysis.⁸

Table S88. Geometries at the transition state for the alkaline hydrolysis of substituted sulfate diesters in the presence of 4 additional explicit water molecules, obtained using the M11L¹ functional.^a

Water Molecules	S-O _{nuc} Distance	S-O _{lg} Distance	S-O _{nuc} BO	S-O _{lg} BO
4-chloro-3-nitro	2.26	1.71	0.2249	0.5191
4-nitro	2.26	1.71	0.2234	0.5166
2,6-difluoro	2.28	1.69	0.2208	0.5397
2-fluoro-4-nitro	2.31	1.69	0.2116	0.5347
2,3,4,5,6-pentafluoro	2.34	1.70	0.1947	0.5122
3-fluoro-4-nitro	2.29	1.71	0.2175	0.5171

^a Bond distances are shown in Å. Bond orders (BO) were calculated based on the Wiberg bond index⁷ using natural bond orbital (NBO) analysis.⁸

Table S89. Geometries at the transition state for the alkaline hydrolysis of substituted sulfate diesters in the presence of 8 additional explicit water molecules, obtained using the M11L¹ functional.^a

Water Molecules	S-O _{nuc} Distance	S-O _{lg} Distance	S-O _{nuc} BO	S-O _{lg} BO
4-chloro-3-nitro	2.22	1.72	0.2459	0.5249
4-nitro	2.22	1.72	0.2432	0.5151
2,6-difluoro	2.23	1.71	0.2311	0.5246
2-fluoro-4-nitro	2.26	1.71	0.2314	0.5172
2,3,4,5,6-pentafluoro	2.25	1.72	0.2213	0.513
3-fluoro-4-nitro	2.23	1.71	0.2377	0.54

^a Bond distances are shown in Å. Bond orders (BO) were calculated based on the Wiberg bond index⁷ using natural bond orbital (NBO) analysis.⁸

Table S90. Geometries at the transition state for the alkaline hydrolysis of substituted sulfate diesters in the presence of 0 additional explicit water molecules (pure implicit solvation), obtained using the M062X⁴ functional.^a

Water Molecules	S-O _{nuc} Distance	S-O _{lg} Distance	S-O _{nuc} BO	S-O _{lg} BO
4-chloro-3-nitro	2.39	1.69	0.2314	0.5774
4-nitro	2.39	1.69	0.2306	0.5775
2,6-difluoro	2.44	1.69	0.196	0.5769
2-fluoro-4-nitro	2.41	1.69	0.2203	0.5659
2,3,4,5,6-pentafluoro	2.47	1.70	0.1949	0.5604
3-fluoro-4-nitro	2.40	1.69	0.2266	0.5701

^a Bond distances are shown in Å. Bond orders (BO) were calculated based on the Wiberg bond index⁷ using natural bond orbital (NBO) analysis.⁸

Table S91. Geometries at the transition state for the alkaline hydrolysis of substituted sulfate diesters in the presence of 2 additional explicit water molecules, obtained using the M062X⁴ functional.^a

Water Molecules	S-O _{nuc} Distance	S-O _{lg} Distance	S-O _{nuc} BO	S-O _{lg} BO
4-chloro-3-nitro	2.35	1.70	0.2195	0.5732
4-nitro	2.35	1.70	0.2173	0.5692
2,6-difluoro	2.40	1.69	0.2047	0.577
2-fluoro-4-nitro	2.38	1.70	0.2041	0.5583
2,3,4,5,6-pentafluoro	2.45	1.69	0.1841	0.5703
3-fluoro-4-nitro	2.36	1.70	0.2125	0.5659

^a Bond distances are shown in Å. Bond orders (BO) were calculated based on the Wiberg bond index⁷ using natural bond orbital (NBO) analysis.⁸

Table S92. Geometries at the transition state for the alkaline hydrolysis of substituted sulfate diesters in the presence of 4 additional explicit water molecules, obtained using the M062X⁴ functional.^a

Water Molecules	S-O _{nuc} Distance	S-O _{lg} Distance	S-O _{nuc} BO	S-O _{lg} BO
4-chloro-3-nitro	2.33	1.71	0.1936	0.553
4-nitro	2.31	1.71	0.2027	0.5577
2,6-difluoro	2.36	1.70	0.1882	0.5676
2-fluoro-4-nitro	2.37	1.69	0.1855	0.5679
2,3,4,5,6-pentafluoro	2.42	1.71	0.1609	0.5367
3-fluoro-4-nitro	2.33	1.70	0.1979	0.5643

^a Bond distances are shown in Å. Bond orders (BO) were calculated based on the Wiberg bond index⁷ using natural bond orbital (NBO) analysis.⁸

Table S93. Geometries at the transition state for the alkaline hydrolysis of substituted sulfate diesters in the presence of 8 additional explicit water molecules, obtained using the M062X⁴ functional.^a

Water Molecules	S-O _{nuc} Distance	S-O _{lg} Distance	S-O _{nuc} BO	S-O _{lg} BO
4-chloro-3-nitro	2.29	1.69	0.2281	0.5897
4-nitro	2.26	1.7	0.2308	0.5915
2,6-difluoro	2.32	1.70	0.1921	0.5599
2-fluoro-4-nitro	2.35	1.7	0.1936	0.5551
2,3,4,5,6-pentafluoro	2.34	1.71	0.1888	0.5625
3-fluoro-4-nitro	2.26	1.7	0.2228	0.5915

^a Bond distances are shown in Å. Bond orders (BO) were calculated based on the Wiberg bond index⁷ using natural bond orbital (NBO) analysis.⁸

Table S94. Geometries at key stationary points for the alkaline hydrolysis of substituted sulfate diesters in the presence of 0 additional explicit water molecules (pure implicit solvation), obtained using the ω B97X-D³ functional.^a

4-chloro-3-nitro	S-O_{nuc} Distance	S-O_{lg} Distance	S-O_{nuc} BO	S-O_{lg} BO
RS	4.04	1.62	0.0037	0.6738
TS	2.35	1.71	0.2621	0.5633
PS	1.59	5.96	0.763	0.0001
4-nitro	S-O_{nuc} Distance	S-O_{lg} Distance	S-O_{nuc} BO	S-O_{lg} BO
RS	3.87	1.61	0.0059	0.6746
TS	2.35	1.71	0.2639	0.5569
PS	1.59	3.99	0.7569	0.0007
2,6-difluoro	S-O_{nuc} Distance	S-O_{lg} Distance	S-O_{nuc} BO	S-O_{lg} BO
RS	4.70	1.62	0.0032	0.6669
TS	2.41	1.70	0.2263	0.5636
PS	1.59	4.62	0.7485	0.0005
2-fluoro-4-nitro	S-O_{nuc} Distance	S-O_{lg} Distance	S-O_{nuc} BO	S-O_{lg} BO
RS	3.90	1.62	0.0059	0.66
TS	2.38	1.72	0.2496	0.5467
PS	1.59	4.10	0.7539	0.0006
2,3,4,5,6-pentafluoro	S-O_{nuc} Distance	S-O_{lg} Distance	S-O_{nuc} BO	S-O_{lg} BO
RS	4.26	1.63	0.0036	0.6431
TS	2.50	1.70	0.1916	0.5556
PS	1.59	4.95	0.7576	0.0003
3-fluoro-4-nitro	S-O_{nuc} Distance	S-O_{lg} Distance	S-O_{nuc} BO	S-O_{lg} BO
RS	3.87	1.62	0.0059	0.666
TS	2.38	1.71	0.2529	0.552
PS	1.59	4.18	0.7542	0.0005

^a RS, TS and PS denote the reactant, transition and product states, respectively. Bond distances are shown in Å. Bond orders (BO) were calculated based on the Wiberg bond index⁷ using natural bond orbital (NBO) analysis.⁸

Table S95. Geometries at key stationary points for the alkaline hydrolysis of substituted sulfate diesters in the presence of 2 additional explicit water molecules, obtained using the ω B97X-D³ functional.^a

4-chloro-3-nitro	S-O_{nuc} Distance	S-O_{lg} Distance	S-O_{nuc} BO	S-O_{lg} BO
RS	4.58	1.62	0.0016	0.676
TS	2.32	1.72	0.2476	0.549
PS	1.59	4.62	0.7432	0.0002
4-nitro	S-O_{nuc} Distance	S-O_{lg} Distance	S-O_{nuc} BO	S-O_{lg} BO
RS	4.62	1.61	0.0013	0.7122
TS	2.32	1.72	0.2456	0.5485
PS	1.59	4.72	0.7438	0.0002
2,6-difluoro	S-O_{nuc} Distance	S-O_{lg} Distance	S-O_{nuc} BO	S-O_{lg} BO
RS	3.48	1.62	0.0097	0.6722
TS	2.35	1.70	0.2195	0.5732
PS	1.59	3.42	0.7332	0.0037
2-fluoro-4-nitro	S-O_{nuc} Distance	S-O_{lg} Distance	S-O_{nuc} BO	S-O_{lg} BO
RS	4.60	1.62	0.0017	0.6573
TS	2.35	1.72	0.2335	0.5353
PS	1.59	4.72	0.7458	0.0002
2,3,4,5,6-pentafluoro	S-O_{nuc} Distance	S-O_{lg} Distance	S-O_{nuc} BO	S-O_{lg} BO
RS	3.88	1.64	0.0066	0.631
TS	2.44	1.72	0.2005	0.5381
PS	1.59	4.65	0.7496	0.0002
3-fluoro-4-nitro	S-O_{nuc} Distance	S-O_{lg} Distance	S-O_{nuc} BO	S-O_{lg} BO
RS	4.62	1.62	0.0017	0.6655
TS	2.34	1.72	0.2381	0.5415
PS	1.59	3.88	0.7551	0.0008

^a RS, TS and PS denote the reactant, transition and product states, respectively. Bond distances are shown in Å. Bond orders (BO) were calculated based on the Wiberg bond index⁷ using natural bond orbital (NBO) analysis.⁸

Table S96. Geometries at key stationary points for the alkaline hydrolysis of substituted sulfate diesters in the presence of 4 additional explicit water molecules, obtained using the ω B97X-D³ functional.^a

4-chloro-3-nitro	S-O_{nuc} Distance	S-O_{lg} Distance	S-O_{nuc} BO	S-O_{lg} BO
RS	4.67	1.61	0.0004	0.6712
TS	2.31	1.73	0.2211	0.5312
PS	1.55	4.41	0.8323	0.0003
4-nitro	S-O_{nuc} Distance	S-O_{lg} Distance	S-O_{nuc} BO	S-O_{lg} BO
RS	4.39	1.61	0.0003	0.6907
TS	2.30	1.73	0.2242	0.5336
PS	1.45	1.59	0.7446	0.0008
2,6-difluoro	S-O_{nuc} Distance	S-O_{lg} Distance	S-O_{nuc} BO	S-O_{lg} BO
RS	3.80	1.63	0.0055	0.6457
TS	2.34	1.72	0.2088	0.551
PS	1.56	4.56	0.8262	0.0003
2-fluoro-4-nitro	S-O_{nuc} Distance	S-O_{lg} Distance	S-O_{nuc} BO	S-O_{lg} BO
RS	3.69	1.63	0.0077	0.6427
TS	2.36	1.71	0.2039	0.5515
PS	1.56	4.67	0.8203	0.0002
2,3,4,5,6-pentafluoro	S-O_{nuc} Distance	S-O_{lg} Distance	S-O_{nuc} BO	S-O_{lg} BO
RS	3.72	1.64	0.0072	0.6151
TS	2.42	1.73	0.1772	0.5216
PS	3.72	1.64	0.0072	0.6151
3-fluoro-4-nitro	S-O_{nuc} Distance	S-O_{lg} Distance	S-O_{nuc} BO	S-O_{lg} BO
RS	4.68	1.62	0.0005	0.6722
TS	2.30	1.72	0.226	0.5462
PS	1.48	4.73	1.0626	0.0001

^a RS, TS and PS denote the reactant, transition and product states, respectively. Bond distances are shown in Å. Bond orders (BO) were calculated based on the Wiberg bond index⁷ using natural bond orbital (NBO) analysis.⁸

Table S97. Geometries at key stationary points for the alkaline hydrolysis of substituted sulfate diesters in the presence of 8 additional explicit water molecules, obtained using the ω B97X-D³ functional.^a

4-chloro-3-nitro	S-O_{nuc} Distance	S-O_{lg} Distance	S-O_{nuc} BO	S-O_{lg} BO
RS	4.41	1.61	0.0005	0.6994
TS	2.26	1.73	0.2475	0.5495
PS	1.59	4.54	0.7378	0.0003
4-nitro	S-O_{nuc} Distance	S-O_{lg} Distance	S-O_{nuc} BO	S-O_{lg} BO
RS	5.08	1.60	0.0004	0.719
TS	2.26	1.73	0.2506	0.5523
PS	1.48	4.40	1.0432	0.0006
2,6-difluoro	S-O_{nuc} Distance	S-O_{lg} Distance	S-O_{nuc} BO	S-O_{lg} BO
RS	5.63	1.61	0.0001	0.6893
TS	2.29	1.73	0.2207	0.5456
PS	1.58	4.6	0.768	0.0003
2-fluoro-4-nitro	S-O_{nuc} Distance	S-O_{lg} Distance	S-O_{nuc} BO	S-O_{lg} BO
RS	5.21	1.62	0.0002	0.6765
TS	2.31	1.73	0.2264	0.5356
PS	1.59	3.52	0.7492	0.0021
2,3,4,5,6-pentafluoro	S-O_{nuc} Distance	S-O_{lg} Distance	S-O_{nuc} BO	S-O_{lg} BO
RS	4.57	1.63	0.0006	0.6744
TS	2.33	1.74	0.207	0.5322
PS	1.47	5.5	1.1459	0.0001
3-fluoro-4-nitro	S-O_{nuc} Distance	S-O_{lg} Distance	S-O_{nuc} BO	S-O_{lg} BO
RS	4.41	1.61	0.0005	0.6994
TS	2.26	1.73	0.2475	0.5495
PS	1.59	4.54	0.7378	0.0003

^a RS, TS and PS denote the reactant, transition and product states, respectively. Bond distances are shown in Å. Bond orders (BO) were calculated based on the Wiberg bond index⁷ using natural bond orbital (NBO) analysis.⁸

Table S98. Geometries at key stationary points for the alkaline hydrolysis of substituted sulfate diesters in the presence of 0 additional explicit water molecules (pure implicit solvation), obtained using the M11L¹ functional.^a

4-chloro-3-nitro	S-O_{nuc} Distance	S-O_{lg} Distance	S-O_{nuc} BO	S-O_{lg} BO
RS	3.76	1.59	0.0032	0.6809
TS	2.31	1.69	0.2428	0.5515
PS	1.56	3.77	0.7547	0.0017
4-nitro	S-O_{nuc} Distance	S-O_{lg} Distance	S-O_{nuc} BO	S-O_{lg} BO
RS	3.79	1.59	0.0027	0.6817
TS	2.31	1.70	0.2543	0.532
PS	1.56	4.09	0.7523	0.0012
2,6-difluoro	S-O_{nuc} Distance	S-O_{lg} Distance	S-O_{nuc} BO	S-O_{lg} BO
RS	4.39	1.59	0.0012	0.6351
TS	2.35	1.68	0.2196	0.554
PS	1.56	3.59	0.7462	0.0022
2-fluoro-4-nitro	S-O_{nuc} Distance	S-O_{lg} Distance	S-O_{nuc} BO	S-O_{lg} BO
RS	3.71	1.60	0.0036	0.6697
TS	2.34	1.70	0.2327	0.5274
PS	1.56	3.81	0.757	0.0011
2,3,4,5,6-pentafluoro	S-O_{nuc} Distance	S-O_{lg} Distance	S-O_{nuc} BO	S-O_{lg} BO
RS	3.82	1.61	0.0013	0.6044
TS	2.41	1.68	0.193	0.5462
PS	1.56	3.76	0.7542	0.0015
3-fluoro-4-nitro	S-O_{nuc} Distance	S-O_{lg} Distance	S-O_{nuc} BO	S-O_{lg} BO
RS	3.77	1.59	0.0026	0.684
TS	2.33	1.70	0.2408	0.5268
PS	1.56	3.86	0.7573	0.0011

^a RS, TS and PS denote the reactant, transition and product states, respectively. Bond distances are shown in Å. Bond orders (BO) were calculated based on the Wiberg bond index⁷ using natural bond orbital (NBO) analysis.⁸

Table S99. Geometries at key stationary points for the alkaline hydrolysis of substituted sulfate diesters in the presence of 2 additional explicit water molecules, obtained using the M11L¹ functional.^a

4-chloro-3-nitro	S-O_{nuc} Distance	S-O_{lg} Distance	S-O_{nuc} BO	S-O_{lg} BO
RS	3.76	1.59	0.0048	0.6801
TS	2.29	1.70	0.2466	0.536
PS	1.56	3.78	0.7415	0.0018
4-nitro	S-O_{nuc} Distance	S-O_{lg} Distance	S-O_{nuc} BO	S-O_{lg} BO
RS	3.75	1.59	0.0047	0.6768
TS	2.30	1.70	0.2412	0.5261
PS	1.56	3.82	0.737	0.0016
2,6-difluoro	S-O_{nuc} Distance	S-O_{lg} Distance	S-O_{nuc} BO	S-O_{lg} BO
RS	4.36	1.59	0.002	0.6482
TS	2.32	1.69	0.2294	0.5407
PS	1.56	3.64	0.7284	0.0022
2-fluoro-4-nitro	S-O_{nuc} Distance	S-O_{lg} Distance	S-O_{nuc} BO	S-O_{lg} BO
RS	3.73	1.60	0.0044	0.6678
TS	2.32	1.71	0.231	0.5176
PS	1.56	3.83	0.7455	0.0012
2,3,4,5,6-pentafluoro	S-O_{nuc} Distance	S-O_{lg} Distance	S-O_{nuc} BO	S-O_{lg} BO
RS	3.71	1.61	0.0119	0.6278
TS	2.34	1.70	0.1947	0.5122
PS	1.52	4.63	0.8365	0.0002
3-fluoro-4-nitro	S-O_{nuc} Distance	S-O_{lg} Distance	S-O_{nuc} BO	S-O_{lg} BO
RS	3.72	1.59	0.005	0.6763
TS	2.31	1.71	0.2377	0.5171
PS	1.56	3.81	0.7411	0.0018

^a RS, TS and PS denote the reactant, transition and product states, respectively. Bond distances are shown in Å. Bond orders (BO) were calculated based on the Wiberg bond index⁷ using natural bond orbital (NBO) analysis.⁸

Table S100. Geometries at key stationary points for the alkaline hydrolysis of substituted sulfate diesters in the presence of 4 additional explicit water molecules, obtained using the M11L¹ functional.^a

4-chloro-3-nitro	S-O_{nuc} Distance	S-O_{lg} Distance	S-O_{nuc} BO	S-O_{lg} BO
RS	4.09	1.59	0.0006	0.6782
TS	2.26	1.71	0.2249	0.5191
PS	1.55	3.95	0.7735	0.0015
4-nitro	S-O_{nuc} Distance	S-O_{lg} Distance	S-O_{nuc} BO	S-O_{lg} BO
RS	4.03	1.59	0.0005	0.676
TS	2.26	1.71	0.2234	0.5166
PS	1.56	3.96	0.7451	0.0012
2,6-difluoro	S-O_{nuc} Distance	S-O_{lg} Distance	S-O_{nuc} BO	S-O_{lg} BO
RS	3.84	1.59	0.0091	0.6506
TS	2.28	1.69	0.2208	0.5397
PS	1.54	3.73	0.791	0.0017
2-fluoro-4-nitro	S-O_{nuc} Distance	S-O_{lg} Distance	S-O_{nuc} BO	S-O_{lg} BO
RS	3.77	1.59	0.0015	0.6547
TS	2.31	1.69	0.2116	0.5347
PS	1.54	3.59	0.7975	0.0016
2,3,4,5,6-pentafluoro	S-O_{nuc} Distance	S-O_{lg} Distance	S-O_{nuc} BO	S-O_{lg} BO
RS	3.71	1.61	0.0119	0.6278
TS	2.34	1.70	0.1947	0.5122
PS	1.52	4.63	0.8365	0.0002
3-fluoro-4-nitro	S-O_{nuc} Distance	S-O_{lg} Distance	S-O_{nuc} BO	S-O_{lg} BO
RS	3.66	1.60	0.0018	0.655
TS	2.29	1.71	0.2175	0.5171
PS	1.56	4.54	0.7564	0.0005

^a RS, TS and PS denote the reactant, transition and product states, respectively. Bond distances are shown in Å. Bond orders (BO) were calculated based on the Wiberg bond index⁷ using natural bond orbital (NBO) analysis.⁸

Table S101. Geometries at key stationary points for the alkaline hydrolysis of substituted sulfate diesters in the presence of 8 additional explicit water molecules, obtained using the M11L¹ functional.^a

4-chloro-3-nitro	S-O_{nuc} Distance	S-O_{lg} Distance	S-O_{nuc} BO	S-O_{lg} BO
RS	4.27	1.59	0.0008	0.6709
TS	2.22	1.72	0.2459	0.5249
PS	1.46	4.8	0.9992	0.0002
4-nitro	S-O_{nuc} Distance	S-O_{lg} Distance	S-O_{nuc} BO	S-O_{lg} BO
RS	5.81	1.58	0.0001	0.6991
TS	2.22	1.72	0.2432	0.5151
PS	1.46	4.6	0.9886	0.0004
2,6-difluoro	S-O_{nuc} Distance	S-O_{lg} Distance	S-O_{nuc} BO	S-O_{lg} BO
RS	4.89	1.59	0.0005	0.6649
TS	2.23	1.71	0.2311	0.5246
PS	1.56	3.62	0.7711	0.0032
2-fluoro-4-nitro	S-O_{nuc} Distance	S-O_{lg} Distance	S-O_{nuc} BO	S-O_{lg} BO
RS	3.39	1.6	0.003	0.6371
TS	2.26	1.71	0.2314	0.5172
PS	1.55	3.64	0.7785	0.001
2,3,4,5,6-pentafluoro	S-O_{nuc} Distance	S-O_{lg} Distance	S-O_{nuc} BO	S-O_{lg} BO
RS	3.77	1.62	0.0008	0.6486
TS	2.25	1.72	0.2213	0.513
PS	1.56	3.93	0.768	0.0021
3-fluoro-4-nitro	S-O_{nuc} Distance	S-O_{lg} Distance	S-O_{nuc} BO	S-O_{lg} BO
RS	4.97	1.6	0.0003	0.6687
TS	2.23	1.71	0.2377	0.54
PS	1.47	4.29	1.0008	0.0009

^a RS, TS and PS denote the reactant, transition and product states, respectively. Bond distances are shown in Å. Bond orders (BO) were calculated based on the Wiberg bond index⁷ using natural bond orbital (NBO) analysis.⁸

Table S102. Geometries at key stationary points for the alkaline hydrolysis of substituted sulfate diesters in the presence of 0 additional explicit water molecules (pure implicit solvation), obtained using the M062X⁴ functional.^a

4-chloro-3-nitro	S-O_{nuc} Distance	S-O_{lg} Distance	S-O_{nuc} BO	S-O_{lg} BO
RS	3.61	1.61	0.0097	0.6705
TS	2.39	1.69	0.2314	0.5774
PS	1.59	3.58	0.752	0.0022
4-nitro	S-O_{nuc} Distance	S-O_{lg} Distance	S-O_{nuc} BO	S-O_{lg} BO
RS	3.53	1.61	0.0112	0.6722
TS	2.39	1.69	0.2306	0.5775
PS	1.59	3.63	0.7535	0.0014
2,6-difluoro	S-O_{nuc} Distance	S-O_{lg} Distance	S-O_{nuc} BO	S-O_{lg} BO
RS	4.31	1.62	0.0042	0.6624
TS	2.44	1.69	0.196	0.5769
PS	1.59	3.28	0.7421	0.0047
2-fluoro-4-nitro	S-O_{nuc} Distance	S-O_{lg} Distance	S-O_{nuc} BO	S-O_{lg} BO
RS	3.54	1.62	0.0113	0.6576
TS	2.41	1.69	0.2203	0.5659
PS	1.59	3.56	0.7545	0.0016
2,3,4,5,6-pentafluoro	S-O_{nuc} Distance	S-O_{lg} Distance	S-O_{nuc} BO	S-O_{lg} BO
RS	3.70	1.64	0.0073	0.6398
TS	2.47	1.70	0.1949	0.5604
PS	1.59	3.49	0.7503	0.0023
3-fluoro-4-nitro	S-O_{nuc} Distance	S-O_{lg} Distance	S-O_{nuc} BO	S-O_{lg} BO
RS	3.57	1.61	0.0105	0.6633
TS	2.40	1.69	0.2266	0.5701
PS	1.59	3.59	0.7545	0.0016

^a RS, TS and PS denote the reactant, transition and product states, respectively. Bond distances are shown in Å. Bond orders (BO) were calculated based on the Wiberg bond index⁷ using natural bond orbital (NBO) analysis.⁸

Table S103. Geometries at key stationary points for the alkaline hydrolysis of substituted sulfate diesters in the presence of 2 additional explicit water molecules, obtained using the M062X⁴ functional.^a

4-chloro-3-nitro	S-O_{nuc} Distance	S-O_{lg} Distance	S-O_{nuc} BO	S-O_{lg} BO
RS	3.8	1.61	0.0066	0.6703
TS	2.43	1.67	0.2193	0.587
PS	4.9	1.55	0.8516	0.0003
4-nitro	S-O_{nuc} Distance	S-O_{lg} Distance	S-O_{nuc} BO	S-O_{lg} BO
RS	3.52	1.61	0.0085	0.6682
TS	2.35	1.70	0.2173	0.5692
PS	1.59	3.60	0.7435	0.0018
2,6-difluoro	S-O_{nuc} Distance	S-O_{lg} Distance	S-O_{nuc} BO	S-O_{lg} BO
RS	3.29	1.62	0.018	0.6546
TS	2.40	1.69	0.2047	0.577
PS	1.59	3.20	0.7509	0.0052
2-fluoro-4-nitro	S-O_{nuc} Distance	S-O_{lg} Distance	S-O_{nuc} BO	S-O_{lg} BO
RS	3.36	1.62	0.0133	0.655
TS	2.38	1.70	0.2041	0.5583
PS	1.58	3.51	0.7607	0.0019
2,3,4,5,6-pentafluoro	S-O_{nuc} Distance	S-O_{lg} Distance	S-O_{nuc} BO	S-O_{lg} BO
RS	3.35	1.63	0.0183	0.638
TS	2.45	1.69	0.1841	0.5703
PS	1.59	3.36	0.7575	0.0032
3-fluoro-4-nitro	S-O_{nuc} Distance	S-O_{lg} Distance	S-O_{nuc} BO	S-O_{lg} BO
RS	3.47	1.62	0.0097	0.6651
TS	2.36	1.70	0.2125	0.5659
PS	1.58	3.58	0.7603	0.0017

^a RS, TS and PS denote the reactant, transition and product states, respectively. Bond distances are shown in Å. Bond orders (BO) were calculated based on the Wiberg bond index⁷ using natural bond orbital (NBO) analysis.⁸

Table S104. Geometries at key stationary points for the alkaline hydrolysis of substituted sulfate diesters in the presence of 4 additional explicit water molecules, obtained using the M062X⁴ functional.^a

4-chloro-3-nitro	S-O_{nuc} Distance	S-O_{lg} Distance	S-O_{nuc} BO	S-O_{lg} BO
RS	4.27	1.61	0.0009	0.6795
TS	2.33	1.71	0.1936	0.553
PS	1.50	4.64	0.9739	0.0002
4-nitro	S-O_{nuc} Distance	S-O_{lg} Distance	S-O_{nuc} BO	S-O_{lg} BO
RS	4.09	1.61	0.0005	0.696
TS	2.31	1.71	0.2027	0.5577
PS	1.59	3.77	0.7513	0.0013
2,6-difluoro	S-O_{nuc} Distance	S-O_{lg} Distance	S-O_{nuc} BO	S-O_{lg} BO
RS	3.19	1.63	0.0181	0.6397
TS	2.36	1.70	0.1882	0.5676
PS	1.60	3.17	0.7007	0.0065
2-fluoro-4-nitro	S-O_{nuc} Distance	S-O_{lg} Distance	S-O_{nuc} BO	S-O_{lg} BO
RS	3.19	1.63	0.0188	0.6392
TS	2.37	1.69	0.1855	0.5679
PS	1.48	4.72	1.0595	0.0002
2,3,4,5,6-pentafluoro	S-O_{nuc} Distance	S-O_{lg} Distance	S-O_{nuc} BO	S-O_{lg} BO
RS	2.98	1.66	0.0297	0.5907
TS	2.42	1.71	0.1609	0.5367
PS	1.58	3.47	0.7484	0.0026
3-fluoro-4-nitro	S-O_{nuc} Distance	S-O_{lg} Distance	S-O_{nuc} BO	S-O_{lg} BO
RS	3.22	1.62	0.0049	0.6592
TS	2.33	1.70	0.1979	0.5643
PS	1.59	3.47	0.7329	0.0021

^a RS, TS and PS denote the reactant, transition and product states, respectively. Bond distances are shown in Å. Bond orders (BO) were calculated based on the Wiberg bond index⁷ using natural bond orbital (NBO) analysis.⁸

Table S105. Geometries at key stationary points for the alkaline hydrolysis of substituted sulfate diesters in the presence of 8 additional explicit water molecules, obtained using the M062X⁴ functional.^a

4-chloro-3-nitro	S-O_{nuc} Distance	S-O_{lg} Distance	S-O_{nuc} BO	S-O_{lg} BO
RS	3.2	1.62	0.0037	0.6745
TS	2.29	1.69	0.2281	0.5897
PS	1.48	4.59	1.1217	0.0003
4-nitro	S-O_{nuc} Distance	S-O_{lg} Distance	S-O_{nuc} BO	S-O_{lg} BO
RS	3.16	1.62	0.004	0.6855
TS	2.26	1.7	0.2308	0.5915
PS	1.48	3.99	1.1272	0.0013
2,6-difluoro	S-O_{nuc} Distance	S-O_{lg} Distance	S-O_{nuc} BO	S-O_{lg} BO
RS	3.32	1.62	0.0027	0.6531
TS	2.32	1.70	0.1921	0.5599
PS	1.59	3.20	0.7749	0.0058
2-fluoro-4-nitro	S-O_{nuc} Distance	S-O_{lg} Distance	S-O_{nuc} BO	S-O_{lg} BO
RS	3.13	1.62	0.0062	0.6462
TS	2.35	1.7	0.1936	0.5551
PS	1.49	4.07	1.0766	0.0006
2,3,4,5,6-pentafluoro	S-O_{nuc} Distance	S-O_{lg} Distance	S-O_{nuc} BO	S-O_{lg} BO
RS	3.08	1.64	0.0074	0.6401
TS	2.34	1.71	0.1888	0.5625
PS	1.48	3.86	1.1097	0.0008
3-fluoro-4-nitro	S-O_{nuc} Distance	S-O_{lg} Distance	S-O_{nuc} BO	S-O_{lg} BO
RS	3.28	1.62	0.0026	0.6761
TS	2.26	1.7	0.2228	0.5915
PS	1.49	4.88	1.0429	0.0004

^a RS, TS and PS denote the reactant, transition and product states, respectively. Bond distances are shown in Å. Bond orders (BO) were calculated based on the Wiberg bond index⁷ using natural bond orbital (NBO) analysis.⁸

Cartesian Coordinates of Optimized Stationary Points

Due to the large number of stationary points involved, Cartesian coordinates of all stationary points have been presented as a separate zip file.

Supplementary References

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